CLINICAL TRIAL REPORT FOR THE 24-WEEK SHORT-TERM TREATMENT PERIOD

A 24-week, single centre, randomized, parallel-group, double-blind, placebo-controlled Phase II study with an optional 28-week open-label extension to evaluate the efficacy on body weight of dapagliflozin 10 mg once daily in combination with exenatide 2 mg once weekly in obese non-diabetic subjects (Part 1)

This report summarizes data collected during the initial 24-week double-blind study period.

Protocol Number:	D1690L00016
EudraCT Number:	2014-03432-39
Trial Development Phase:	Phase IIa
Tested Drug Substances:	Dapagliflozin and Exenatide
Proposed Indication:	Obesity
Date of Report:	FINAL version 1.1, 11 Jan 2017
Sponsor:	Uppsala University
First Subject Enrolled (date):	08 Dec 2014
Last Subject Completed (date):	31 Aug 2015
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1. SIGNATURES

Trial Title: A 24-week, single centre, randomized, parallel-group, double-blind, placebo controlled Phase II study with an optional 28-week open-label extension to evaluate the efficacy on body weight of dapagliflozin 10 mg once daily in combination with exenatide 2 mg once weekly in obese non-diabetic subjects (Part 1)

Report No.: D1690L00016

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the trial.

Principal Investigator and Sponsor Representative:

2017-04-21

Prof Jan Eriksson, MD, PhD — Date

Biostatistician:

2017-05-02

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2017-04-21

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2. SYNOPSIS

Name of Sponsor/Company:
Uppsala University

Name of Finished Product:
FORXIGA® and BYDUREON®

Name of Active Ingredient:
Dapagliflozin and Exenatide

Title of Study:
A 24-week, single centre, randomized, parallel-group, double-blind, placebo-controlled Phase II study with an optional 28-week open-label extension to evaluate the efficacy on body weight of dapagliflozin 10 mg once daily in combination with exenatide 2 mg once weekly in obese non-diabetic subjects

Investigators:
Prof. Jan Eriksson, MD, PhD

Study Centre(s):
Department of Medical Sciences, Clinical Diabetes and Metabolism, Uppsala University and Section for Diabetes and Endocrinology at the Uppsala University Hospital, SE-751 85 Uppsala, Sweden

Publication (reference):
Not applicable

Studied period (years):	**Phase of development:**
(date of first screening visit): 08 Dec 2014 (date of last completed): 31 Aug 2015	IIa

Objectives:

Primary Objective

To assess the efficacy of dapagliflozin 10 mg once daily and exenatide 2 mg once weekly in combination compared to placebo on change of body weight (kg) after 24 weeks of treatment in obese subjects.

Secondary Objective

To assess the efficacy of dapagliflozin 10 mg once daily and exenatide 2 mg once weekly in combination compared to placebo on body weight (percent change) after 24 weeks of treatment in obese subjects.

Exploratory objectives

- To assess the proportion of subjects responding to treatment with dapagliflozin 10 mg once daily and exenatide 2 mg once weekly in combination when compared to placebo, with respect to change in body weight.
- To assess the efficacy of dapagliflozin once daily and once weekly exenatide in combination compared to placebo on total body fat mass, percentage body fat, total lean body mass, percentage liver fat, visceral fat mass and subcutaneous fat mass.
- To assess the efficacy of dapagliflozin once daily and exenatide once weekly in combination compared to placebo on glucose tolerance, insulin secretion, insulin sensitivity and lipolysis regulation.
- To assess the efficacy of dapagliflozin once daily and once weekly exenatide in combination compared to placebo on blood lipid profile, blood pressure and other anthropometric measurements.
- To collect and store blood samples and DNA for future exploratory research of circulating biomarkers and pharmacogenetics.

Safety objective

To evaluate the safety and tolerability of dapagliflozin 10 mg once daily and exenatide 2 mg once weekly in combination in obese non-diabetic subjects.

Methodology:

The study used a randomized, double-blind and placebo-controlled design with 2 treatment arms, the combined active treatment (dapagliflozin/exenatide) vs placebo. Placebo was used as control due to the lack of any known comparator treatment with weight reducing effects in obese subjects. The study was powered to detect a difference in the mean change in body weight of 4 kg between active treatment and placebo.

Besides an incremental change in body weight, measures of body composition (total adipose tissue, visceral adipose tissue and liver fat) together with measures of glucose, insulin, glucagon, lipids and signs of lipolysis were included as outcome measures to further clarify the effects of the combined treatment with dapagliflozin and exenatide.

The 24-week treatment period comprised 6 visits at the clinic; screening visit (week -2-[-1]), randomization visit (week 0) and 4 treatment follow-up visits at weeks 4, 8, 12 and 24. One to 2 weeks after randomization, there was a telephone contact with the study nurse (or site visit).

All subjects who completed the initial 24-week double-blind study per protocol were offered to enter the 28-week open-label extension study given that they did not fulfil any of the original exclusion criteria and that they signed a novel informed consent form specifically written for the extension study. For subjects entering the open-label extension study the total study period was extended from 24 to 52 weeks and comprised 2 additional follow-up visits at the clinic. This clinical study report describes the efficacy and safety results obtained as of week 24.

Throughout the screening and treatment period, subjects received lifestyle counselling and were instructed to follow a balanced diet and to increase physical activity.

Number of patients (planned and analysed):

	Test drug	Placebo	Total
No. planned:	24	24	48
No. randomized and treated:	25	25	50
Females/Males (FAS):	15/10	15/9	30/19
Mean age (range) (FAS):	53 years (20-69)	50 years (23-68)	52 years (20-69)
Mean body weight at baseline (FAS):	106.4 kg	102.7 kg	104.6 kg
No. analysed for efficacy			
Full analysis set (FAS):	25	24	49
Per-protocol analysis set:	22	20	42
No. analysed for safety			
Safety analysis set:	25	25	50
No. completed:	23	20	43

Diagnosis and main criteria for inclusion:

Female or male obese non-diabetic subjects aged 18 to 70 years with body mass index (BMI) between 30 and 45 kg/m^2 and without significant co-morbidities. Females had to use a highly effective means of contraception.

Test product, dose and mode of administration, batch number:

Dapagliflozin 10 mg tablet administered orally once daily, batch number: 3035126/3035127, plus exenatide 2 mg, batch number: 3035170/3035171, administered as once weekly subcutaneous injection during the 24-week double-blind period.

Duration of treatment:

24 weeks

Reference therapy, dose and mode of administration, batch number:

Corresponding dapagliflozin 10 mg placebo tablet administered orally once daily, batch number: 3035126/3035127, plus exenatide 2 mg placebo, batch number 3035170/3035171, administered as once weekly subcutaneous injection during the 24-week double blind period.

Criteria for evaluation:

Efficacy

- Body weight and other anthropometric measurements including calculation of waist-hip ratio (WHR) and BMI were performed at screening (week -2-[-1]), randomization (week 0) and at weeks 4, 8, 12 and 24.
- Whole body Magnetic Resonance Imaging (MRI) scans (optional) were performed for assessment of the percentage liver fat, visceral fat, total fat volume and total lean tissue at randomization and week 24. Total body fat (%) was also assessed by bioimpedance at randomization and weeks 12 and 24.
- Blood sampling was performed for evaluation of efficacy laboratory variables including: HbA1c, fasting plasma glucose, impaired fasting glucose (IFG), impaired glucose tolerance (IGT), insulin, C-peptide, glucagon, glycerol, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), free fatty acids (FFA), ketones in blood. Blood samples were collected at screening, weeks 12 and 24. At screening and week 24, a 3-hour oral glucose tolerance test (3h-OGTT) was performed to assess glucose tolerance, insulin secretion, insulin sensitivity and lipolysis regulation following ingestion of a glucose solution (75 g glucose in water). During the 3h-OGTT, urine was collected for measurement of urinary glucose excretion (UGE). All blood samples, except those collected during OGTT, were taken under fasting conditions.
- The proportion of subject with impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) was calculated at baseline and week 24.
- Insulin sensitivity was assessed at baseline and week 24 using the QUICKI index, the Revised QUICKI index and the weighted Matsuda index adjusted for UGE. Insulin secretion was assessed using the Insulinogenic index.
- Estimated glomerular filtration rate (eGFR) was assessed at screening and weeks 12 and 24.

Safety

- Clinical laboratory tests (clinical chemistry, haematology) were performed at screening and weeks 12 and 24. Urinalysis was performed at screening.
- Creatinine clearance was assessed at screening and weeks 12 and 24.
- Vital signs were assessed at screening, randomization and weeks 4, 8, 12 and 24.
- Incidence and type of adverse events (AEs) and serious adverse events (SAEs). Adverse event reporting started at screening and continued throughout the entire treatment period until week 24. At each visit, subjects were asked for the occurrence of AEs since the last visit at the clinic. Subjects were specifically asked about the occurrence of symptoms related to hypoglycaemia (e.g. fatigue, dizziness, tremor, palpitations, sweating).

Exploratory

- Blood samples for exploratory purposes were collected at screening and week 24, just prior to start of the 3h-OGTT, and an additional blood sample was collected during OGTT at 120 minutes. The samples were frozen and stored at the Uppsala Biobank for future research.

Statistical methods:

General

The statistical analyses were described in the Statistical Analysis Plan (SAP) which was finalized prior to database lock. After code-breaking, the SAP was updated with additional post-hoc analyses as described in the Clinical Study Report. Continuous data are summarized using descriptive statistics where the following parameters are reported: number of observations (n), number of missing observations (nmiss), mean, standard deviation (SD), minimum (min), Q1 (first quartile), median, Q3 (third quartile), maximum (max). Categorical data are presented using frequency (n) and percentage (%). All efficacy variables are assessed at a two-sided 0.050 significance level. The results of significance tests are reported with p-value.

Data analysis sets

Patients were classified into the following 3 analysis sets prior to breaking the blind:

- The **Full analysis set (FAS)**: all randomized subjects who received at least one dose of study medication during the 24-week double-blind treatment period, who had a non-missing baseline value and at least one post-baseline value for at least one efficacy variable during the double-blind period. In case of severe non-compliance with the protocol, a subject could be excluded from the FAS.

- The **Per-protocol analysis set (PPAS)**: a subset of the FAS, consisted of subjects who had sufficiently complied with the protocol, e.g. no major protocol deviations, had available data at 24 weeks for the primary variable and had been compliant to IP (at least 20 weeks of IP treatment and 80% to 120% of intended IPs).
- The **Safety analysis set**: all randomized subjects who received at least one dose of study medication and who provided any safety records.

Patient and baseline data

Descriptive statistics were provided for the following: patient disposition, demographics, body weight and other anthropometric measures, waist-hip ratio, compliance, medical history and concurrent diseases, prior and concomitant medications.

Efficacy

All efficacy analyses were performed on both the FAS and the PPAS.

Primary efficacy variable

The primary efficacy variable was change in body weight (kg) from baseline to 24 weeks. The treatment effect was tested and estimated using a Mixed Model for Repeat Measurements (MMRM) model including treatment, week, treatment-by-week interaction and gender as well as the continuous fixed covariate of baseline body weight measurement. An unstructured matrix for the within-subject error variance-covariance was used. The longitudinal repeated measures mixed model was used to derive a least squares (LS) estimate of the treatment difference at Week 24 with 95% confidence interval and corresponding p-value. To assess whether this model was adequate, the interaction between treatment group and gender was tested in the longitudinal model. As the interaction term was not significant ($p > 0.10$), the model without the treatment by gender interaction term was used.

Alternative primary efficacy variable (post-hoc analysis)
The treatment effect on the mean change in body weight (kg) from baseline to week 24 compared to placebo was estimated using an MMRM adjusted for treatment, week, the interaction between treatment and week, gender, baseline body weight and the interaction between baseline body weight and week. The MMRM was used to derive an LS estimate of the treatment difference at week 24 with 95% CI and corresponding p value.

Secondary efficacy variable

The secondary efficacy variable was percentage change in body weight (%) from baseline to 24 weeks and was analysed with the same method as the primary variable.

Exploratory efficacy variables

The proportion of subjects with at least 10% and 5% reduction in weight at 24 weeks, respectively, are presented. However, the number of subjects with at least 5% and 10% reduction in weight at 24 weeks was too low for statistical analyses to be performed.

Mean change in body weight (kg) and percentage change in body weight from the screening visit to 24 weeks was analysed using an MMRM including treatment, week, treatment-by-week interaction and gender as well as the covariate of baseline (screening) body weight.

For MRI data, i.e., liver fat percentage, liver volume, total liver fat, visceral adipose tissue, abdominal subcutaneous adipose tissue, total adipose tissue and total lean tissue, an analysis of covariance (ANCOVA) model including treatment, gender as well as the continuous fixed covariate of baseline value was applied.

During the OGTT, blood samples for insulin sensitivity and lipolysis were taken at 15, 30, 60, 90, 120 and 180 minutes after ingestion of the oral glucose solution. The following laboratory variables were tested: glucose, glucagon, glycerol, FFAs, insulin, ketones and C-peptide. The treatment effect on change from baseline was tested and estimated using an ANCOVA model adjusted for treatment, gender and the continuous fixed covariate of baseline value.

For the laboratory variables glucose, glycerol, FFA and insulin, the area under the curve (AUC) was calculated. AUC is the total area under the curve from time 0 minutes to last observed concentration at each visit. For each variable the treatment effect on change from baseline was tested and estimated using an ANCOVA model adjusted for treatment, gender and the continuous fixed covariate of baseline value. The incremental AUC was analysed for glycerol and FFA and for blood ketones, the delta between the OGTT at screening and week 24 was calculated.

The proportion of subjects with impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) at screening and week 24 within the treatment groups was tested using a paired McNemar test. The difference in proportions between the treatment groups was tested using a Cochran-Mantel-Haenszel test. Further, descriptive statistics for the number of subjects with normal and raised values at screening and at week 24 as well as the number of subjects shifting categories between points of measurement were presented by treatment group.

Laboratory efficacy variables included total cholesterol (TC), low density lipoprotein cholesterol (LDL C), high-density

lipoprotein cholesterol (HDL-C), triglycerides (TG), HbA1c and fasting plasma glucose (FPG). These variables were analysed with the same method as the primary efficacy variable.

The following indices were evaluated: QUICKI index, Revised QUICKI index, weighted Matsuda index adjusted for UGE and Insulinogenic index. The treatment effect on change from baseline was tested and estimated using an ANCOVA model adjusted for treatment, gender and the continuous fixed covariate of baseline value.

The ANCOVA models were used to derive an LS estimate of the treatment difference at Week 24 with 95% confidence interval and corresponding p-value. Further, two-sided 95% confidence intervals for the adjusted mean change within each treatment group were calculated.

Vital signs, waist circumference, WHR and BMI were also analysed with the same method as the primary efficacy variable.

Urinary glucose excretion during the 3h-OGTT (UGE = concentration * volume (mL) expressed in [mL x mmol/l / 1000 = mmol]) was also calculated and summary statistics are presented.

Estimated glomerular filtration rate (eGFR) based on MDRD was analysed with the same method as the primary efficacy variable.

Descriptive statistics are presented for all efficacy variables alongside the statistical analyses.

Exploratory model building

Exploratory model building of potential prognostic factors and covariates was performed using a stepwise procedure with limits for inclusion and exclusion in the model. Baseline values and patient characteristics for potential inclusion as prognostic factors/covariates in the models for weight change and % weight change: weight, gender, age, BMI, HbA1c, urinary glucose, % liver fat, % body fat, WHR, indices based on glucose and insulin levels (QUICKI index, Revised QUICKI index, weighted Matsuda index adjusted for UGE and Insulinogenic index), OGTT glucose $AUC_{0\text{-}2h}$ and MRI variables.

Safety Evaluation

Safety data are presented descriptively using the Safety analysis set. The safety parameters included clinical chemistry, haematology, vital signs, creatinine clearance and adverse events (AEs).

Sample Size Calculation

Base on previous studies, a conservative measure of 4.0 kg for the standard deviation was selected for the sample size calculation. To detect a difference of 4 kg between the treatment groups, 17 evaluable subjects per treatment group were required for 90% power at a 2-sided significance level of 0.050. Accounting for 10% of the randomized subjects to be excluded from the primary analysis because of missing data (e.g., lost to follow-up) and a potentially lower treatment effect of dapagliflozin

EFFICACY RESULTS:

Primary Efficacy Variable

Mean Change in Body Weight (kg)

- A statistically significant treatment effect of dapagliflozin/exenatide on the mean change from baseline to week 24 in body weight (kg) was observed compared to placebo. Twenty-four weeks of treatment with dapagliflozin/exenatide reduced the mean body weight by -4.1 kg (95% CI=-6.4 to -1.8; p=0.0008) compared to placebo.

  Similar results were obtained for the PPAS: -3.7 kg (95% CI=-6.1 to -1.3; p=0.0036).
- A statistically significant dapagliflozin/exenatide-induced reduction of body weight compared to placebo was observed at weeks 8 and 12 (-1.7 kg [95% CI=-3.0 to -0.4; p=0.0136] and -3.5 kg [95% CI=-5.2 to -1.8; p=0.0002], respectively).
- A majority of the weight loss in the dapagliflozin/exenatide group occurred during the first 12 weeks of the 24-week treatment period. After week 12, the weight reduction diminished.

Alternative Primary Efficacy Model

Mean Change in Body Weight (kg)

- A statistically significant treatment effect of dapagliflozin/exenatide on the mean change from baseline to week 24 in body weight (kg) was observed compared to placebo. Twenty-four weeks of treatment with dapagliflozin/exenatide reduced the mean body weight by -4.2 kg (95% CI=-6.5 to -1.8; p=0.0008) compared to placebo.

  Similar results were obtained for the PPAS: -3.7 kg (95% CI=-6.2 to -1.3; p=0.0036).

Secondary Efficacy Variable

Percentage Change in Body Weight

- A statistically significant treatment effect of dapagliflozin/exenatide on the mean percentage change from baseline to week 24 in body weight (%) was observed compared to placebo. Twenty-four weeks of treatment with dapagliflozin/exenatide reduced the mean body weight by -4.2% (95% CI=-6.5 to -1.9; p=0.0006) compared to placebo.

  Similar results were obtained for the PPAS: -3.7% (95% CI=-6.1 to -1.4; p=0.0026).

Exploratory Variables

Proportion of subjects with at least 5% and 10% reduction of body weight at week 24

- The proportion of subjects with more than or equal to 5% weight loss at week 24 was 36.0% vs 0.0% in the dapagliflozin/exenatide and placebo group, respectively (FAS). Similar results were obtained for the PPAS (40.9% vs 0.0%).
- The proportion of subjects with more than or equal to 10% weight loss at week 24 was 12.0% vs 0.0% in the dapagliflozin/exenatide and placebo group, respectively. Similar results were obtained for the PPAS (13.6% vs 0.0%).

Mean change in body weight (kg) between screening and week 24

- A statistically significant treatment effect of dapagliflozin/exenatide on the mean change from screening to week 24 in body weight (kg) was observed compared to placebo.
  Twenty-four weeks of treatment with dapagliflozin/exenatide reduced the mean body weight by -4.5 kg (95% CI=-6.9 to -2.2; p=0.0003) compared to placebo.

  Similar results were obtained for the PPAS: -4.4 kg (95% CI=-6.9 to -1.9; p=0.0010).

Percentage change in body weight (%) between screening and week 24

- A statistically significant treatment effect of dapagliflozin/exenatide on the mean percentage change from screening to week 24 in body weight (%) was observed compared to placebo. Twenty-four weeks of treatment with dapagliflozin/exenatide reduced the mean body weight by -4.5% (95% CI=-6.8 to -2.2; p=0.0002) compared to placebo.

  Similar results were obtained for the PPAS: -4.3% (95% CI=-6.7 to -1.9; p=0.0009).

Body fat composition

- Statistically significant treatment effects of dapagliflozin/exenatide on the mean change from baseline to week 24 in total adipose tissue (L), visceral adipose tissue (L) and abdominal subcutaneous adipose tissue (L) were observed compared to placebo. Twenty-four weeks of treatment with dapagliflozin/exenatide reduced the mean volume of total adipose tissue by -4.09 L (95% CI=-6.23 to -1.94; p=0.0004), visceral adipose tissue by -0.62 L (95% CI=-0.95 to -0.29; p=0.0005) and abdominal subcutaneous adipose tissue by -1.44 L (95% CI=-2.16 to -0.71; p=0.0003) compared to placebo.
- No statistically significant treatment effect of dapagliflozin/exenatide on the mean change from baseline to week 24 in percentage liver fat (%), liver volume (L), total liver fat (L) or total lean tissue (L) were observed compared to placebo.
- A discrepancy between whole body MRI and bioimpedance for assessment of total body fat was observed. MRI data revealed a statistically significant reduction of total adipose tissue (L) in the dapagliflozin/exenatide group compared to placebo. In contrast, no statistically significant difference between treatment groups was achieved when bioimpedance was used for assessment of the percentage total body fat (%).

Haemoglobin A1c

- A statistically significant treatment effect of dapagliflozin/exenatide was observed on the mean change from baseline to week 24 in plasma HbA1c levels compared to placebo. Twenty-four weeks of treatment with dapagliflozin/exenatide significantly reduced the mean levels of HbA1c by -2.3 mmol/mol (95% CI=-3.5 to -1.1; p=0.0004) compared to placebo.

Fasting plasma glucose

- In response to a glucose challenge (3h-OGTT, 75 g glucose), a statistically significant treatment effect of dapagliflozin/exenatide was observed on the mean change from baseline to week 24 in both preprandial (Time 0) and 120 min postprandial plasma glucose levels compared to placebo. Twenty-four weeks of treatment with dapagliflozin/exenatide reduced the preprandial plasma glucose levels by -0.7 mmol/L (95% CI=-0.9 to -0.4; p<0.0001), the 2h-postprandial plasma glucose levels by -1.5 mmol/L (95% CI=-2.7 to -0.3; p=0.0131) and the mean AUC_{0-2h} by -223.1 mmol/L x 180 min (95% CI=-366.6 to -79.7; p=0.0032) compared to placebo.

Impaired fasting plasma glucose and impaired glucose tolerance

- The proportion of subjects with IFG (FPG ≥5.6 mmol/L) was significantly lower in the dapagliflozin/exenatide group compared to the placebo group (34.8% vs 85.0%; p=0.0009) at week 24. Within the dapagliflozin/exenatide group, but not within the placebo group, there was a statistically significant reduction in the proportion of subjects with IFG between baseline and week 24; 30.4% shifted from raised to normal and 0% shifted from normal to raised (p=0.0082).
- No statistically significant difference between treatment groups was observed with regard to the proportion of subjects with IGT (postprandial plasma glucose ≥7.8 mmol/L at Time 120 minutes during the 3h-OGTT) at week 24. Within the dapagliflozin/exenatide group, but not within the placebo group, there was a statistically significant reduction in the proportion of subjects with IGT between baseline and week 24; 34.8% shifted from raised to normal and 4.3% shifted from normal to raised (p=0.0196).
- The proportion of subjects with IFG and/or IGT was significantly lower in the dapagliflozin/exenatide group compared to the placebo group (34.8% vs 85.0%; p=0.0017) at week 24. Within the dapagliflozin/exenatide group, but not within the placebo group, there was a statistically significant reduction in the proportion of subjects with IFG and/or IGT between baseline and week 24; 34.8% shifted from raised to normal and 0% shifted from normal to raised (p=0.0047).

Insulin secretion and insulin sensitivity

- No statistically significant treatment effect of dapagliflozin/exenatide on the mean change from baseline to week 24 in either preprandial, 2h-postprandial serum insulin levels, or AUC_{0-3h} during the 3h-OGTT was observed compared to placebo.
- No statistically significant treatment effect of dapagliflozin/exenatide on the mean change from baseline to week 24 in insulin sensitivity, as estimated by the QUICKI index, the Revised QUICKI index or the weighted Matsuda index adjusted for UGE, was observed compared to placebo.
- No statistically significant treatment effect of dapagliflozin/exenatide on the mean change from baseline to week 24 in insulin secretion as estimated by the Insulinogenic index was observed compared to placebo.

Lipolysis regulation

- A statistically significant treatment effect of dapagliflozin/exenatide was observed on the mean change from baseline to week 24 in postprandial (but not preprandial) plasma FFA levels. Exposure to dapagliflozin/exenatide increased the postprandial plasma FFA levels during the 3h-OGTT at Time 30, 60 and 120 minutes and the treatment difference in mean change from baseline in AUC_{0-2h} was 2871.5 µmol/L x 120 min (95% CI=1156.0 to 4586.9; p=0.0016) compared to placebo.

  No statistically significant treatment effect of dapagliflozin/exenatide was observed on the mean change from baseline in $iAUC_{0-2h}$ for plasma FFA at week 24 compared to placebo.

Other variables

- No statistically significant treatment effects of dapagliflozin/exenatide on the mean change from baseline to week 24 in preprandial or postprandial blood levels of glucagon, glycerol, ketones or C-peptide during the 3h-OGTT were observed compared to placebo.

Blood lipid profile

- No statistically significant treatment effects of dapagliflozin/exenatide on the mean change from baseline to week 24 in the blood lipid profile, as estimated by serum levels of TC, LDL-C, HDL-C and TG, were observed compared to placebo.

Vital signs

- A statistically significant treatment effect of dapagliflozin/exenatide on the mean change from baseline to week 24 in systolic blood pressure (mm Hg) was observed compared to placebo. Exposure to dapagliflozin/exenatide lowered the mean systolic blood pressure by -6.7 mmHg (95% CI=-12.4 to -1.0; p=0.0220) compared to placebo.

  Also, at week 8, a statistically significant reduction of systolic blood pressure was observed in the dapagliflozin/exenatide group (-8.7 mmHg [95% CI=-14.4 to -3.1]; p=0.0032) compared to placebo.
- No statistically significant treatment effects of dapagliflozin/exenatide on the mean change from baseline to week 24 in diastolic blood pressure or pulse were observed compared to placebo.

Other anthropometric measurements

- A statistically significant treatment effect of dapagliflozin/exenatide on the mean change from baseline to week 24 in BMI (kg/m^2) was observed compared to placebo. Exposure to dapagliflozin/exenatide reduced the mean BMI by -1.4 kg/m^2 (95% CI=-2.2 to -0.6; p=0.0008) compared to placebo.
- No statistically significant treatment effect of dapagliflozin/exenatide on the mean change from baseline to week 24 of waist circumference or WHR were observed compared to placebo, possibly due to limited precision

in the measurement of waist and hip circumference throughout the study.

Urinary excretion of glucose

- Twenty-four weeks of exposure to dapagliflozin/exenatide increased the excretion of glucose into the urine compared to placebo (189.5 mmol [SD=107.3] vs 0.95 mmol [SD=2.1]) during the 3h-OGTT.

Estimated glomerular filtration rate

- No statistically significant treatment effect of dapagliflozin/exenatide on the mean change from baseline to week 24 in eGFR was observed compared to placebo.

Model building to identify potential covariates

- Baseline BMI and baseline WHR were identified as significant covariates (p=0.0011 and p=0.0236) for prediction of the outcome of the primary variable. This means that the higher BMI at baseline, the lower weight reduction was observed at week 24. Conversely, a greater WHR at baseline is associated with a greater loss of weight after 24 weeks. As both BMI and WHR are measures of obesity the contradicting results should be interpreted with caution.

SAFETY RESULTS:

- No safety concerns were identified for the combined treatment with dapagliflozin (10 mg once daily) and exenatide (2 mg weekly injections) during 24 weeks in obese otherwise healthy subjects based on clinical laboratory tests, creatinine clearance, vital signs and AEs/SAEs.
- The mean duration of exposure and treatment compliance was largely similar in both treatment groups.
- There were no major changes in mean laboratory values during the study and no apparent differences between treatment groups.
- All 50 randomized subjects reported AEs (281 AEs in total, 168 AEs in the dapagliflozin/exenatide group and 113 AEs in the placebo group). Thus, the total number of AEs reported in the dapagliflozin/exenatide group was approximately 20 percentage points higher compared to the total number of AEs reported in the placebo group.
- A majority of the AEs (206 of 281 AEs in total; 73.3%) were of mild intensity. Most AEs were assessed as related or possibly related to treatment (181 of 281 AEs in total; 64.4%). There were no apparent differences in AE severity or relationship to IP between the groups.
- Six subjects were prematurely withdrawn from the study due to the occurrence of AEs or SAEs; 2 subjects in the dapagliflozin/exenatide group and 4 subjects in the placebo group. The primary reason for withdrawal of one of these subjects (E129, placebo) was non-compliance to the study protocol.
- The most common SOCs, reported by >50% of subjects in any group, were: gastrointestinal disorders (72.0% vs 52.0% of all subjects in the dapagliflozin/exenatide and placebo group, respectively) and general disorders and administration site conditions (64.0% vs 68.0%).
- The most common PTs were: nasopharyngitis (36.0% vs 16.0%), headache (32.0% vs 16.0%), decreased appetite (32.0% vs 12.0%) and injection site mass (28.0% vs 20.0%).
- Few AEs of special interest with regard to the mode of action of dapagliflozin (urinary tract infections, genital infections, volume depletion-related events or renal impairment-related events) were reported in the study and there was no major difference in reporting frequency between treatment groups.
- Gastrointestinal AEs of special interest with regard to the mode of action of exenatide treatment were more frequently reported in the dapagliflozin/exenatide group compared to the placebo group: 64.0% vs 40.0% of all subjects in the dapagliflozin/exenatide and placebo group, respectively. The 3 most common gastrointestinal symptoms were: nausea (28.0% vs 12.0%), diarrhoea (12.0% vs 12.0%) and abdominal distension (12.0% vs 8.0%).
- Injection site-related AEs were more frequently reported in the dapagliflozin/exenatide group compared to the placebo group: 44.0% vs 32.0% of all subjects in the dapagliflozin/exenatide and placebo group, respectively, experienced injection site-related AEs. The 3 most common injection site-related AEs were: injection site mass (28.0% vs 20.0%), injection site pruritus (28.0% vs 8.0%) and injection site erythema (12.0% vs 4.0%).
- The combined treatment with dapagliflozin/exenatide was not associated with any signs indicative of hypoglycaemia.

OVERALL CONCLUSIONS:

EFFICACY

24 weeks of combined treatment with dapagliflozin and exenatide in obese, otherwise healthy subjects resulted in a statistically significant weight loss of 4.1 kg compared to placebo (p=0.0008). The weight loss was essentially accounted for by a loss of adipose tissue (-4.1L; p=0.0004). In addition to its weight-reducing effect, the combined treatment with dapagliflozin and exenatide significantly lowered the plasma levels of both HbA1c (p=0.0004) and FPG (p<0.0001) with no clear signs of hypoglycaemia. In response to a glucose challenge at week 24, both postprandial plasma glucose levels (p=0.0131) and $AUC_{0\text{-}3h}$ (p=0.0032) were significantly reduced in the dapagliflozin/exenatide group compared to placebo. A statistically significant reduction of the proportion of subjects with IFG and IFG and/or IGT (p=0.0009 and p=0.0017) was observed in the dapagliflozin/exenatide group compared to placebo at week 24. No statistically significant differences between treatment groups were observed with regard to pre- and postprandial insulin levels, insulin sensitivity, insulin secretion, C-peptide, glucagon, glycerol, ketones or blood lipids. Finally, 24 weeks of combined treatment with dapagliflozin and exenatide led to a statistically significant reduction of mean systolic blood pressure (-6.7 mmHg; p=0.0220) compared to placebo.

SAFETY

No major safety issues were identified for the combined treatment with dapagliflozin (10 mg once daily) and exenatide (2 mg weekly injections) during 24 weeks of treatment in obese, otherwise healthy, subjects based on clinical laboratory tests, creatinine clearance, vital signs and AEs/SAEs.

The AE reporting did not reveal any sign of new patterns not previously noted for the individual drugs. Importantly there were no signs of an increased frequency of events related to hypovolemia or impaired renal function when patients were given the combination of dapagliflozin and exenatide.

Notice to the reader:

The final CTR version 1.0 dated 21 September 2016, has been amended as follows:

- **Conclusions (Synopsis and Section 11.4.7)**
  - Previous: The proportion of subjects with more than or equal to 5% weight loss at week 24 was 36.0% vs **4.2%** in the dapagliflozin/exenatide and placebo group, respectively (FAS). Similar results were obtained for the PPAS (40.9% vs **5.0%**).
  - Current: The proportion of subjects with more than or equal to 5% weight loss at week 24 was 36.0% vs **0.0%** in the dapagliflozin/exenatide and placebo group, respectively (FAS). Similar results were obtained for the PPAS (40.9% vs **0.0%**).
- **Section 11.2.10 Concomitant medication**
  - Previous: Drugs for obstructive airway disease: **3** subjects (**12.0%**) in the dapagliflozin/exenatide group and 5 subjects (20.0%) in the placebo group of which the most common medication was terbutaline sulphate (n=4).
  - Current: Drugs for obstructive airway disease: **2** subjects (**8.0%**) in the dapagliflozin/exenatide group and 5 subjects (20.0%) in the placebo group of which the most common medication was terbutaline sulphate (n=4).
  - Table 78, 79 (Prior medication Safety analysis set and FAS) and Table 80, 81 (Concomitant medication Safety analysis set and FAS) have been updated.

- **Section 11.4.3.1 Proportion of subjects with at least 5% and 10% reduction of body weight at week 24**
  - Previous: In the FAS, 9 of 25 subjects (36.0%) had more than, or equal to, 5% weight loss at week 24 in the dapagliflozin/exenatide group compared to 1 of 24 subjects (4.2%) in the placebo group (Table 19). Three of 25 subjects (12.0%= had more than, or equal to, 10% weight loss in the dapagliflozin/exenatide group compared to 0 of 24 subjects (0.0%) in the placebo group.
  - Current: In the dapagliflozin/exenatide group, 9 of 25 subjects (36.0%) had more than, or equal to, 5% weight loss and 3 of 25 subjects (12.0%) had more than, or equal to, 10% weight loss at week 24 (Table 19). **None of the subjects in the placebo group exhibited a weight reduction of 5% or more** (Table 19).
  - Table 19 (FAS) and Table 88 (PPAS) have been updated to reflect that no placebo subjects had a weight reduction of 5% or more.

- **Discussion Section 13.1.1 Efficacy**
  - Previous: Thirty-six percent (36.0%) of all subjects in the FAS had more than or equal to 5% weight loss at week 24 in the dapagliflozin/exenatide group compared to 4.2% in the placebo group. Twelve percent (12.0%) had more than or equal to 10% weight loss at week 24 in the dapagliflozin/exenatide group compared to 0.0% in the placebo group.
  - Current: Thirty-six percent (36.0%) of all subjects in the FAS had more than, or equal to, 5% weight loss and 12% had more than, or equal to, 10% weight loss at week 24 in the dapagliflozin/exenatide group **whereas no subject in the placebo group had a weight reduction of 5% or more**.

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Notice to the Reader

This report summarizes the results from the initial 24-week double-blind treatment period.

4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
ACS	Acute Coronary Syndrome
ADA	American Diabetes Association
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area under the curve
βhCG	human Chorionic Gonadotropin, beta subunit
BID	Twice daily
Bioimpedance	Bioelectrical impedance analysis
BMI	Body Mass Index
CK	Creatine Kinase
CRF	Case Report Form (electronic/paper)
CRO	Contract Research Organisation
CRP	C-reactive protein
CSP	Clinical Study Protocol
CV	Coefficient of Variation
DPP	Dipeptidyl peptidase
eGFR	Estimated glomerular filtration rate
FAS	Full analysis set
IEC	Independent Ethics Committee
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
FFA	Free Fatty Acids
FPG	Fasting Plasma Glucose
GCP	Good Clinical Practice
GLP	Glucagon-like peptide
Hb	Haemoglobin
HbA1c	Haemoglobin A1c
HDL-C	High-Density Lipoprotein Cholesterol
iAUC	Incremental Area Under the Curve
ICH	International Conference on Harmonisation
ICF	Informed Consent Form
IFG	Impaired Fasting Glucose

IP	Investigational Product
LCHF	Low-Carbohydrate-High-Fat
LDL-C	Low-Density Lipoprotein Cholesterol
LS	Least Squares (estimate)
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NA	Not applicable
od	Once daily
OGTT	Oral Glucose Tolerance Test
3h-OGTT	3 hour Oral Glucose Tolerance Test
2h-PG	2 hour Plasma Glucose
PPAS	Per-protocol analysis set
PPG	Postprandial glucose
PT	Preferred Term
QUICKI	Quantitative insulin sensitivity check index
RA	Regulatory Authorities
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDV	Source Data Verification
SGLT	Sodium-glucose cotransporter
SOC	System Organ Class
SPC	Summary of Product Characteristics
T2DM	Type 2 Diabetes Mellitus
TB	Total Bilirubin
TC	Total Cholesterol
TG	Triglycerides
TIA	Transient Ischemic Attack
UGE	Urinary Glucose Excretion
ULN	Upper Limit of Normal
WHO	World Health Organization
WHR	Waist-Hip Ratio
vs	versus

5. ETHICS

5.1 INDEPENDENT ETHICS COMMITTEE (IEC) OR INSTITUTIONAL REVIEW BOARD (IRB)

The original study Clinical Study Protocol (CSP, dated 27 Oct 2014) was approved in writing on 19 Nov 2014 by the Independent Ethics Committee (IEC) in Uppsala, Sweden and by the Regulatory authorities (RA) on 18 Nov 2014.

There was 1 substantial amendment to the original CSP (dated 15 Apr 2015) approved by the RA on 19 May 2015 and by the IEC on 04 May 2015.

All protocol versions and amendments are provided in Appendix 16.1.1. Contact details to the IEC and approval dates are found in Appendix 16.1.3. Details of all amendments are provided in Section 9.8.

5.2 ETHICAL CONDUCT OF THE TRIAL

The study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki that are consistent with International Conference on Harmonization (ICH)/Good Clinical Practice (GCP) and applicable regulatory requirements.

5.3 SUBJECT INFORMATION AND CONSENT

Informed consent was obtained from all subjects prior to initiation of any study related activities. Subjects who entered the 28-week open-label study after completion of the initial 24-week double-blind treatment period also signed a novel informed consent form prior to receiving open-label study treatment. Copies of the subject information and informed consent forms used for the initial 24-week double blind study and for the 28-week open-label study, respectively, are provided in Appendix 16.1.3.

6. INVESTIGATORS AND TRIAL ADMINISTRATIVE STRUCTURE

The key study personnel are listed in Table 1. Curriculum Vitaes for all important participants in the study is provided in Appendix 16.1.4

Table 1 Key Study Personnel

Role	Name, affiliation	Address
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7. INTRODUCTION

The worldwide prevalence of obesity is rapidly increasing and authorities view it as one of the most serious public health problems of the 21st century. The World Health Organization (WHO) predicts that overweight and obesity may soon replace more traditional public health concerns such as undernutrition and infectious diseases as the most significant cause of poor health. Obesity increases the risk of metabolic syndrome, a combination of medical disorders which includes: diabetes mellitus type 2 (T2DM), high blood pressure, high blood cholesterol, and high triglyceride levels. Raised body mass index (BMI) also increases the risk of cancer of the breast, colon, prostate, endometrium, kidney and gall bladder.[1]

Dapagliflozin (FORXIGA®) is a highly selective and orally active inhibitor of the human renal sodium-glucose transporter 2 (SGLT2)[2,3]. Dapagliflozin lowers plasma glucose by inhibiting the renal reabsorption of glucose and thereby by promoting its urinary excretion. This compound has been developed as an oral agent for the treatment of T2DM, and represents a novel therapeutic approach for the treatment of this disorder. Dapagliflozin treatment leads to significant and clinically relevant reductions in fasting plasma glucose (FPG), postprandial glucose (PPG), and haemoglobin A1c (HbA1c) levels throughout the dose range of 5 to 10 mg administered orally once daily, and is also associated with weight loss and blood pressure reduction.[4] A study in obese T2DM subjects demonstrated that the dapagliflozin-induced weight loss was mainly accounted for by reduction of body fat, with significant loss both in the subcutaneous and visceral adipose depots.[5] Dapagliflozin treatment has also resulted in an improved long-term weight control in overweight/obese T2DM subjects for up to 4 years.[6]

Exenatide (BYDUREON®) is a glucagon-like peptide-1 (GLP-1) receptor agonist approved as a once-weekly injection administered to improve glycaemic control in T2DM. Exenatide exhibits many of the same glucoregulatory or glucose-lowering actions of GLP-1, a naturally occurring incretin hormone, but exenatide is not substantially degraded by dipeptidyl peptidase-IV (DPP-4), which efficiently degrades GLP-1 in vivo.[7,8] Exenatide has demonstrated robust glucose-lowering effects in the fasting, preprandial, and postprandial states, resulting in improvement in 24-h glucose control, augmented endogenous insulin secretion, reduced blood pressure and weight loss in patients with T2DM.[9]

Dapagliflozin leads to body weight reduction via a continuous loss of energy (up to 300 kcal/day) via the urine. In clinical trials, this has resulted in an improved long-term weight control in overweight/obese T2DM subjects for up to 4 years.[6] Exenatide, on the other hand, leads to weight loss mainly via reduced energy intake, most likely via a central effect on appetite regulation. For each of these two mechanisms compensatory alterations are expected to occur that will attenuate body weight reduction over time, *i.e.,* increased food intake and reduction in energy expenditure, respectively. By combining the two different modes of action of dapagliflozin and exenatide, such compensatory phenomena will partly be prevented which may lead to synergistic, or at least additive, effects on body weight reduction.

Both dapagliflozin and exenatide are approved worldwide for treatment of patients with T2DM and their efficacy and safety profiles have been extensively documented through their respective development programs. The current study was designed to investigate the combined effect of dapagliflozin and exenatide on weight reduction when co-administered in obese non-diabetic subjects.

This study was a 24-week randomized, double-blind, placebo-controlled Phase IIa study with an optional 28-week open-label extension period. The purpose of the 28-week open-label extension is to demonstrate maintained, or additional, weight reduction by active treatment up to 12 months. This report describes the results obtained after the initial 24-week double-blind placebo-controlled treatment period.

8. TRIAL OBJECTIVES

8.1 PRIMARY OBJECTIVE

To assess the efficacy of dapagliflozin 10 mg once daily and exenatide 2 mg once weekly in combination compared to placebo on change of body weight (kg) after 24 weeks of treatment in obese subjects.

8.2 SECONDARY OBJECTIVE

To assess the efficacy of dapagliflozin 10 mg once daily and exenatide 2 mg once weekly in combination compared to placebo on body weight (percent change) after 24 weeks of treatment in obese subjects.

8.3 EXPLORATORY OBJECTIVES

- To assess the proportion of subjects responding to treatment with dapagliflozin 10 mg once daily and exenatide 2 mg once weekly in combination when compared to placebo, with respect to change in body weight.
- To assess the efficacy of dapagliflozin once daily and once weekly exenatide in combination compared to placebo on total body fat mass, percentage body fat, total lean body mass, percentage liver fat, visceral fat mass and subcutaneous fat mass.
- To assess the efficacy of dapagliflozin once daily and exenatide once weekly in combination compared to placebo on glucose tolerance, insulin secretion, insulin sensitivity and lipolysis regulation.
- To assess the efficacy of dapagliflozin once daily and once weekly exenatide in combination compared to placebo on blood lipid profile, blood pressure and other anthropometric measurements.
- To collect and store blood samples and DNA for future exploratory research of circulating biomarkers and pharmacogenetics.

8.4 SAFETY OBJECTIVE

To evaluate the safety and tolerability of dapagliflozin 10 mg once daily and exenatide 2 mg once weekly in combination in obese non-diabetic subjects.

9. INVESTIGATIONAL PLAN

9.1 OVERALL TRIAL DESIGN AND PLAN-DESCRIPTION

A flow chart of the study design is shown in Figure 1.

This was a 24-week, single centre, randomized, parallel-group, double-blind, placebo-controlled Phase IIa study with an optional 28-week open-label extension to evaluate the efficacy and safety of dapagliflozin once daily therapy when added to once weekly exenatide in obese non-diabetic subjects.

Forty-eight (48) subjects were planned to be enrolled and randomized in 2 parallel groups: 24 subjects receiving active treatment and 24 subjects receiving placebo. The study was conducted at 1 study site in Sweden. The number of subjects willing to enter the 28-week extension study was estimated to be between 30 to 40 subjects.

The 24-week double-blind treatment period comprised 6 visits; screening visit (week -2-[-1]), randomization visit (week 0) and 4 treatment follow-up visits (weeks 4, 8, 12 and 24).

The screening visit was to take place 7 to 14 days prior to randomization. In addition, there was also a telephone contact (or site visit) with the study nurse 1 to 2 weeks after randomization.

At screening, each subject received training by a medically qualified person at the study site in how to reconstitute the exenatide/placebo powder in diluent and how to prepare a syringe for injection. Thereafter, each subject administered a placebo injection under supervision of the study nurse.

All efficacy and safety measurements performed during the study are described in detail in Section 9.5.

All subjects who completed the initial 24-week double-blind study were offered to enter the 28-week open-label extension study given that they did not fulfil any of the original exclusion criteria and that they signed a novel informed consent form specifically written for the extension study.

The open-label extension study comprised 2 additional treatment follow-up visits at the clinic at weeks 38 and 52. In addition, there was a telephone contact with the study nurse (or site visit) at week 25. For subjects entering the extension study the total study period was extended from 24 to 52 weeks. For details on timing of all visits, refer to Figure 1. Note that the first visit at the clinic for the subjects entering the 28-week open-label extension study coincided with the study completion visit for the 24-week double-blind period (*i.e.,* Visit 7/8 was the last visit of the initial 24-week study and the first visit of the 28-week open-label extension study).

Throughout the screening and treatment periods, subjects were instructed to follow a balanced diet and to increase physical activity.

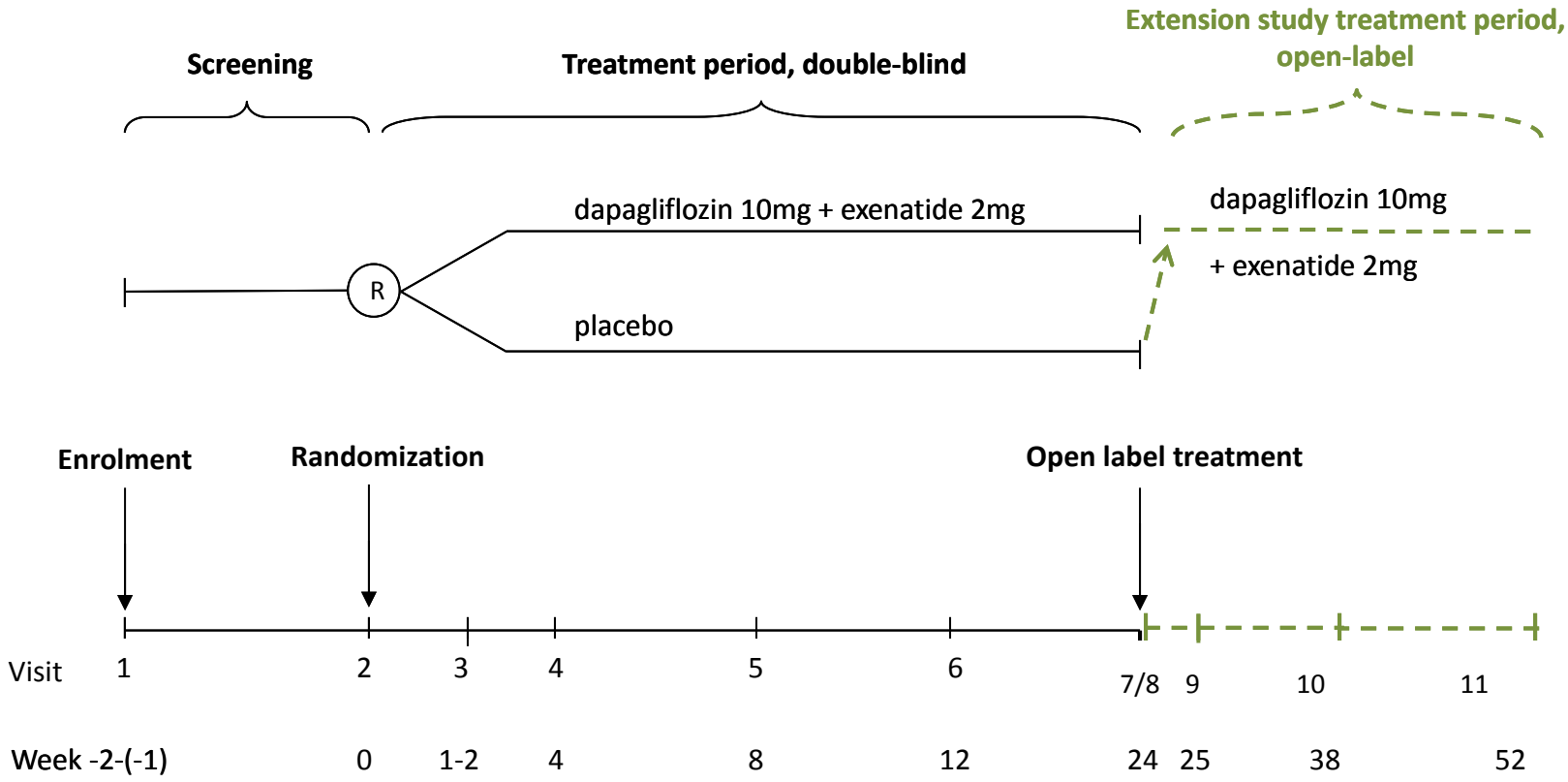
An administrative interim analysis, blinded to the study team and Principal Investigator, was planned after all subjects had conducted 12 weeks of treatment. A copy of the database at 12 weeks was stored. A full database lock was conducted on 5 Oct 2015 after all subjects had completed 24 weeks of blinded treatment.

A second full database lock will be conducted after all subjects participating in the 28-week extension study completed the study at week 52.

This report summarizes data collected during the initial 24-week double-blind study period.

For further details on the study procedures, refer to Table 2 or Section 4.1 in the CSP (Appendix 16.1.1).

Figure 1 **Trial Flow Chart**



9.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS

The study was designed to investigate the combined effect of dapagliflozin and exenatide on weight reduction in obese, otherwise healthy subjects.

The study used a randomized, double-blind and placebo-controlled design with 2 treatment arms, the combined active treatment vs placebo. The randomized double-blind study design enabled a non-biased and well-controlled collection of data. Placebo was used as control due to the lack of any known comparator treatment with weight reducing effects in obese subjects.

The study was powered to detect a difference in mean change in body weight of 4.0 kg between active treatment and placebo. Since obese but otherwise healthy subjects were randomized to blinded treatment including subcutaneous injections of exenatide (extended release formulation) or placebo, the intention was to restrict the sample size by the design of only 2 study arms.

Besides an incremental change in body weight, measures of body composition (total adipose tissue, visceral adipose tissue and liver fat) together with measures of glucose, insulin and glucagon profiles were included as outcome measures to further clarify the effects of the combined treatment with dapagliflozin and exenatide.

The length of the 24-week double-blind treatment period was chosen based on previous clinical studies showing detectable and maximal weight loss with either dapagliflozin or exenatide after 24 weeks of treatment.

The purpose of the 28-week open-label extension following the 24-week double-blind treatment period was to demonstrate maintained, or additional, weight reduction by active treatment up to 12 months. In addition, the 28-week extension study offered active treatment to subjects having received placebo during the first 24 weeks. This provided an opportunity also for those subjects to benefit from potential drug effects in terms of body weight reduction.

9.3 SELECTION OF TRIAL POPULATION

The target population in this study was female or male obese non-diabetic subjects aged 18-70 years with BMI of 30 to 45 kg/m^2 and without significant co-morbidities. Each subject had to meet all of the inclusion criteria and none of the exclusion criteria for participation in the study.

9.3.1 Inclusion Criteria

For inclusion in the study subjects had to fulfil the following criteria:

1) Provision of signed informed consent prior to any study specific procedures

2) Female and/or male aged 18 to 70 years with BMI (measured as body weight (kg)/(height (m))^2) 30 to 45 kg/m^2

3) Female subjects had to meet all of the following criteria:
    a) Not breastfeeding
    b) Negative pregnancy test result (human chorionic gonadotropin, beta subunit [βhCG]) at screening (Visit 1) (not applicable to hysterectomized females).
    c) If of childbearing potential (including perimenopausal women who have had a menstrual period within 1 year), must practice and be willing to continue to practice one of the following highly effective birth control methods during the entire duration of the study:

i. Diaphragm or partner use of condom in combination with combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
   - Oral
   - Intravaginal
   - Transdermal

ii. Diaphragm or partner use of condom in combination with progestogen-only hormonal contraception associated with inhibition of ovulation:
   - Oral
   - Injectable
   - Implantable

iii. Placement of an intrauterine device

iv. Placement of an intrauterine hormone-releasing system

v. Bilateral tubal occlusion

vi. Vasectomised partner (provided that the partner is the sole sexual partner of the female subject and that the vasectomised partner has received medical assessment of the surgical success)

vii. Sexual abstinence (defined as refraining from heterosexual intercourse)

d) Must practice appropriate birth control as stated above for 10 weeks after the last dose of study medication

9.3.2 Exclusion Criteria

Subjects were not to enter the study if any of the following exclusion criteria were fulfilled:

1) Involvement in the planning and/or conduct of the study
2) Previous enrolment in the present study
3) Participation in another clinical study with an Investigational product (IP) during the last 3 months prior to Visit 1 (screening visit)
4) History of any clinically significant disease, disorder or condition which, in the opinion of the Investigator, may either put the subject at risk because of participation in the study, or influence the results or the subject's ability to participate in the study
5) Previous or new diagnosis of diabetes mellitus. For subjects being diagnosed with diabetes at screening, this should be judged by an experienced diabetologist and be based on composite laboratory measures according to American Diabetes Association (ADA) guidelines. These criteria include FPG >7.0 mmol/L, 2h-PG at OGTT >11.1 mmol/L and/or HbA1c > 48 mmol/mol. Subjects with FPG ≥7.0 mmol/L or 2h-PG ≥11.1 mmol/L at Visit 1, should have a second FPG measurement on a separate day, and if diabetes diagnosis is confirmed the subject will be excluded

   Note: Exclusion criterion No.5 was rephrased during the study period as described in the substantial amendment No.1 (dated 19 May 2015). In the original CSP (dated 27 Oct 2014) the exclusion criterion No.5 read: *"Previously diagnosed diabetes mellitus, or fasting P-glucose ≥7.0 mmol/L at Visit 1 confirmed by one more measurement; or P-glucose ≥11.1 mmol/L at 120 minutes of the oral glucose tolerance test (OGTT) at Visit 1 confirmed by one more measurement. Note: Subjects with a fasting P-glucose of ≥7.0 mmol/L at Visit 1 or ≥11.1 mmol/L at 120 minutes of the OGTT at Visit 1 may be offered an extra visit before Visit 2 for a second fasting P-glucose measurement. If P-glucose is still ≥7.0 mmol/L at the second measurement, the subject will be excluded."* The substantial amendment No.1 was approved by the IEC on 19 May 2015 and eligible subjects randomized in the study after this date were obliged to meet exclusion criterion No.5 as

formulated in the substantial amendment No.1. For further details, see also Changes to the conduct of the trial, Section 9.8.1.

6) Any clinically significant abnormalities in physical examination or clinical chemistry results as judged by the Investigator. The following specific exclusion criteria apply to the selected Clinical Chemistry results:
    a) Creatinine clearance <60 mL/min (estimated with Cockcroft-Gault formula)
    b) Severe hepatic insufficiency and/or significant abnormal liver function defined as aspartate aminotransferase (AST) >3x upper limit of normal (ULN) and/or alanine aminotransferase (ALT) >3x ULN
    c) Total bilirubin (TB) >2.0 mg/dL (34.2 µmol/L)
7) Positive serologic evidence of current infectious liver disease including Hepatitis B viral antibody IgM, Hepatitis B surface antigen and Hepatitis C virus antibody
8) Volume depleted patients. Patients at risk for volume depletion due to co-existing conditions or concomitant medications, such as loop diuretics should have careful monitoring of their volume status
9) Acute Coronary Syndrome (ACS) within 2 months prior to Visit 1. Hospitalization for unstable angina or acute myocardial infarction within 2 months prior to enrolment. Acute Stroke or transient ischemic attack (TIA) within two months prior to Visit 1. Less than two months post coronary artery revascularization
10) History of gastroparesis or pancreatitis
11) History of malignancy within the last 5 years, excluding successful treatment of basal or squamous cell skin cancer
12) Body weight loss greater than 5% within 3 months prior to Visit 1
13) Treatment with any drug known to affect body weight within the last month, e.g. systemic glucocorticoids, antipsychotics or orlistat
14) Multiple Endocrine Neoplasia syndrome type 2
15) Personal or family history of medullary thyroid carcinoma

9.3.3 Restrictions

Eligible subjects were instructed to adhere the following restrictions throughout the study period:

- Take no new prescription medications or over-the-counter preparations without prior approval of the Investigator
- Continue existing therapy (if applicable) with antihypertensive or lipid-lowering agents at current dosages
- Fast overnight for at least 8 hours prior to Visit 1, Visit 2, Visit 6, and Visit 7/8 i.e., no food or beverage except water
- Withhold excessive alcohol consumption and refrain from intense exercise 24 hours prior to Visits 2 to Visit 7/8
- Delay administration of the morning dose of study drug (as applicable) on the morning of each study-site visit and bring study drug to each study-site visit

Subjects were asked to undergo Magnetic Resonance Imaging (MRI) at Visit2 and Visit 7/8. The MRI investigation was not conducted for subjects meeting one of the following criteria:

- Claustrophobia
- Pacemaker, implanted electronic devices or clips within the brain
- Previous brain or heart surgery
- History of metal in the eye
- Unwillingness to undergo MRI
- MRI not possible due to logistical or practical circumstances

9.3.4 Removal of Patients from Therapy or Assessment

The study was to be stopped if, in the judgment of the Investigator, subjects were placed at undue risk because of clinically significant findings that:

- Met individual stopping criteria or are otherwise considered significant
- Were assessed as causally related to study drug
- Were not considered to be consistent with continuation of the study

Regardless of the reason for termination, all data available for the subject at the time of discontinuation of follow-up were to be recorded in the Case Report Form (CRF). All reasons for discontinuation of treatment were to be documented.

9.3.4.1 Stopping Criteria

Subjects could be prematurely withdrawn from IP under the following circumstances:

- Subject decision. The subject was at any time free to discontinue treatment, without prejudice to further treatment
- Adverse Event: Subjects were to be discontinued from treatment if the initial and repeated laboratory tests met any of the following criteria:
    - ALT and/or AST were >3x ULN and TB >2x ULN
    - ALT and/or AST were >5x ULN for ≥14 consecutive days, at any time after initial confirmatory results
    - ALT and/or AST were >8x ULN
    - Calculated creatinine clearance <60 mL/min (if not normalized upon repeated test, to be performed within 5 days)
- Severe non-compliance with the study protocol

9.3.5 Withdrawal of Consent

Subjects were free to withdraw from the study at any time (IP and assessments), without prejudice to further treatment.

A subject who withdrew consent was asked about the reason(s) and the presence of any adverse events (AEs). The subject was to be followed-up outside of the study for safety reasons (including follow-up of any AEs ongoing at the time of withdrawal) and medical needs as applicable. No additional study assessments were performed unless specifically agreed to by the subject. However, data collected before the withdrawal were used in the trial.

9.4 TREATMENTS

9.4.1 Treatments Administered

Treatment groups	Dose	Dosage	Route of administration
Dapagliflozin Exenatide	10 mg 2 mg	Once daily Once weekly	Oral administration of tablet Subcutaneous injection
Matching placebo to dapagliflozin Matching placebo to exenatide	NA NA	Once daily Once weekly	Oral administration of tablet Subcutaneous injection

9.4.2 Identity of Investigational Product(s) for the 24-week Double-blind Study Period

Investigational product	Dosage form and strength	Batch numbers	Manufacturer
Dapagliflozin (FORXIGA®)	Biconvex, diamond shape, green tablets 10 mg (Size 11 mm)	3035126/3035127	AstraZeneca
Matching placebo for dapagliflozin	Biconvex, diamond shape, green tablets (Size 11 mm)	3035126/3035127	AstraZeneca
Exenatide once-weekly suspension (BYDUREON™)	2 mg injection	3035170/3035171	AstraZeneca
Placebo to match exenatide once-weekly suspension	Placebo injection	3035170/3035171	AstraZeneca

Exenatide once-weekly suspension was an extended release formulation of exenatide and consisted of 5% exenatide, sucrose, and 50:50 poly D,L lactic-co-glycolic acid (PLG). The vial containing the white to off-white dry powder (2.8 mg of exenatide in microspheres to deliver 2 mg of exenatide) had to be stored in a refrigerator between 2°C and 8°C and protected from light. The exenatide matching placebo had identical formulation as exenatide with the active ingredient omitted.

The microsphere diluent for suspension of exenatide and matching placebo microspheres contained carboxymethylcellulose low viscosity, polysorbate 20, sodium chloride, and water for injection. The microsphere diluent had to be stored between 2°C and 25°C.

The exenatide or matching placebo dose was prepared by reconstitution of the microspheres in the diluents provided. The reconstituted dose of study medication (exenatide or matching placebo) was not to be stored for future use. The injection had to be administered via subcutaneous injection using a 23 Gauge x 5/16 inches needle immediately after preparation of the dose.

9.4.3 Method of Assigning Patients to Treatment Groups

Eligible subjects were randomized to 1 of 2 treatment arms, active treatment or matching placebo, in a 1:1 ratio. Random assignment to study treatment was done in balanced blocks and was stratified by gender.

9.4.4 Selection of Doses in the Trial

The doses of dapagliflozin and exenatide selected for this study were the standard doses for treatment of T2DM (dapagliflozin 10 mg once daily and exenatide 2 mg once weekly).

Dapagliflozin has been well tolerated at doses of up to 500 mg/day in single dose testing in healthy volunteers and up to 100 mg/day in repeat dose testing for 14 days in healthy volunteers and patients with T2DM. Exenatide once weekly has been well-tolerated with no major safety concerns when given in doses of up to 10 mg/day in patients with T2DM. For details, refer to the Investigator's Brochure.

9.4.5 Selection and Timing of Dose for Each Patient

Dapagliflozin (or matching placebo) was taken orally once daily, preferably in the morning and at the same time each day, during the treatment period.

Exenatide (or matching placebo) was administered once weekly via a subcutaneous injection according to instructions provided by the study nurse at the clinic.

9.4.6 Blinding

All personnel involved in the study (subjects, Investigator, study site personnel, CRO personnel, AstraZeneca collaborators) remained blinded until database lock with one exception: an unblinded evaluation of overall safety of the combination treatment was performed by AstraZeneca after all subjects had conducted 12 weeks of treatment. During the evaluation, patient level data and randomization codes were only made available to firewalled AstraZeneca staff, a statistician and a physician, who performed the safety evaluation based on unblinded data, as this was found to exclude any major safety issue. For further details about the interim safety evaluation, refer to Section 11.4.4.3.

To preserve the blinding, access to the treatment codes was limited to personnel not involved in the daily conduct of the trial or data review and analysis prior to database lock at the end of the 24-week study.

Individual treatment codes, indicating the treatment randomization for each randomized subject, were available in sealed envelopes to the Investigators at the study site. The treatment code was not to be broken except in medical emergencies when the appropriate management of the subject required knowledge of the treatment randomization.

AstraZeneca retained the right to break the code for serious adverse events (SAEs) that were unexpected and suspected to be causally related to an IP and that potentially required expedited reporting to regulatory authorities. No treatment code was broken until after data base lock.

9.4.7 Prior and Concomitant Therapy

Medications were classified as prior if the stop date was before or on the date of baseline (randomization, week 0) and as concomitant if ongoing at or stopped after baseline or started after baseline. Medical history and concurrent disease as well as prior and concomitant procedures were defined in an analogous way.

Subjects had to follow the medication restrictions outlined in Section 9.3.3 during the treatment period. Dosages for certain concomitant medications were to be maintained constant during the study, unless instructed otherwise by the Investigator or a treating physician. Any change in regimen for any concomitant medication, including restricted concomitant medications, were to be reported to the Investigator and recorded in the eCRF.

9.4.8 Treatment Compliance

Subjects were asked to return all unused study medication and ancillary medication as well as empty packages and bottles to the clinic at each visit. The subject was asked about compliance at each study visit; compliance was also assessed based on returned amounts of investigational and ancillary products and reported dosing information. Patients judged to be non-compliant (defined as taking less than 80% or more than 120% of the prescribed dose of IP) could continue in the study, but were counselled on the importance of taking their study medication and applicable ancillary medications as prescribed.

The administration of all study medications (including IPs) was recorded in the appropriate sections of the CRF. Treatment compliance (number of injections and number of tablets received relative to planned) was summarized by treatment.

9.5 EFFICACY AND SAFETY VARIABLES

9.5.1 Efficacy and Safety Measurements Assessed and Flow Chart

The efficacy and safety measurements assessed in this study are presented in Table 2.

Table 2 Study Plan Detailing the Procedures

	Screening	Randomization	Treatment period							
Visit Visit window Days -14 to 7 for Visit 1 Days 7-14 for Visit 3 ±3 days starting at Visit 4	**1**	**2**	**(3)**	**4**	**5**	**6**	**7/8**	**(9)**	**10**	**11**
Week	**-2-(-1)**	**0**	**1-2**	**4**	**8**	**12**	**24**	**25**	**38**	**52**
Day	**-14-(-7)**	**0**	**7-14**	**28**	**56**	**84**	**168**	**175**	**266**	**364**
Site visit	X	X		X	X	X	X		X	X
Telephone contact or site visit			X					X		
Written informed consent	X									
Written informed consent, extension							X			
Inclusion/exclusion criteria	X	X								
Inclusion/exclusion criteria, extension							X[a]			
Pregnancy Test (urine), WOCBP[b] only	X					X	X			X
Demographics	X									
Medical/surgical history	X									
Vital signs	X	X		X	X	X	X		X	X
Height	X									
Body weight	X[c]	X[c]		X	X	X[c]	X[c]		X	X[c]
Body fat (%) by bioelectrical impedance (bioimpedance)		X[c]				X[c]	X[c]		X	X[c]
Waist- and hip circumference	X[c]	X[c]		X	X	X[c]	X[c]		X	X[c]

	Screening	Randomization	Treatment period							
Visit Visit window Days -14 to 7 for Visit 1 Days 7-14 for Visit 3 ±3 days starting at Visit 4	**1**	**2**	**(3)**	**4**	**5**	**6**	**7/8**	**(9)**	**10**	**11**
Week	**-2-(-1)**	**0**	**1-2**	**4**	**8**	**12**	**24**	**25**	**38**	**52**
Day	**-14-(-7)**	**0**	**7-14**	**28**	**56**	**84**	**168**	**175**	**266**	**364**
Concomitant medication	X	X		X	X	X	X		X	X
Dietary and life style counselling	X	X		X	X	X	X		X	X
Syringe administration training with placebo injection	X									
Adverse event review (AEs and SAEs) including review of hypoglycaemic symptoms		X	X	X	X	X	X	X	X	X
Randomization to study treatment		X								
Blinded treatment dispensed/returned		X		X	X	X	X			
Open-label treatment dispensed/returned							X		X	X
Subject to come fasting to study site	X	X				X	X			X
Bedside glucose testing	X	(X[d])								
Blood samples for haematology and clinical chemistry	X					X	X			X
Blood sample for exploratory analyses	X						X			X
Urinalysis	X									
HbA1c	X					X	X			X
Fasting serum: TC, LDL-C, HDL-C and TG[c]	X					X[e]	X[e]			X[e]

	Screening	Randomization	Treatment period							
Visit Visit window Days -14 to 7 for Visit 1 Days 7-14 for Visit 3 ±3 days starting at Visit 4	**1**	**2**	**(3)**	**4**	**5**	**6**	**7/8**	**(9)**	**10**	**11**
Week	**-2-(-1)**	**0**	**1-2**	**4**	**8**	**12**	**24**	**25**	**38**	**52**
Day	**-14-(-7)**	**0**	**7-14**	**28**	**56**	**84**	**168**	**175**	**266**	**364**
Fasting plasma glucose, glucagon, glycerol, insulin, C-peptide, FFA and ketones[c]	X					X[e]	X[e]			X[e]
MRI [f, g]		X					X			X[h]
3h OGTT[i] Including urine collection	X						X[e]			X[e,j]

[a] All subjects completing the 24-week double-blind study were eligible for the extension study given that they (1) signed a novel ICF, (2) had shown compliance and had taken >80% of the prescribed dose of study medication during the first part of the study, (3) did not fulfil any of the original exclusion criteria (for exclusion criteria, refer to Section 9.3.2).

[b] WOCBP women of childbearing potential.

[c] Was to be performed under fasting conditions.

[d] Was to be performed if fasting glucose was ≥ 7.0 mmol/L at Visit 1 or glucose was ≥ 11.1 mmol/L at 120 min at the OGTT test at Visit 2.

[e] Dapagliflozin or matching placebo were administered 30 minutes prior to fasting samples were taken at Visit 6 and prior to start of OGTT at Visit 7/8 and Visit 11. Exenatide or matching placebo was not to be administered before blood sampling at Visit 6 or before OGTT at Visit 7/8 and Visit 11.

[f] Not mandatory. Refer to Section 5.1.4 in the CSP for details (see Appendix 16.1.1)

[g] The MRI examination could be performed up to 1 week ahead of Visit 2 and/or up to 3 days ahead of Visit 7/8 and Visit 11 but not after Visit 7/8 and 11.

[h] The subgroup of patients who received active treatment during the initial 24-week study were asked to undergo an optional MRI examination at Visit 11 (Week 52). Depending on results from the initial 24-week study, the MRI at Visit 11 might be cancelled.

[i] During OGTT, blood samples were taken prior to ingestion of the oral glucose solution and at the following time points: 15, 30, 60, 90, 120 and 180 minutes after glucose ingestion. For details regarding the blood sampling procedure, refer to Section 5.1.5 in the CSP for details (see Appendix 16.1.1).

[j] At Visit 11, only subjects who had received active treatment with dapagliflozin and exenatide during the initial 24-week double-blind treatment period were asked to undergo OGTT at Visit 11. Subjects from the initial placebo group were not to undergo OGTT at Visit 11. Fasting blood samples withdrawn at Time 0 minutes prior to OGTT were taken from all subjects (active treatment and placebo). For details regarding the blood sampling procedure, refer to Section 5.1.5 in the CSP for details (see Appendix 16.1.1).

9.5.2 Appropriateness of Measurements

The anthropometric measurements and laboratory tests are regarded as current standard in healthy subjects.

9.5.3 Efficacy Variables

9.5.3.1 Body Weight and Other Anthropometric Measurements

Body weight and other anthropometric measurements were performed at screening (week -2-[-1]), randomization (week 0) and at weeks 4, 8, 12 and 24 (Table 2). The subject's weight was recorded in kilogram (kg), to one decimal place, wearing light clothing and no shoes. All readings were recorded as accurately as possible and the same scale was used for all assessments for a given subject. The subject's height was recorded in centimetres at screening only, with no shoes and using a steady meter.

The waist circumference was measured midway between the lowest rib and the iliac crest. The hip circumference was measured at the maximal circumference over the buttocks (WHO Report 1987). Measurements were done at the end of a normal exhalation. Both measurements were done in a standing position.

In addition, all subjects were fasting when the anthropometric measurements were performed.

9.5.3.2 Efficacy Laboratory Variables

Blood samples for the analysis of efficacy laboratory variables were collected at screening, weeks 12 and 24 (Table 2). All efficacy laboratory variables are summarized in Table 3.

Table 3 Efficacy Laboratory Variables

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7/8**
Study week	**-2-(-1)**	**0**	**1-2**	**4**	**8**	**12**	**24**
HbA1c	X					X	X
FPG	X	(X[a])				X	X
IFG	X						X
IGT	X						X
Insulin	X					X	X
C-peptide	X					X	X
Glucagon	X					X	X
Glycerol	X					X	X
3h-OGTT	X						X
TC	X					X	X
LDL-C	X					X	X
HDL-C	X					X	X
TG	X					X	X
FFA	X					X	X
Ketones in blood	X					X	X
eGFR	X					X	X
Exploratory analysis	X						X

[a] Was only performed if fasting glucose was ≥ 7.0 mmol/L at Visit 1 or if glucose was ≥ 11.1 mmol/L at 120 min at the OGTT test at Visit 1.

A 3h-OGTT was performed at screening and week 24. All samples, except those during OGTT, were taken under fasting condition. Urine was collected during OGTT for measurement of glucose excretion. For details regarding blood and urine sampling during OGTT, refer to Section 9.5.3.5.

Analyses of urine, glycerol, free fatty acids (FFA) and glucagon were performed at the Department of Medical Sciences, Akademiska sjukhuset, SE-751 85 Uppsala, Sweden.

Bedside measurements (FPG, ketones, urine volume during OGTT) were performed at the study site at Akademiska sjukhuset, Uppsala, Sweden.

All other laboratory tests were performed at the Clinical Chemistry Laboratory at Akademiska sjukhuset, SE751 85 Uppsala, Sweden.

9.5.3.3 Waist-hip Ratio

The waist-hip ratio (WHR) is a calculated ratio between waist circumference and hip circumference (waist circumference / hip circumference, measured in centimetres) and was computed centrally. WHR was measured at screening, randomization and weeks 4, 8, 12 and 24 (Table 2).

9.5.3.4 Percentage Liver Fat, Visceral Fat, Total Fat Mass and Total Lean Tissue

Magnetic Resonance Imaging (MRI) was performed at randomization (week 0) and week 24 to assess liver fat and body composition (Table 2). The MRI examinations was not mandatory and was only to be performed on subjects who did not fulfil any of the restriction criteria listed in Section 9.3.3.

The MRI procedure was carried out at the clinical MRI scanner at Uppsala University Hospital. A detailed description of the MRI methods is provided in Appendix 16.1.1.

A scan covering the entire body using a Dixon technique was performed. Additional scans to identify the liver was also done. A Dixon-scan enabled quantitative assessment of liver lipids while the subject held their breath for approximately 20 seconds.

The variables were: Liver Fat (%) calculated as: liver fat *100 / (liver fat + liver water)

Liver volumes were also measured to investigate the total liver fat content: total liver fat(l)= liver fat (%) * liver volume.

The total adipose tissue was assessed from the whole body MRI scans.

Abdominal subcutaneous adipose tissue and visceral adipose tissue in this study were measured between the hip joint and up to the lower pol of the lungs (diaphragm).

All fat volumes were measured in litres.

In addition, total body fat (%) was assessed at randomization and weeks 12 and 24s using bioimpedance.

9.5.3.5 Oral Glucose Tolerance Test

A 3 hour-oral glucose tolerance test (3h-OGTT) was performed at screening and week 24 (Visit 7/8).

At week 24, dapagliflozin or matching placebo was administered 30 minutes prior to blood sampling and 3h-OGTT. If Visit 7/8 coincided with an administration day for exenatide (or matching placebo), the injections were to be performed after the 3h-OGTT test had been performed.

Blood sampling procedure during OGTT at screening and week 24: Just prior to Time 0 minutes (= time point for ingestion of glucose solution, 75 gram glucose in 300 mL water) fasting blood samples were taken for: haematology, clinical chemistry, glucose, Haemoglobin A1c (HbA1c), insulin, glucagon, glycerol, ketones, C-peptide, FFA, total cholesterol (TC), triglycerides (TG), high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C) and exploratory biomarker analysis. The haematology and clinical chemistry variables are listed in Table 4.

At Time 0 minutes, when all Time 0 blood samples were taken, the oral glucose solution (75 grams of glucose in 300 ml water) was administered and was to be consumed within 5 minutes.

Thereafter, blood samples were taken at the following time points: 15, 30, 60, 90, 120 and 180 minutes after ingestion of the oral glucose solution. At each time point, blood samples were taken for glucose, insulin, glycerol, and FFA. At time point 120 minutes, additional blood samples were taken for ketones, glucagon and exploratory biomarker analysis. Samples for C-peptide was collected at time 0, 30 and 60 minutes. The area under the concentration-curve was estimated for the following variables: glucose, glycerol, insulin and FFA.

Urine sampling procedure during OGTT at screening and week 24. The urine produced during OGTT was to be collected for measurement of urinary glucose excretion. Subjects were instructed to void just before the glucose ingestion (Time 0) and this urine was discarded. Then the subject was asked to void again at 180 minutes in a container. The total volume of urine collected during the 3h-OGTT period was measured and recorded. Ten mL of urine was taken from the container and frozen for glucose measurement and calculation of glucose excretion at the Clinical Chemistry Laboratory. At Visit 1 (randomization), only subjects with glucosuria at baseline, as assessed with dipstick, had their urine collected during the OGTT period.

9.5.3.6 Impaired Fasting Glucose and Impaired Glucose Tolerance

Calculation of the proportion of subjects in each treatment group with impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) at week 24 and shift from baseline was amended to the SAP after code-breaking and database lock, see the summary of post-hoc analyses in Section 9.8.3.

9.5.3.7 Assessment of Insulin Sensitivity and Insulin Secretion

Based on results from measurements of plasma glucose and serum insulin levels during the 3h-OGTT performed at baseline and week 24, the insulin sensitivity was estimated using the Quantitative insulin sensitivity check index (QUICKI), the Revised QUICKI index and the weighted Matsuda index adjusted for UGE, for details see Section 9.7.10.3 (Statistical methods). Insulin secretion (β-cell function) was estimated using an Insulinogenic index.

9.5.3.8 Estimated Glomerular Filtration Rate

Calculation of the median change from screening to week 24 in eGFR, per treatment group, was amended to the SAP after code-breaking and database lock, see the summary of post-hoc analyses Section 9.8.3.

9.5.4 Safety Variables

The safety variables were:

- Laboratory safety measurements
- Vital signs
- Incidence and nature of AEs

9.5.4.1 Laboratory Safety Measurements

Blood and urine samples for determination of haematology, clinical chemistry were collected the time points indicated in Table 2.

Table 4 Laboratory safety variables

Haematology/Haemostasis (whole blood)	**Clinical Chemistry (serum or plasma)**
B-Haemoglobin (Hb)	S/P-Creatinine
	S/P-Bilirubin, total
	S/P-Alkaline phosphatise (ALP)
	S/P-Aspartate transaminase (AST)
	S/P-Alanine transaminase (ALT)
Urinalysis (dipstick)	S/P-Albumin
U-Glucose	S/P-Potassium
	S/P-Calcium, total
	S/P-Sodium
	S/P-Creatine kinase (CK)
	S/P-C-reactive protein (CRP)

9.5.4.2 Vital Signs

Vital sign measurements included systolic and diastolic blood pressure and heart rate. Vital signs were measured after the patient had rested for approximately 5 minutes and with the patient in a sitting position.

Vital signs were assessed at screening, randomization and weeks 4, 8, 12 and 24 (Table 2).

9.5.4.3 Other Safety Variable; Creatinine Clearance

Creatinine clearance was assessed at screening, weeks 12 and 24.

Creatinine clearance was calculated using the method of Cockcroft-Gault:
Males:

$$\text{Creatinine clearance (mL/min)} = \frac{\text{Weight (kg) x (140-Age [years])}}{\text{serum creatinine (µmol/L)}} \times 1{,}23$$

Females:

$$\text{Creatinine clearance (mL/min)} = \frac{\text{Weight (kg) x (140-Age [years])}}{\text{serum creatinine (µmol/L)}} \times 1{,}04$$

9.5.4.4 Adverse Events

Adverse event reporting started at randomization (week 0) and continued throughout the entire treatment period until week 24 for subject participating in the initial 24-week study and up to week 52 for subjects participating in the extension study.

At each visit, the subjects were asked for the occurrence of AEs since the last visit at the clinic. AEs could also be identified from signs and symptoms detected during an examination, laboratory test results, direct observation by study site personnel or spontaneous reports from the subjects.

At all visits, subjects were specifically asked about the occurrence of symptoms indicative of hypoglycaemia (e.g. fatigue, dizziness, tremor, palpitations, sweating).

Adverse events were reported with onset date and time, intensity (mild, moderate, severe), whether any corrective actions had been undertaken and the outcome. All AEs were assessed for seriousness and causality to treatment (not related, unlikely related, possibly related, probably related). All AEs were followed up by the Investigator until the AE was fully resolved (i.e. AEs not recovered at study completion were also followed up by the Investigator until the AEs were resolved but without further recording in the eCRF). At the discretion of the Investigator, subjects could be referred to a general practitioner for follow-up.

Deterioration, as compared to baseline, in protocol-mandated laboratory values or vital signs were only reported as AEs if they fulfilled any of the SAE criteria or were the reason for discontinuation of treatment with the IP. If deterioration of protocol-mandated laboratory tests/vital signs was associated with clinical signs and symptoms, the sign or symptom was to be reported as an AE and the associated laboratory test result was considered as additional information.

In the absence of clinical signs and symptoms, clinically relevant deteriorations in non-mandated parameters were reported as AEs. Deterioration of a laboratory value, which was unequivocally due to disease progression, was not be reported as an AE/SAE. Any new or aggravated clinically relevant abnormal medical finding at a physical examination was reported as an AE.

Serious AEs, whether or not considered related to the IP, were recorded in an SAE form in the eCRF and the Investigator or other site personnel were obliged to inform the external provider about representative about the SAE within 24 hours.

For further information about the definitions of serious and non-serious AEs and SAE reporting, refer to Section 6.4 in the CSP in Appendix 16.1.1.

9.5.5 Exploratory Analyses of Biomarkers and Pharmacogenetics

Additional blood samples were collected for future exploratory research with the aim to identify circulating biomarkers in the blood and genes/genetic variations in the DNA related to obesity and treatment response to dapagliflozin and exenatide.

Blood samples of 40 mL were collected at screening and week 24, just prior to start of the 3h-OGTT, and an additional blood sample of 15 mL was collected during OGTTs at 120 minutes at the same visits. The samples were frozen and stored at the Uppsala Biobank for future research. Samples were to be destroyed and discarded if a subject withdrew his/hers consent during the study.

The results from biomarker- and pharmacogenetic analyses are presented separately.

9.6 DATA QUALITY ASSURANCE

This trial was performed in compliance with the ICH Note for Guidance on Good Clinical Practice (ICH E6, 1996), applicable regulations and standard operating procedures at PCG Clinical Services AB. The quality of data was assured via appropriate training of study personnel, data management procedures, monitoring of trial sites and site audits.

9.6.1 Training of Study Site Personnel

Before the first subject was entered into the study, site monitoring staff reviewed and discussed the requirements of the CSP and related documents with the study site personnel and trained them in study specific procedures and eCRF application Viedoc™, provided by PCG Solutions AB. It was the Investigator's responsibility to ensure that appropriate training was given to all personnel involved in the study and that any new information relevant to the performance of this study was forwarded to

the staff involved. During the study, monitoring was performed on a regular basis by PCG Clinical Services AB.

The Investigator and other study site personnel were listed together with their function on a signature and delegation list. The roles and responsibilities of the key study personnel including the curriculum vitae for the Principal are provided in Appendix 16.1.4.

9.6.2 Monitoring of the Study

During the study, monitoring was performed on a regular basis by PCG Clinical Services AB, in order to confirm that:

- Information and support was provided to the Investigator
- Facilities remained acceptable
- The investigational team was adhering to the CSP
- Data were accurately and timely recorded in the CRFs
- Biological samples were handled in accordance with the Laboratory Manual
- Study drug accountability checks were being performed
- Source data verification (SDV) (a comparison of the data in the CRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects was performed
- Biological samples from subjects who had withdrawn their consent during the study period were identified and destroyed accordingly and that the action was documented and reported to the subject

9.6.3 Centralized Analyses of Laboratory Tests

Analyses of all laboratory tests (haematology and clinical chemistry) were centralized to ensure consistency of laboratory data and unbiased evaluation of the results. All laboratory tests were performed at the Clinical Chemistry Laboratory at Akademiska sjukhuset, SE-751 85 Uppsala, Sweden.

Analyses of urine, glycerol, FFA and glucagon were performed at the Department of Medical Sciences

Akademiska sjukhuset, SE-751 85 Uppsala, Sweden.

Bedside measurements (FPG, ketones, urine volume during OGTT) were performed at the study site at Akademiska sjukhuset, Uppsala, Sweden.

Laboratory data was provided to PCG Clinical Services AB as external files and imported to the datasets. Quality of imported laboratory data was the responsibility of the provider and no cleaning or quality check was performed at PCG Clinical Services AB.

9.6.4 Data Management

Data management was performed by PCG Clinical Services AB in accordance with the Data Management Plan. The data management routines included procedures for handling of the eCRF, database set-up and management, data entry and verification, data validation, quality control of the database, and documentation of the performed activities including information about discrepancies.

The eCRF included password protection and internal quality checks, such as automatic range checks, to identify data that appeared inconsistent, incomplete, or inaccurate. Data cleaning was performed during site monitoring, by built-in data checks that raised automatic alerts to the Investigators for immediate action and by offline logical checks programmed in SAS. Queries were raised in Viedoc™

by monitors and by Data Management. Any encountered discrepancies were sent to the Investigator/monitor for further action. When all data had been coded, validated, signed and locked, clean file was declared and the database was locked.

All CRF data with the exception of laboratory and MRI data were entered electronically at the study site using the eCRF application Viedoc™.

MRI data were uploaded to Viedoc™ by Antaros Medical. The quality of imported laboratory and MRI data was the responsibility of the provider and no cleaning of data was performed by PCG Clinical Services AB.

A full database lock was conducted on 05 Oct 2015 after all subjects had completed 24 weeks of blinded treatment.

A second full database lock will be conducted when all subjects participating in the 28-week extension study have completed the study at week 52.

9.7 STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

The principal features of the statistical analyses are described in this section. A more detailed elaboration of the statistical analyses is provided in the Statistical Analysis Plan (SAP) in Appendix 16.1.9.

Amendments to the original SAP (dated 02 Oct 2015) were made after code-breaking as described in Section 9.8.2 (Summary of changes to the planned analyses, see Table 6) and Section 9.8.3 (Post-hoc analyses). The original SAP and the final version (dated 13 May 2016) are provided in Section Appendix 16.1.9.

9.7.1 Statistical and Analytical Plans

All statistical analyses were performed using SAS® (Version 9.4), SAS Institute Inc., Cary, NC, USA) by PCG Clinical Services AB.

Continuous data were summarized using descriptive statistics where the following parameters were reported: number of observations (n), number of missing observations (nmiss), mean, standard deviation (STD), minimum (min), Q1 (first quartile), median, Q3 (third quartile), maximum (max). Categorical data were presented using frequency (n) and percentage (%).

All efficacy variables were assessed at a 2-sided 0.050 significance level. The results of significance tests were reported with p-value.

9.7.2 Analysis Data Sets

All efficacy analyses were performed on both the Full analysis set (FAS) and the Per protocol analysis set (PPAS). The safety analyses were performed on the Safety analysis set. The classification of subjects to each analysis set was decided prior to breaking the blind.

9.7.2.1 Full Analysis Set

Prior to breaking the blind, the SAP was updated with a new definition of the FAS, see Section 9.8.2.The full analysis set included all randomized subjects (according to randomization) who received at least one dose of study medication during the 24-week double-blind treatment period who had a non-missing baseline value and at least one post-baseline value for at least one efficacy variable during the double-blind period. The intention-to-treat principle was preserved despite the exclusion of subjects who took no study medication, as the decision of whether or not to begin treatment during the randomized treatment period could not be influenced by knowledge of the assigned treatment. In case of severe noncompliance with the protocol a subject could be excluded from the full analysis set.

9.7.2.2 Per-protocol Analysis Set

The PPAS – being a subset of the full analysis set – included all subjects who have taken IPs during at least 20 weeks and 80% to 120% of intended IPs, and who had no major protocol deviations which might affect the study outcome significantly.

Thus, the PPAS is a subset of the FAS and consists of subjects who also fulfilled the following:

1. Subjects had sufficiently complied with the protocol, e.g. no major protocol deviations
2. Subjects had available data at 24 weeks for the primary variable
3. Subjects had been compliant; a duration of at least 20 weeks of IP treatment and 80% to 120% of intended IPs

Subjects were counted in the treatment group according to medication taken.

9.7.2.3 Safety Analysis Set

The Safety analysis set included all randomized subjects who received at least one dose of study medication and who provided any safety records. Subjects were counted in the treatment group according to medication taken.

9.7.3 Disposition of Patients

Number of patients screened, randomized, randomized and not taken IPs, randomized and taken IPs, study completion, withdrawals and number of patients in each analysis set was summarized by treatment group and in total. The number of patients attending each visit was also summarized by treatment group and in total.

9.7.4 Demographics

Age, gender, race and whether of childbearing potential including reason if not, were summarized as appropriate depending on the data type by treatment group and in total.

9.7.5 Body Weight and Other Anthropometric Measures

Height, body weight, BMI, waist circumference and hip circumference are summarized as appropriate depending on the data type by treatment group for each visit and in total for each the Safety analysis set and the FAS. Body weight (kg) over the 24-week period is also presented in a line chart.

Spaghetti charts for body weight over the 24-week treatment period are presented for the FAS and the PPAS.

9.7.6 Waist-Hip Ratio (WHR)

Summary statistics are presented by treatment group for each visit. Line charts are presented by treatment group from baseline to week 24.

9.7.7 Compliance

Treatment compliance (number of injections and number of tablets received relative to planned) were summarized by treatment group.

9.7.8 Medical History and Concurrent Diseases

Obesity history, including time since started, maximum weight and weight 3 and 12 months ago, were summarized by treatment.

Medical and surgical history and concurrent diseases were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 18.0 by PCG Clinical Services AB and are presented by system organ class (SOC) and preferred term (PT). For each SOC and PT, the number and percentage of subjects with a condition in that SOC or PT are presented for the safety analysis set.

9.7.9 Prior and Concomitant Medication

Medications were coded using the AstraZeneca Drug Dictionary version 14.2 by PCG Clinical Services AB (see Section 9.8.2, Changes to the planned analyses). For each therapeutic main group (the second level term in the Anatomical Therapeutic Chemical [ATC] classification system) and preferred name, the number and percentage of patients are presented for the Safety analysis set. If the preferred name was not available for a medication, the chemical subgroup (ATC level 4) is displayed instead.

Prior medication was defined as medication stopped at or prior to signing the informed consent. Ongoing medication, medication stopped after the informed consent date and medication started at or after informed consent date is considered as concomitant.

9.7.10 Efficacy Evaluation

9.7.10.1 Primary Efficacy Variable

The primary objective was to assess the efficacy of dapagliflozin 10 mg once daily and exenatide 2 mg once weekly in combination when compared to placebo on change of body weight after 24 weeks of treatment in obese subjects. The primary efficacy variable was change in body weight (kg) from baseline to 24 weeks.

The null hypothesis was that there is no difference in body weight change between the treatment groups; the alternative hypothesis being there was a difference.

The treatment effect was tested and estimated using an MMRM including treatment, week, treatment-by-week interaction and gender as well as the continuous fixed covariate of baseline body weight measurement. An unstructured matrix for the within-subject error variance-covariance was used. The longitudinal repeated measures mixed model was used to derive a least squares (LS) estimate of the treatment difference at Week 24 with 95% confidence interval and corresponding p-value. Further, two-sided 95 % confidence intervals for the adjusted mean change within each treatment group were calculated.

To assess whether this model was adequate, the interaction between treatment group and gender was tested in the longitudinal model. As the interaction term was not significant (p >0.10), the model without the treatment by gender interaction term was used.

9.7.10.2 Secondary Efficacy Variables

The secondary efficacy variable was the percentage change in body weight from baseline to 24 weeks. This variable was analysed with the same method as the primary efficacy variable.

9.7.10.3 Exploratory Efficacy Variables

9.7.10.3.1 Weight Loss Proportions

Proportion of subjects with at least 5% and 10% reduction in weight at 24 weeks, respectively (*i.e.*, more than or equal to 5% or 10% weight loss), were analysed using a logistic regression model for repeat measures, and the GEE method was to be used to estimate the parameters of the model. The model included treatment, week, treatment-by-week interaction and gender as well as the continuous fixed covariate of baseline body weight measurement. An unstructured matrix for the within-subject error variance-covariance was used.

After breaking the blind it was decided that the number of subjects with at least 5% and 10% reduction in weight at 24 weeks was too low for statistical analyses to be performed, see Table 6 in Section 9.8.2.

9.7.10.3.2 Body Weight Change from Screening (Post-hoc Analysis)

Absolut change in body weight (kg) and percentage change in body weight from the screening visit to 24 weeks was analysed as an exploratory endpoint using an MMRM including treatment, week, treatment-by-week interaction and gender as well as the covariate of baseline (screening) body weight.

9.7.10.3.3 Alternative Primary Efficacy Model (Post-hoc Analysis)

In the same way as the primary efficacy endpoint, an alternative primary endpoint model including the interaction between baseline body weight and week was analysed. Analyses was performed for the FAS and the PPAS (see Post-hoc analysis in Section 9.8.3).

9.7.10.3.4 MRI Variables

For MRI data, i.e. liver fat percentage, liver volume, total liver fat, visceral adipose tissue, abdominal subcutaneous adipose tissue, total adipose tissue and total lean tissue, an analysis of covariance (ANCOVA) model including treatment, gender as well as the continuous fixed covariate of baseline value was applied. The model will be used to derive a least squares estimate of the treatment difference at Week 24 with 95 % confidence interval and corresponding p-value. Further, two-sided 95 % confidence intervals for the mean change within each treatment group was calculated.

Body fat percentage was analysed with the same method will as the primary efficacy variable including the continuous fixed covariate of baseline body fat percentage instead of body weight.

In this study, subcutaneous adipose tissue was defined as abdominal subcutaneous fat positioned between the hip joint and up to the lower pol of the lungs.

9.7.10.3.5 OGTT Variables

During the 3h-OGTT, blood samples for insulin sensitivity and lipolysis were taken at 15, 30, 60, 90, 120 and 180 minutes after ingestion of the oral glucose solution. The following laboratory variables were tested: glucose, glucagon, glycerol, FFAs, insulin, ketones and C-peptide. The treatment effect on change from baseline was tested and estimated using an ANCOVA model adjusted for treatment, gender and the continuous fixed covariate of baseline value. The model was used to derive a least squares estimate of the treatment difference at Week 24 with 95% confidence interval and corresponding p-value. Further, two-sided 95% confidence intervals for the mean change within each treatment group were calculated. Glucose and insulin were analysed at time 0 and 120 minutes. Remaining variables were analysed at each time point where samples were collected.

9.7.10.3.6 Area Under the Curve (Post-hoc Analysis)

For the laboratory variables glucose, glycerol, FFAs and insulin the area under the curve (AUC) was calculated. The AUC was calculated using the trapezium (trapezoidal) rule and corresponds to the total area under curve from time 0 minutes to last observed concentration at each visit. For each variable the treatment effect on change from baseline was tested and estimated using an ANCOVA model adjusted for treatment, gender and the continuous fixed covariate of baseline value. The model was used to derive a least squares estimate of the treatment difference at Week 24 with 95 % confidence interval and corresponding p-value. Further, two-sided 95 % confidence intervals for the mean change within each treatment group was calculated.

In the same way, the incremental AUC (iAUC) was analysed for glycerol and FFA. The iAUC was calculated using the trapezium (trapezoidal) rule and corresponds to the net incremental area under curve.

9.7.10.3.7 Delta-delta (Post-hoc Analysis)

For the laboratory variable ketones, the delta during the OGTT was calculated. The treatment effect on change from baseline was tested and estimated using an ANCOVA model adjusted for treatment, gender and the continuous fixed covariate of baseline ketone value. The model was used to derive a least squares estimate of the treatment difference at Week 24 with 95 % confidence interval and corresponding p-value. Further, two-sided 95 % confidence intervals for the mean change within each treatment group was calculated.

Delta-delta for blood ketones was calculated as follows:

Delta-delta = (Ketones_w24_120min – Ketones_w24_0min) - (Ketones_w0_120min – Ketones_w0_0min)

9.7.10.3.8 Impaired Fasting Glucose and Impaired Glucose Tolerance (Post-hoc Analysis)

The difference in proportions of subjects with impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) at screening and week 24 within each treatment group was tested using a paired McNemar test. The difference in proportions between treatment groups at week 24 was tested using a Cochran-Mantel-Haenszel test. Further, descriptive statistics for the number of subjects with normal and raised values at screening and at week 24 as well as the number of subjects shifting categories between points of measurement were presented by treatment group.

9.7.10.3.9 Indices

The following indices were calculated for assessment of insulin sensitivity and insulin secretion:

Quicki = 1 / (log(G_0 mg/dL) + log(I_0 µU/mL))

Revised Quicki = 1/(log(G_0 mg/dL) + log(I_0 µU/mL) + log(FFA_0 mmol/L))

Insulinogenic index = $\Delta I_{30}/\Delta G_{30}$ = (I_{30} µU/mL − I_0 µU/mL) / (G_{30} mmol/L − G_0 mmol/L)

G=glucose level

I=Insulin level

0=Time 0/fasting

30 = Time 30 minutes/under OGTT

Weighted average Matsuda index adjusted for urinary glucose excretion (UGE) (Post-hoc Analysis)

$$\frac{10000}{\sqrt{g_o * i_o * \ g_a * \ i_a}} * \sqrt{(\frac{75 - UGE}{75})}$$

UGE = Urinary glucose excretion in grams

g_0 = glucose at zero minutes

i_0 = insulin at zero minutes

g_a = weighted average glucose = $\frac{(\ g_0 * 7.5 + \ g_{15} * 15 + \ g_{30} * 22.5 + \ g_{60} * 30 + \ g_{90} * 30 + \ g_{120} * 45 + \ g_{180} * 30)}{180}$

i_a weighted average insulin = $\frac{(\ i_0 * 7.5 + \ i_{15} * 15 + \ i_{30} * 22.5 + \ i_{60} * 30 + \ i_{90} * 30 + \ i_{120} * 45 + \ i_{180} * 30)}{180}$

9.7.10.3.10 Laboratory Efficacy Variables

Laboratory efficacy variables include total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), HbA1c and fasting plasma glucose (FPG). These variables were analysed with the same method will as the primary efficacy variable.

9.7.10.3.11 Vital Signs and Anthropometric Efficacy Variables

Vital signs, waist circumference, WHR and BMI were analysed with the same method will as the primary efficacy variable.

9.7.10.3.12 Urinary Glucose Excretion

Urinary glucose excretion (UGE) during the 3h-OGTT = concentration * volume (ml) expressed in mmol (ml x mmol/l / 1000).

9.7.10.3.13 Estimated Glomerular Filtration Rate (Post-hoc Analysis)

Estimated glomerular filtration rate (eGFR) based on Modification of Diet in Renal Disease (MDRD)[16] was analysed with the same method as the primary efficacy variable.

S_{cr} = Serum creatinine.

GFR (mL/min/1.73 m^2) = 175 x $(S_{cr}/88.4)^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if female) x (1.212 if African American).

9.7.10.3.14 Model Building

Exploratory model building of potential prognostic factors and covariates was performed using a stepwise procedure with limits for inclusion and exclusion in the model.

Baseline values and patient characteristics for potential inclusion as prognostic factors/covariates in the models for weight change and % weight change:

- Weight
- Gender
- Age
- BMI
- % Body fat
- HbA1c
- Urinary glucose
- % Liver fat
- % Body fat
- WHR
- Indices based on glucose and insulin levels (QUICKI, revised QUICKI and Insulinogenic Index)
- OGTT glucose AUC_{0-2h}
- MRI variables

Potential prognostic factors and covariates were tested for inclusion in the model in a stepwise selection process. Initial screening based on a univariate model of the entire set of candidate

prognostic factors and covariates was performed using a critical significance level of 0.15 to be included in the multivariate model.

In a second step, each retained variable was tested with the other retained variables at the 0.001 level to confirm that there is no strong link between them. For continuous variables Pearson correlation was used, for categorical variables Chi-square test/Fisher's exact test was used and for a mix of categorical and continuous variables Kruskal-Wallis test was used. If the independence is not met for two parameters ($p<0.001$) the choice was done according to clinical relevance.

Thereafter all of the retained prognostic factors and covariates that met this first-stage and the second-stage criterion and/or that had biological/clinical justification was subjected to the model-building process. The variables were entered and kept in the model at each step if the p-value was <0.15.

9.7.10.3.15 Baseline Values for Efficacy Variables

- The baseline value of body weight, waist and hip circumference, vital signs, MRI-based efficacy variables and total body fat (%) measurements by bioimpedance are derived from the randomization visit (week 0) for all efficacy variables except absolute change in body weight between screening and week 24.
- For the laboratory efficacy variables (HbA1c, TC, LDL-C, HDL-C, TG, fasting plasma glucose, glucagon, glycerol, insulin, C-peptide, FFA, ketones, AUC, eGFR, IFG and IGT, the baseline sample was collected at the screening visit.

9.7.11 Safety Evaluation

The analysis of safety was based on the Safety analysis set. Safety data obtained from randomization at Visit 2 (Week 0) to the final Study Completion Visit at Visit 7(Week 24) were evaluated and variables were summarized descriptively.

9.7.11.1 Extent of Exposure

Exposure of exenatide injections (weekly) and dapagliflozin tablets (once daily) will be summarised by treatment.

9.7.11.2 Laboratory Safety

Chemistry, haematology and urinalysis are presented by treatment groups as absolute value and change from baseline for each visit for continuous variables and as n and percentage for categorical variables.

9.7.11.3 Other Safety Assessments; Creatinine Clearance

Creatinine clearance was calculated by the method of Cockcroft-Gault as described in Section 9.5.4.3. Creatinine clearance is summarized as absolute value and change from baseline.

9.7.11.4 Adverse Events

Adverse events were coded by SOC and PT according to MedDRA version 18.0 by PCG Clinical Services AB. An overview of the AEs including intensity, relationship to IP, SAEs and AEs leading to withdrawals or death is presented by treatment group. Incidence of AEs by SOC and PT is presented and percentage of subjects and number of events for each treatment is presented broken down by intensity and relationship to IP.

9.7.12 Determination of Sample Size

This study aimed to show a difference in the mean change in body weight from baseline to week 24 between a combined treatment of dapagliflozin and exenatide compared to placebo in obese non-diabetic subjects.

The sample size calculations were based on previous studies with dapagliflozin and exenatide suggesting that the additive effect of the two compounds would result in approximately 4.0 kg weight reduction versus placebo after 24 weeks of treatment. However, for dapagliflozin, no data on weight reduction in non-diabetic subjects was available when this trial was designed. A conservative measure of 4.0 kg for the standard deviation was selected for the sample size calculation. To detect a difference of 4 kg between the treatment groups, 17 evaluable subjects per treatment group were required for 90% power at a two-sided significance level of 0.050. Accounting for 10% of the randomized subjects to be excluded from the primary analysis because of missing data (e.g., lost to follow-up) and a potentially lower treatment effect of dapagliflozin in non-diabetic subjects, 24 subjects per treatment arm were needed.

9.7.13 Rounding

In all tables, raw data are presented to the number of decimal places collected and derived data are presented to an appropriate number of decimal places. The appropriate number of decimal places was determined by general practice, mathematical rationale or scientific rationale.

Extreme values are presented with a number of decimals equal to the appropriate number for the variable that is being summarised; the other descriptive statistics are presented with one decimal more. Percentages will be presented with one decimal and a percentage sign. Confidence interval bounds will be presented with the same number of decimals as the corresponding point estimate, and p-values will be presented with 4 decimals or as '<.0001'.

To facilitate readability, data described in the body text of the report are rounded as considered appropriate based on the value presented in the corresponding table.

9.8 CHANGES IN THE CONDUCT OF THE TRIAL OR PLANNED ANALYSES

9.8.1 Changes to the Conduct of the Trial

There was 1 substantial amendment to the original CSP (dated 27 Oct 2014). The details of the amendment are specified in Table 5.

The changes to the original CSP were not implemented until regulatory and ethical approvals had been received for the substantial amendment No.1.

The substantial amendment No.1 was incorporated in protocol version 2 (dated 15 Apr 2015) and was approved by the RA on 19 May 2015 and by the IEC on 04 May 2015.

Table 5 Summary of changes to the conduct of the study

Amendment	Key details of amendment	Reason for Amendment
CSP Substantial Amendment No.1 dated 15 Apr 2015	**Study extension** To extend the 24-week double-blind, placebo controlled Phase II study with a 28-week open-label study period for those subjects who were willing to continue treatment with study medication for an additional 28 weeks. Thus the total study period was extended from 24 to 52 weeks. During the 28-week open label study period, both the placebo group and the active treatment group received unblinded active treatment with dapagliflozin and exenatide with a similar dosing regimen as during the first part of the study. All subjects having completed the initial 24-week double-blind study were eligible given that they did not fulfil any of the original exclusion criteria and that they signed a novel informed consent form specifically written for the extension study.	The aim of the extension study was to demonstrate maintained, or additional, weight reduction by active treatment up to 12 months. In addition, the 28-week extension study offered active treatment to the subjects having received placebo during the first 24 weeks. This provided an opportunity also for those subjects to benefit from potential drug effects in terms of body weight reduction.
	Exclusion criterion No.5: "Previously diagnosed diabetes mellitus, or fasting P-glucose ≥7.0 mmol/L at Visit 1 confirmed by one more measurement; or P-glucose ≥11.1 mmol/L at 120 minutes of the oral glucose tolerance test (OGTT) at Visit 1 confirmed by one more measurement. Note: Subjects with a fasting P-glucose of ≥7.0 mmol/L at Visit 1 or ≥11.1 mmol/L at 120 minutes of the OGTT at Visit 1 may be offered an extra visit before Visit 2 for a second fasting P-glucose measurement. If P-glucose is still ≥7.0 mmol/L at the second measurement, the subject will be excluded." *was rephrased to* "Previous or new diagnosis of diabetes mellitus. For subjects being diagnosed with diabetes at screening, this should be judged by an experienced diabetologist and be based on composite laboratory measures according to American Diabetes Association (ADA) guidelines. These criteria include FPG >7.0 mmol/l, 2h-PG at OGTT >11.1 mmol/l and/or HbA1c >48 mmol/mol. Subjects with FPG ≥7.0 mmol/L or 2h-PG ≥11.1 mmol/l at Visit 1, should have a second FPG measurement on a separate day, and if diabetes diagnosis is confirmed the subject will be excluded."	The purpose of the rephrasing of exclusion criteria No. 5 was to clarify that the intention of the fasting glucose sampling was to ensure that no previously undiagnosed diabetic patients were included in the study.

9.8.2 Changes to the Planned Analyses

Amendments to the original SAP (dated 29 Sep 2015) were made after code-breaking and database-lock. The final version of the SAP (dated 04 May 2016) is provided in Appendix 16.1.9. A summary of changes to the planned analyses, with reason for change included, is presented in Table 6.

Table 6 Summary of changes to planned analyses

Scope	Change	Reason for change	Responsible
Medical coding	The AstraZeneca Drug Dictionary version 14.2 was used and not the WHO Drug Dictionary version 18.2 as specified in the SAP.	AstraZeneca AB is the manufacturer and provider of the IP in the study. The medical coding was performed by PCG Clinical Services AB.	Sponsor
Efficacy analysis	During data cleaning, prior to breaking the blind and database lock, an addition was made to the SAP regarding the definition of the FAS. In case of severe noncompliance with the protocol a subject may be excluded from the full analysis set.	To allow exclusion of subjects severely non-compliant with the protocol.	Sponsor
Efficacy analysis	After code-breaking, the planned statistical analysis method for the variables derived from the 3h-OGTT was changed from MMRM to an ANCOVA model.	To provide analyses more common to diabetes trials for comparison purposes.	Sponsor
Efficacy analysis	During data analysis, it was decided that no statistical analyses of the proportions of subjects with at least 5% and 10% reduction in weight at 24 weeks could be performed.	The number of subjects with at least 5% and 10% reduction in weight at 24 weeks was too low for statistical analyses to be performed	Biostatistician

9.8.3 Post-hoc Analyses

A list of additional efficacy variables added to the original SAP (dated 29 Sep 2015) after code-breaking are presented in Section 9.8.3. The final version of the SAP (dated 04 May 2016) is provided in Appendix 16.1.9.

Table 7 Post-hoc analyses

Scope	Addition	Reason for addition	Responsible
Efficacy analysis	**Alternative primary efficacy model:** Mean change in body weight from baseline to week 24: A mixed model for repeated measures (MMRM) adjusted for treatment, week, the interaction between treatment and week, gender, baseline body weight and the interaction between baseline body weight and week was used to test a null hypothesis of no difference between the treatment groups against a 2-sided alternative hypothesis at the 5% level of significance.	To test an alternative primary efficacy model adjusted also for *the interaction between baseline body weight and week*.	Sponsor
	Additional exploratory efficacy variables:		
Efficacy analysis	**Absolute change in body weight from screening** Absolute change in body weight (kg) and percentage change in body weight from the screening visit (week -2-[-1]) to week 24 was analysed as an exploratory endpoint using an MMRM including treatment, week, treatment-by-week interaction and gender as well as the covariate of screening body weight.	To evaluate the change in body weight from screening	Sponsor
Efficacy analysis	**Impaired fasting glucose** Fasting plasma glucose (glucose at time 0 minutes during the OGTT) was categorised as follows: < 5.6 mmol/L ≥ 5.6 mmol/L If FPG was categorised as ≥ 5.6 mmol/L, then flagged as impaired fasting glucose (IFG).	To include analyses common to diabetes trials for comparison purposes.	Sponsor
Efficacy analysis	**Impaired glucose tolerance** Glucose at time 120 minutes during the OGTT was categorised as follows: < 7.8 mmol/L ≥ 7.8 mmol/L If glucose at time 120 minutes was categorised as ≥ 7.8 mmol/L, then flagged as impaired glucose tolerance (IGT).	To include analyses common to diabetes trials for comparison purposes.	Sponsor

Efficacy analysis	**Additional variables** Weighted Matsuda index adjusted for UGE AUC for glucose, glycerol, insulin and FFA Incremental AUC for glycerol and FFA Delta-delta calculation for ketones Estimated glomerular filtration rate using MDRD	To include analyses common to diabetes trials for comparison purposes.	Sponsor

10. TRIAL SUBJECTS

The disposition of subjects is presented in Section 10.1, screening failures in Section 10.1.1 and reasons for premature withdrawal in Section 10.1.2. Summary tables pertaining to this section are presented in Section 14.1. Individual data listings are provided in Appendix 16.2.1 to Appendix 16.2.3.

10.1 DISPOSITION OF SUBJECTS

An overview of the subject flow in the study is presented in Figure 2 and a summary table is provided in Section 14.1.1 (Table 62).

A total of 61 subjects were screened and 50 were randomized in the study, which was conducted at a single site in Sweden. The estimated sample size needed for the primary endpoint was 48 subjects, 24 per treatment arm. Eligible subjects were randomized to 1 of 2 treatment arms, active treatment or matching placebo, in a 1:1 ratio.

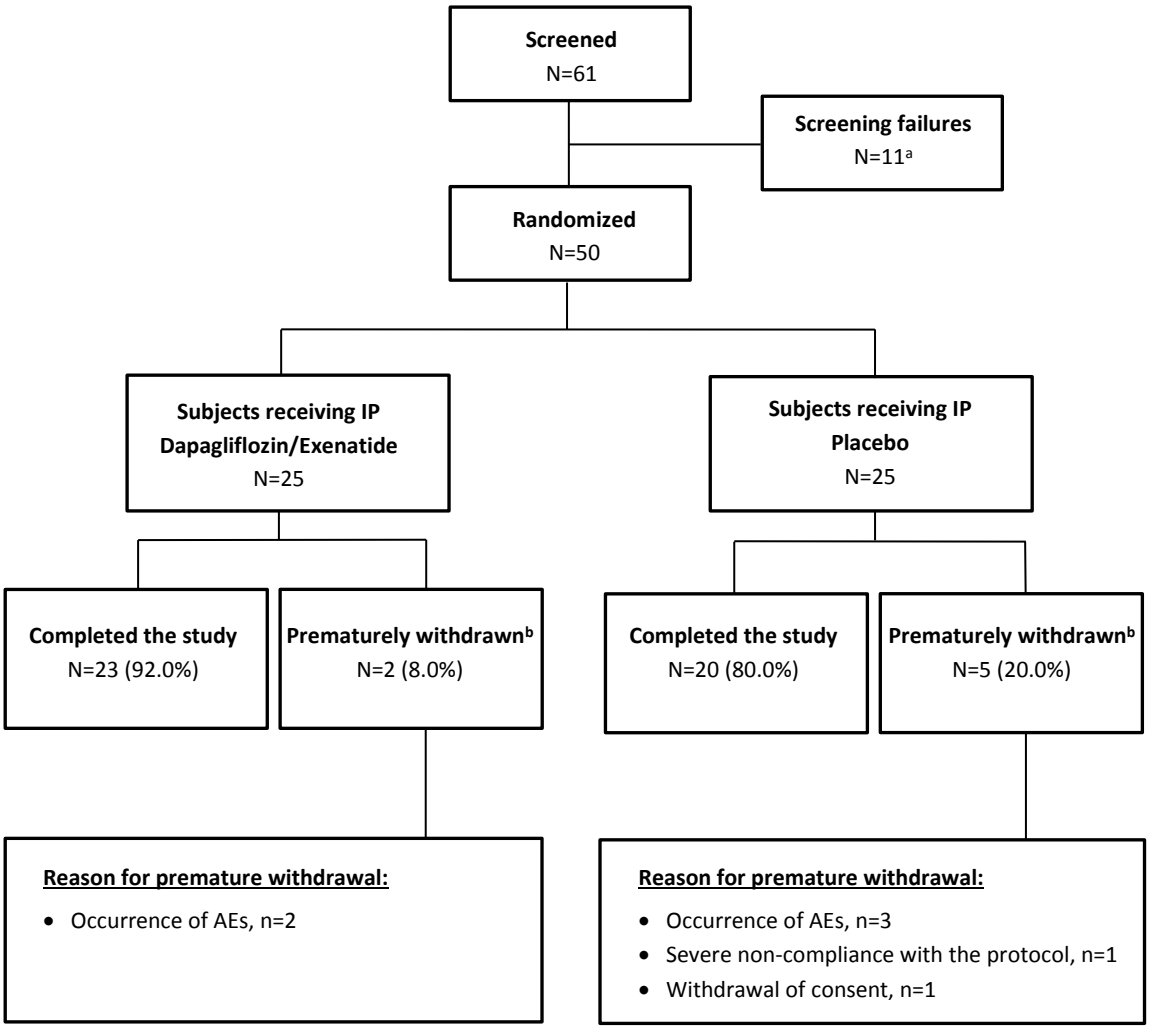
Eleven subjects were screening failures and were never randomized in the study: 8 of these were not eligible at screening and 3 were eligible at screening but were classified as screening failures prior to randomization for other reasons. A summary of all screening failures is presented in Table 8.

There were no non-eligible subjects randomized in the study and all randomized subjects received study medication.

The first subject was screened on 08 Dec 2014, the first subject was dosed 19 Dec 2014 and the last subject completed the last visit of the initial 24-week treatment period on 31 Aug 2015.

In total 43 subjects (86.0%) completed the study: 23 subjects (92.0%) in the dapagliflozin/exenatide group and 20 subjects (80.0%) in the placebo group.

Figure 2 Disposition of subjects



[a] A summary of all screening failures is presented in Table 8.

[b] A summary of reasons for premature withdrawals is provided in Table 9.

Source: Table 9, Table 62 and Appendix 16.2.1 to 16.2.3.

10.1.1 Screening Failures

All screening failures in the study are shown in Table 8. The most common reason for screening failure was fulfilment of exclusion criterion No. 5 (assessment of diabetic conditions).

Table 8 Screening failures

Subject id	Reason for screening failure	Total no. of subjects
E154	**Subject did not meet inclusion criterion No.3:** Female subjects must not be breast-feeding, be pregnant at screening or unwilling to practice strict birth control during the entire duration of the study.	1
E108 E136	**Subjects fulfilled exclusion criterion No.4:** History of any clinically significant disease, disorder or condition which, in the opinion of the Investigator, may either put the subject at risk because of participation in the study, or influence the results or the subject's ability to participate in the study.	2
E124 E125 E147 E159	**Subjects fulfilled exclusion criterion No.5**: Previous or new diagnosis of diabetes mellitus. For subjects being diagnosed with diabetes at screening, this should be judged by an experienced diabetologist and be based on composite laboratory measures according to American Diabetes Association (ADA) guidelines. These criteria include FPG >7.0 mmol/l, 2h-PG at OGTT >11.1 mmol/l and/or HbA1c >48 mmol/mol. Subjects with FPG ≥7.0 mmol/L or 2h-PG ≥11.1 mmol/l at Visit 1, should have a second FPG measurement on a separate day, and if diabetes diagnosis is confirmed the subject will be excluded. **Subject E124 also did not meet inclusion criterion No.2:** Female and/or male aged 18 to 70 years with BMI (measured as body weight (kg)/(height (m))^2) 30 to 45 kg/m^2.	4
E119	**Subject fulfilled exclusion criterion No.10**: History of gastroparesis or pancreatitis.	1
E110	Subject E110 was eligible at screening but was later excluded due to a planned knee operation which might have had impact on the subject's weight.	1
E132	Subject E132 was excluded by mistake during screening and declined participation when invited a second time.	1
E151	Subject E151 withdrew consent prior to randomization for unknown reason.	1
Total		**11**

Source: Appendix 16.2.1

10.1.2 Reasons for Premature Withdrawals

Seven subjects (14.0%) were prematurely withdrawn during the study: 2 subjects (8.0%) in the dapagliflozin/exenatide group and 5 subjects (20.0%) in the placebo group (Table 9).

Five of the 7 subjects were prematurely withdrawn due to the occurrence of AEs or SAEs (primary reason): 2 subjects in the dapagliflozin/exenatide group and 3 subjects in the placebo group (Table 9). One subject (E161; placebo) withdrew consent whereas one (E129; placebo) was primarily withdrawn due to severe non-compliance with the protocol. However, a concomitant AE (PT: blood ketone body increased) contributed to the withdrawal of E129 as outlined in Section 12.4.4. All AEs/SAEs leading to premature withdrawal are further discussed in Section 12.4.4 (Table 59 and Table 60).

An individual subject data listing of premature withdrawals is provided in Appendix 16.2.1.

Table 9 Primary reasons for premature withdrawals. Randomized subjects

	Dapagliflozin/ Exenatide N=25	Placebo N=25	Total N=50
Prematurely withdrawn	2 (8.0%)	5 (20.0%)	7 (14.0%)
Primary reason			
Adverse Event[a]	2 (100.0%)	3 (60.0%)	5 (71.4%)
Severe non-compliance with the study protocol[b]	0	1 (20.0%)	1 (14.3%)
Withdrawal of consent[c]	0	1 (20.0%)	1 (14.3%)

Percentages are based on the number of randomized subjects.
Percentages are based on the number of withdrawn subjects.
[a] Subjects E145 and E156 (dapagliflozin/exenatide) and subjects E103, E115 and E153 (placebo) were prematurely withdrawn due to AEs. The nature and severity of these AEs are further discussed in Section 12.4.4.
[b] Subject E129 (placebo) was prematurely withdrawn due to severe non-compliance with the protocol (primary reason for discontinuation), see Section 10.2.1. Concomitantly, the IP was withdrawn due to AE, see Section 12.4.4.
[c] Subject E161 (placebo) prematurely terminated the study due to withdrawal of consent.

10.2 PROTOCOL DEVIATIONS

Prior to database lock, all protocol deviations were reviewed for potential effect on the study results by the project manager at PCG Clinical Services AB in collaboration with the Sponsor. An individual assessment was made for each subject to decide whether the protocol deviation was major or minor, had any impact on efficacy data and whether the subject should be excluded from the FAS and/or PPAS.

A complete list of all protocol deviations registered in the eCRF is provided in Appendix 16.2.2.

10.2.1 Protocol Deviations

Two major protocol deviations occurred in the study (Table 10 and Table 63 in Section 14.1.2).

One major protocol deviation was identified for subject E129 (placebo). The subject was judged to have been severely non-compliant with the study protocol and was excluded from both the FAS and the PPAS.

The other major protocol deviation was identified for subject E108 and occurred during screening (the date of the signed informed consent form did not match with source data), however, this subject was non-eligible and never randomized and this is the reason to why this subject is not included in Table 63 in Section 14.1.2.

Most of the minor protocol deviations (14 deviations, 14 subjects) referred to a visit performed outside the allowed visit window as detailed in the protocol (±3 days).

Two minor deviations referred to the fact that subjects were not specifically asked about symptoms suggestive of hypoglycaemia.

One minor deviation was registered for the lack of appropriate training in handling of syringe and injection of placebo at the screening visit.

One minor deviation was registered for a randomization visit performed 1 day outside the allowed visit window as detailed in the protocol (7 to 14 days after screening). No subjects with minor protocol deviations were excluded from any of the analysis sets.

Table 10 Protocol deviations

Subject id	Details of protocol deviations	Major /minor	Total number of subjects	Included in Safety Y/N	Included in PPAS Y/N
E129	During data cleaning (prior to database lock and unblinding), significant weight loss (-27.2 kg) was noted for subject E129. It became clear that the patient practiced a strict LCHF diet, not 'balanced' as indicated in study protocol. He started this directly after enrolment, by his own decision. This major diet change was considered to significantly contribute to the exceptional weight loss and abnormal elevation of blood ketones that were observed in this subject and therefore the Sponsor and PCG Project manager decided that subject E129 should be excluded from both the FAS and PPAS.	Major	1	N	N
E108[a]	The date of the signed informed consent form was not unequivocally verifiable from source data. The subject was however never randomized due to violation of eligibility criterion No.4, see Table 8.	Major	1	N	N
E103, E104, E105, E107, E113, E114, E116, E117, E120, E126, E130, E140, E146, E152	A visit at the clinic occurred outside the visit window described in the protocol (±3 days). In total 14 visits (14 subjects) were performed -4 days up to +7 days to the proposed date.	Minor	14	Y	Y
E113, E145	Subjects were not specifically asked about symptoms suggestive of hypoglycaemia.	Minor	2	Y	Y
E113	The randomization visit was performed 1 day outside the visit window described in the protocol (7 to 14 days post-screening visit).	Minor	1	Y	Y
E135	Subject had not received appropriate training in handling of syringe and injection of placebo	Minor	1	Y	Y

[a] Subject E108 is not included in Table 63 in Section 14.1.2 since subject E108 was never randomized.

Source: Table 63 in Section 14.1.2 and Appendix 16.2.2

10.2.2 Other Discrepancies in the Study

- Two subjects receiving active treatment (E113 and E145) had taken less than 80% of the planned doses for at least one of the IPs. Subject E113 took 75.6% of the tablets and 85.5% of the injections and subject E145 took 51.7% of the tablets and 48.3% of the injections. Both subjects were excluded from the PPAS (see also Section 11.3).
- A file note was written for subject E101 regarding a third measurement of P-glucose during screening. According to the original protocol, glucose measurements were to be repeated once if the glucose was ≥7.0 mmol/L. If glucose was still ≥7.0 mmol/L the subject should be excluded from the study. For subject E101, 2 laboratory tests for P-glucose were taken during screening and both measured 7.1 mmol/L. However, since the glucose levels measured at bedside was <7.0 mmol/L, it was decided to take a third sample which measured 6.8 mmol/L. The Sponsor and the Project manager at PCG Clinical Services AB decided that subject E101 could be included in the study and that the third measurement was not to be recorded as a protocol deviation due to previous inconsistency between laboratory results.

10.2.3 Deviations Identified after Data Cleaning and Database-lock

One female subject (E144) was erroneously registered in the eCRF as being of no child-bearing potential due to premenarcheal state but the true reason was koriocarcinoma (see individual data listings in Appendix 16.2.4-1). The subject practiced appropriate birth control (barrier methods) as stated in Section 9.3.1 during the entire treatment duration and for 10 weeks after the last dose of study medication.

10.2.4 Prohibited Medications

Administration of systemic glucocorticoids during the study period was regarded as prohibited medication. Three subjects received systemic glucocorticoids for treatment of AEs/SAEs:

- Subject E122 and E160 received injections of glucocorticoids during the study as corrective treatments for AEs. These injections were considered to be local and not systemic and were therefore not recorded as use of prohibited concomitant medications (and not registered as protocol deviations).
- Subject E153 was prescribed systemic glucocorticoid as corrective treatment for an SAE. The SAE caused the subject's immediate withdrawal from the study and the treatment with systemic glucocorticoids was therefore not recorded as use of prohibited concomitant medication (and not registered as a protocol deviation).

11. EFFICACY EVALUATION

11.1 DATA SETS ANALYZED

Three analysis datasets were defined in the study: Safety, FAS and PPAS (Table 11). For definitions of analysis populations, see Section 9.7.2.

For the primary, secondary and exploratory efficacy variables, analyses on both the FAS and PPAS were performed.

All 50 randomized subjects were included in the Safety analysis set, 49 subjects were included in the FAS and 42 subjects were included in the PPAS (Table 11).

The decision to include or exclude subjects from each analysis set was taken by the Sponsor and the Project manager under blinded conditions during data cleaning prior to database lock. The PPAS population consisted of subjects who:

1. Had sufficiently complied with the protocol
2. Had available data at 24 weeks for the primary variable
3. Had been compliant to IP

Eight randomized subjects were excluded from the PPAS: 5 subjects (E145 and E156 receiving active treatment and E103, E115 and E153 receiving placebo) were prematurely withdrawn due to AEs of which 1 was an SAE (E153), 1 subject (E113; active group) was non-compliant to IP and 1 subject (E161; placebo group) withdrew the informed consent and discontinued the study. One subject (E129; placebo group) was excluded both from the FAS and the PPAS due to severe non-compliance with the protocol regarding diet instructions (Table 12).

For more details, see Section 10.1.2 (Reasons for premature withdrawals), Section 10.2 (Protocol deviations) and Section 12.4.4 (Withdrawals due to AEs).

Individual subject data listings are provided in Appendix 16.2.1 and 16.2.3.

Table 11 Analysis datasets

Analysis population	Dapagliflozin/ Exenatide	Placebo	Total
Safety analysis set	25 (100.0%)	25 (100.0%)	50 (82.0%)
Full analysis set, FAS	25 (100.0%)	24 (96.0%)	49 (80.3%)
Per-protocol analysis set, PPAS	22 (88.0%)	20 (80.0%)	42 (68.9%)

Percentages are based on the number of randomized subjects.
Source: Table 62 in Section 14.1.1

Table 12 Summary of reasons for exclusion of randomized subjects from the FAS and PPAS

Subject id	Treatment group	Reason for exclusion	Included in FAS Y/N	Included in PPAS Y/N
E113[a]	dapagliflozin/exenatide	Non-compliant with IP	Y	N
E145 [b]	dapagliflozin/exenatide	Prematurely withdrawn due to AE	Y	N
E156 [b]	dapagliflozin/exenatide	Prematurely withdrawn due to AE	Y	N
E103[b]	placebo	Prematurely withdrawn due to AE	Y	N
E115 [b]	placebo	Prematurely withdrawn due to AE	Y	N
E129[c]	placebo	Non-compliant with protocol	N	N
E153 [b]	placebo	Prematurely withdrawn due to SAE	Y[d]	N
E161 [e]	placebo	Withdrawal of consent	Y	N

[a] Subject E113 had taken less than 80% of the planned doses of IP, for details see Section 11.3.

[b] Subjects prematurely withdrawn from the study due to AEs lacked available efficacy data at week 24 and were excluded from the PPAS:
- Subject E145 (abdominal pain, moderate AE, possibly related to IP)
- Subject E156 (injection site mass and pruritus, moderate AEs, possibly related to IP)
- Subject E103 (skin ulcer and vasculitis, moderate AEs, possibly related to IP)
- Subject E115 (malaise, mild AE, possibly related to IP)
- Subject E153 (dyspnoea and fatigue, severe SAEs, unlikely related to IP)

[c] Subject E129 was not adhering to diet instructions described in the protocol (major protocol deviation, primary reason for withdrawal), see Section 10.1.2 and 10.2.1. Concomitantly, subject E129 discontinued IP due to an AE (PT blood ketone body increased).

[d] Subject E153 completed Visit 4 and discontinued the study 2 days later due to SAEs (dyspnoea and fatigue).

[e] Subject 161 received nodules at the injection site (reported as a mild AE, drug withdrawn) and withdrew consent after completing Visit 5.

Source: Appendix 16.2.1 and 16.2.3

11.2 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

The results from demographics, body weight and other anthropometric measures at baseline, obesity history, medical history, concurrent diseases, prior and concomitant procedures and prior and concomitant medications are described in Section 11.2.1 to Section 11.2.10.

The definitions of prior vs concomitant procedures and medications are defined in Section 9.4.7.

Individual subject data listings of the demographics and other baseline characteristics are provided in Appendix 16.2.4.

11.2.1 Demographics

The demographics for the FAS are summarized in Table 13. The corresponding table for the Safety analysis set is provided in Section 14.1.3 (Table 64). Individual subject data listings of the demographics are provided in Appendix 16.2.4.

All 49 subjects in the FAS, 30 females and 19 males were treated with IP. The ratio of females to males was 15/10 in the dapagliflozin/exenatide group and 15/9 in the placebo group.

In terms of race, the majority of subjects were White (95.9%), 1 subject was Asian (2.0%) and 1 was Iranian (reported as Other; 2.0%).

The age of all subjects ranged between 20 and 69 years and the mean age was 52 years. The mean age in each treatment groups was 53 years (dapagliflozin/exenatide) and 50 years (placebo).

No pregnancies occurred during the study. Ten of 30 female subjects were of child-bearing potential.

Overall, the demographics were well balanced between the treatment groups.

Table 13 Demographics. Full analysis set

	Dapagliflozin/ Exenatide N=25	Placebo N=24	Total N=49
Age (years)			
n/nmiss	25/0	24/0	49/0
Mean (SD)	53.48 (13.48)	50.00 (11.83)	51.78 (12.69)
Median	53.00	50.50	51.00
Q1, Q3	48.00, 65.00	44.50, 57.00	46.00, 62.00
Min, Max	20.0, 69.0	23.0, 68.0	20.0, 69.0
Gender			
Female	15 (60.0%)	15 (62.5%)	30 (61.2%)
Male	10 (40.0%)	9 (37.5%)	19 (38.8%)
Race			
Asian	1 (4.0%)	0	1 (2.0%)
Other	1 (4.0%)	0	1 (2.0%)
White	23 (92.0%)	24 (100.0%)	47 (95.9%)
Childbearing potential			
Yes	4 (26.7%)	6 (40.0%)	10 (33.3%)
No	11 (73.3%)	9 (60.0%)	20 (66.7%)
Reason			
Postmenopausal	8 (72.7%)	8 (88.9%)	16 (80.0%)
Surgically sterile	1 (9.1%)	1 (11.1%)	2 (10.0%)
Premenarcheal[a]	1 (9.1%)	0	1 (5.0%)
Other	1 (9.1%)	0	1 (5.0%)

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
Percentages are based on the number of subjects in the applicable analysis set.
[a] One female subject (E144) in the dapagliflozin/exenatide group was erroneously registered in the eCRF as being of no child-bearing potential due to premenarcheal state but the true reason was due to koriocarcinoma.

11.2.2 Body Weight and Other Anthropometric Measures at Baseline

Body weight and other anthropometric measures for the FAS and Safety analysis sets is provided in Section 14.1.4.1 (Table 65 and Table 66). Charts presenting the mean change in body weight over 24 weeks is shown in Section 11.4.1.1 (Figure 3) for the FAS and in Section 14.1.4.1 (Figure 14) for the Safety analysis set. Individual subject data listings of body weight and other anthropometric measures are provided in Appendix 16.2.4.

The mean body weight at baseline (week 0) was 106.4 kg (SD=15.6) in the dapagliflozin/exenatide group and 102.7 kg (SD=17.3) in the placebo group whereas the mean BMI was 35.8 kg/m^2 (SD=2.9) and 35.0 kg/m^2 (SD=3.7) in the dapagliflozin/exenatide and placebo groups, respectively (Table 65).

In the dapagliflozin/exenatide group, the mean waist and hip circumference was 117.6 cm (SD=11.3) and 121.2 cm (SD=7.5), respectively. In the placebo group the corresponding numbers were 114.4 cm (SD=12.6) and 117.6 cm (SD=6.5), respectively. The mean waist-hip ratio (WHR) at baseline is presented in Section 11.2.3.

Overall, the mean body weight, waist and hip circumferences and BMI were slightly higher in the dapagliflozin/exenatide group compared to placebo. However, all statistical analyses of body weight and anthropometric measurements in this study were adjusted for baseline values.

11.2.3 Waist-hip Ratio

The WHR is presented Section 14.1.4.2 (Table 67 and Table 68) for the FAS and Safety analysis set, respectively. Charts presenting the mean change in waist-hip ratio over 24 weeks is shown in

Section 11.4.3.8.2 (Figure 13) for the FAS and in Section 14.1.4.2 (Figure 15) for the Safety analysis set. Individual subject data listings of the WHR are provided in Appendix 16.2.4.

At baseline (week 0), the mean WHR was 0.97 in both treatment groups (SD=0.10 and SD=0.09 in the dapagliflozin/exenatide and placebo groups, respectively), see Table 67.

11.2.4 Obesity History

The obesity history for the FAS is summarized in Table 14 and for the Safety analysis set in Section 14.1.5 (Table 69). Individual subject data listings of the obesity history are provided in Appendix 16.2.4.

The mean time since start of obesity was longer in the dapagliflozin/exenatide group than in the placebo group; 27 years (SD=17) vs 20 years (SD=13) (Table 14). The corresponding median values were 23 and 17 years.

In both treatment groups, a small but similar increase in mean body weight was observed during the 12-month period prior to baseline (week 0): +2.1 kg in the dapagliflozin/exenatide group (from 104.3 kg at 12 months prior to baseline to 106.4 kg at baseline) and +2.5 kg in the placebo group (from 100.3 kg at 12 months prior to baseline to 102.7 kg at baseline), see Table 14 and Table 65.

Table 14 Obesity history. Full analysis set

	Dapagliflozin/ Exenatide N=25	Placebo N=24
Time since obesity started (years)		
n/nmiss	25/0	24/0
Mean (SD)	27.32 (17.29)	19.67 (13.49)
Median	23.00	16.50
Q1, Q3	15.00, 35.00	9.50, 31.00
Min, Max	5.0, 69.0	0.0, 50.0
Max weight (kg)		
n/nmiss	25/0	24/0
Mean (SD)	111.05 (18.15)	107.73 (19.87)
Median	111.00	102.50
Q1, Q3	98.00, 120.80	94.50, 118.50
Min, Max	83.0, 157.0	74.0, 152.0
Weight (kg) 12 months before baseline		
n/nmiss	25/0	24/0
Mean (SD)	104.32 (16.70)	100.25 (16.05)
Median	103.00	95.75
Q1, Q3	93.00, 117.00	89.00, 107.50
Min, Max	79.0, 148.0	74.0, 146.0
Weight (kg) 3 months before baseline		
n/nmiss	25/0	24/0
Mean (SD)	105.53 (15.65)	101.33 (16.89)
Median	105.00	95.50
Q1, Q3	93.00, 115.00	92.00, 110.50
Min, Max	79.0, 144.0	74.0, 146.0

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.

11.2.5 Medical History

Summary tables pertaining to this section are presented in Section 14.1.6 (Table 70 for the Safety analysis set and Table 71 for the FAS). Individual subject data listings of the medical history are provided in Appendix 16.2.4.

Medical history was reported by 11 subjects (44.0%) in the dapagliflozin/exenatide group and 10 subjects (40.0%) in the placebo group (Safety analysis set), see Appendix 16.2.4. The most common type of medical history (SOC) was Injury poisoning and procedural complications reported by 4 subjects in total. All other SOCs and PTs were reported by 2 subjects or fewer in each treatment group (Table 70).

Overall, the treatment groups were comparable with regard to medical history. No conditions reported as medical history were considered as having any impact on the efficacy analyses in the study.

11.2.6 Concurrent Diseases

Summary tables pertaining to this section are presented in Section 14.1.7 (Table 72 for the Safety analysis set and Table 73 for the FAS). Individual subject data listings of concurrent diseases are provided in Appendix 16.2.4.

Concurrent diseases were reported by 19 subjects (76.0%) in the dapagliflozin/exenatide group and 18 subjects (72.0%) in the placebo group (Safety analysis set), see Appendix 16.2.4. The most common type of concurrent diseases (SOCs; Table 72), reported by ≥10 subjects, were:

- Gastrointestinal disorders: 7 vs 3 subjects in the dapagliflozin/exenatide and placebo groups, respectively.
- Muscoskeletal and connective tissue disorders: 4 vs 6 subjects in the dapagliflozin/exenatide and placebo groups, respectively.
- Respiratory, thoracic and mediastinal disorders: 4 vs 6 subjects in the dapagliflozin/exenatide and placebo groups, respectively.
- Vascular disorders: 6 vs 4 subjects in the dapagliflozin/exenatide and placebo groups, respectively.

Overall, concurrent diseases were comparable between the treatment groups. No conditions reported as concurrent diseases were considered as having an impact on the efficacy analyses in the study.

11.2.7 Prior Procedures

Summary tables pertaining to this section is presented in Section 14.1.8 (Table 74 for the Safety analysis set and Table 75 for the FAS). Individual subject data listings of prior procedures are provided in Appendix 16.2.4 (listing named “Surgical history”).

Prior procedures were reported by 15 subjects (60.0%) in the dapagliflozin/exenatide group and 10 subjects (40.0%) in the placebo group (Safety analysis set), see Appendix 16.2.4. The most common conditions reported as prior procedures, based on PTs, were: appendectomy (n=8), cholecystectomy (n=4), knee arthroplasty (n=3) and knee operation (n=3), see Table 74.

Overall, prior procedures were comparable between the treatment groups. No events reported as prior procedures were considered as having an impact on the efficacy analyses in the study.

11.2.8 Concomitant Procedures

Summary tables pertaining to this section are presented in Section 14.1.9 (Table 76 for the Safety analysis set and Table 77 for the FAS). Individual data listings for the concomitant procedures are provided in Appendix 16.2.4 (listing named “Concurrent surgical procedures”).

Concomitant procedures were reported by 3 subjects (12.0%) in the dapagliflozin/exenatide group and 6 subjects (24.0%) in the placebo group (Safety analysis set). Three of the concomitant

procedures were related to contraception. Other concomitant procedures were e.g. hysterectomy, knee arthroplasty or nasal polypectomy (Table 76).

No concomitant procedures occurring during the study period were considered as having any impact on the efficacy analyses in the study.

11.2.9 Prior Medication

For definitions of prior and concomitant medications, refer to Section 9.4.7. Summary tables pertaining to this section are presented in Section 14.1.10 (Table 78 for the Safety analysis set and Table 79 for the FAS). Individual data listings for prior medication are provided in Appendix 16.2.4.

Prior medications were reported by 9 subjects (36.0%) in the dapagliflozin/exenatide group and 4 subjects (16.0%) in the placebo group (Safety analysis set), see Appendix 16.2.4. The most common type of prior medications, based on therapeutic main group were:

- Antiobesity preparations (excluding diet products): 6 subjects (24.0%) in the dapagliflozin/exenatide group and 1 subject (4.0%), in the placebo group. The medications taken were orlistat (n=5) and sibutramine hydrochloride (n=3).

All other therapeutic main groups were reported by single subjects in each treatment group (Table 78).

In general, the use of prior medications was very limited and no prior medications were considered as having any impact on the efficacy analyses in the study.

11.2.10 Concomitant Medication

For definitions of prior and concomitant medications, refer to section 9.4.7. Summary tables pertaining to this section is presented in Section 14.1.11 (Table 80 for the Safety analysis set and Table 81 for the FAS). Individual subject data listings of concomitant medication are provided in Appendix 16.2.4.

Due to technical reasons, some 'Anti-inflammatory and anti-rheumatic products, non-steroids' terms for concomitant medications could not be coded in the eCRF Viedoc™. The affected terms were therefore coded manually and integrated directly into the analysis datasets.

Concomitant medications were reported by 24 subjects (96.0%) in the dapagliflozin/exenatide group and 23 subjects (92.0%) in the placebo group (Safety analysis set), see Appendix 16.2.4 and Table 80.

The most common types of medications reported as concomitant medications (used by ≥20% of the subjects in one treatment group), based on therapeutic main group and preferred names, were:

- Agents acting on the renin-angiotensin system: 4 subjects (16.0%) in the dapagliflozin/exenatide group and 6 subjects (24.0%), in the placebo group of which the most common medication was losartan (n=5).
- Analgesics: 12 subjects (48.0%) in the dapagliflozin/exenatide group and 9 subjects (36.0%), in the placebo group of which the most common medication was paracetamol (n=20).
- Antianemic preparations: 5 subjects (20.0%) in the dapagliflozin/exenatide group and 1 subject (4.0%) in the placebo group of which the most common medication was cyanocobalamin (n=5).
- Anti-inflammatory and antirheumatic products: 9 subjects (36.0%) in the dapagliflozin/exenatide group and 9 subjects (36.0%) in the placebo group of which the most common medication was ibuprofen (n=10).

- Drugs for acid-related disorders: 8 subjects (32.0%) in the dapagliflozin/exenatide group and 3 subjects (12.0%) in the placebo group of which the most common medication was omeprazole (n=8).
- Drugs for obstructive airway disease: 2 subjects (8.0%) in the dapagliflozin/exenatide group and 5 subjects (20.0%) in the placebo group of which the most common medication was terbutaline sulphate (n=4).
- Sex hormones and modulators of the genital system: 2 subjects (8.0%) in the dapagliflozin/exenatide group and 6 subjects (24.0%) in the placebo group of which the most common medication was desogestrel (n=2).
- Thyroid therapy: 5 subjects (20.0%) in the dapagliflozin/exenatide group and 2 subjects (8.0%) in the placebo group of which the most common medication was levothyroxine sodium (n=7).

No subjects used any antiobesity preparations (e.g. orlistat) during the study period.

For details on the use of prohibited medications during the study, refer to Section 10.2.4.

In general, the use of concomitant medications was similar in both treatment groups. No concomitant medications were considered as having any impact on the efficacy analyses in the study.

11.3 MEASUREMENTS OF TREATMENT COMPLIANCE

Treatment compliance was measured based on returned amounts of IP to the clinic and reported dosing information from the subjects. Treatment compliance (number of doses received relative to doses planned) is summarized by treatment group for the FAS in Table 15. Individual subject data listings for compliance are provided in Appendix 16.2.5.

Non-compliance was defined as taking less than 80% or more than 120% of the prescribed dose of IP.

Two subjects (E113 and E145) were identified as non-compliant with the protocol as they had taken less than 80% of the planned doses for at least one of the IPs. Subject E113 took 75.6% of the tablets and 85.5% of the injections and subject E145 took 51.7% of the tablets and 48.3% of the injections (see individual data listings for treatment compliance in Appendix 16.2.5). E145 was withdrawn from the study E145 after Visit 4, due to abdominal pain. Both subjects were excluded from the PPAS (see Table 12 in Section 11.1). No subjects were identified as having taken more than 120% of the planned doses for any of the IPs.

In general, the compliance was high (mean >95%) for both IPs and similar in both treatment groups: In the dapagliflozin/exenatide group, the mean percentage of the planned dose of IP that was administered was 97.5% (SD=12.0) for exenatide (injections) and 96.0% (SD=12.7) for dapagliflozin (tablets). In the placebo group, the mean percentage of the planned dose of IP that was administered was 99.0% (SD=3.9) for injections and 98.8% (SD=5.5) for the tablets.

Similar results were obtained for the Safety analysis set, see Section 14.1.12 (Table 82).

Table 15 Compliance. Full analysis set

	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Number of injections (received/planned)		
n/nmiss	25/0	24/0
Mean (SD)	97.46 (12.03)	99.00 (3.94)
Median	101.80	100.00
Q1, Q3	100.00, 102.90	98.20, 100.60
Min, Max	48.3, 104.8	86.0, 104.2
Number of tablets (received/planned)		
n/nmiss	25/0	23/1
Mean (SD)	96.02 (12.70)	98.82 (5.49)
Median	100.00	98.80
Q1, Q3	91.40, 101.20	97.60, 100.60
Min, Max	51.7, 115.6	88.9, 111.9

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.

11.4 EFFICACY RESULTS AND TABULATIONS OF INDIVIDUAL PATIENT DATA

The results of the primary, secondary and exploratory efficacy variables are presented in Section 11.4.1 to Section 11.4.3. The efficacy conclusions are presented in Section 11.4.7 and in Section 13.2 (overall conclusions).

Tables and figures for the FAS are in general presented in the body text of the report if statistically significant results were obtained. Other FAS tables and all corresponding tables for the PPAS are provided in Section 14.2.

Individual subject data listings for all efficacy variables are provided in Appendix 16.2.6.

11.4.1 Primary Efficacy Variable

11.4.1.1 Mean Change in Body Weight from Baseline to Week 24

Body weight measurements were performed at screening, at week 0 (baseline) and at weeks 4, 8, 12 and 24.

A statistically significant reduction in mean body weight between baseline (week 0) and week 24 was observed for the dapagliflozin/exenatide group compared to the placebo group (p=0.0008; Table 16). The LS estimate of the difference in weight reduction between the treatment groups was -4.1 kg (95% CI=-6.4 to -1.8) at week 24.

The adjusted mean change from baseline in body weight at week 24 was -4.5 kg (95% CI=-6.1 to -2.9) in the dapagliflozin/exenatide group as compared to -0.4 kg (95% CI=-2.0 to 1.3) in the placebo group.

There was a corresponding statistically significant difference compared to placebo for the PPAS at week 24 (LS estimate: -3.7 kg [95% CI=-6.1 to -1.3]; p=0.0036), see Section 14.2.1 (Table 83).

Table 16 Mixed model for repeated measures of change from baseline in Body weight (kg) at week 24. Full analysis set

Body weight (kg)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Number of subjects included in analysis	25	24
Adjusted mean change (95% CI)	-4.48 (-6.08, -2.87)	-0.35 (-2.02, 1.32)
Difference (95% CI)	-4.13 (-6.44, -1.81)	
p-value	0.0008	

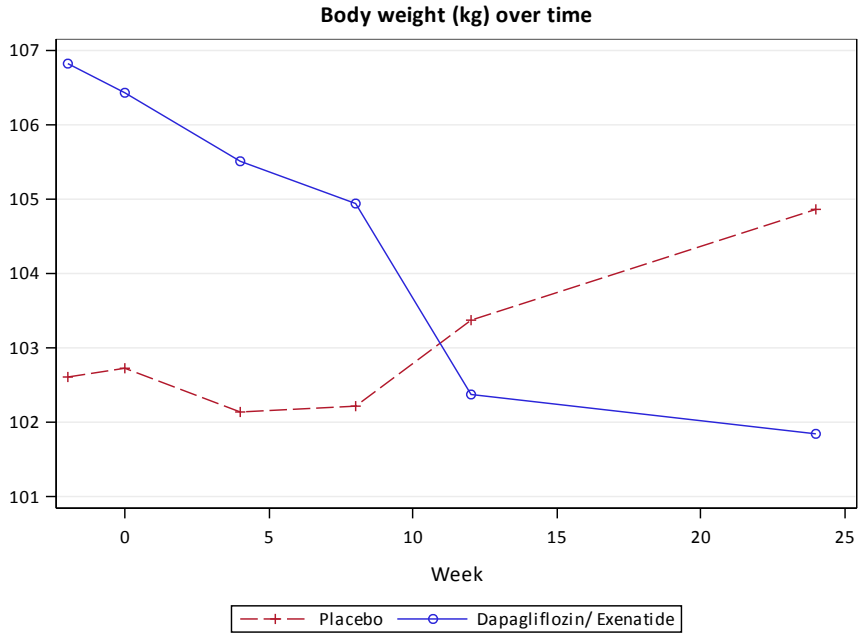
A mixed model for repeated measures (MMRM) adjusted for treatment, week, treatment*week, gender and baseline body weight was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.

A majority of the weight loss observed in the dapagliflozin/exenatide group occurred during the first 12 weeks of the 24-week treatment period, see Figure 3 and Table 84 in Section 14.2.1. Compared to placebo, the reduction in mean body weight from baseline was statistically significant at both week 8 and week 12 (-1.7 kg [95% CI=-3.0 to -0.4; p=0.0136] and -3.5 kg [95% CI=-5.2 to -1.8; p=0.0002], respectively), Section 14.2.1 (Table 84).

There was a corresponding statistically significant difference compared to placebo for the PPAS at week 12 (p=0.0019) but not at week 8, see Section 14.2.1 (Table 85).

Spaghetti plots illustrating the individual change in body weight from screening to week 24 are provided in Section 14.2.2.4 (Figure 16 to Figure 19).

Figure 3 **Body weight (kg) series plot by week. Full analysis set**



11.4.1.2 Alternative Primary Efficacy Model

The combined treatment effect of dapagliflozin/exenatide on the mean change in body weight (kg) from baseline to week 24 compared to placebo was estimated using the same adjustments as for the primary model and with an additional adjustment for the interaction between baseline body weight and week.

In agreement with the primary efficacy model, a statistically significant reduction in mean body weight between baseline (week 0) and week 24 was observed for the dapagliflozin/exenatide group compared to the placebo group (p=0.0008; Table 17). The LS estimate of the difference in weight reduction between the treatment groups was -4.2 kg (95% CI=-6.5 to -1.8) at week 24.

The adjusted mean change from baseline in body weight at week 24 was -4.5 kg (95% CI=-6.1 to -2.9) in the dapagliflozin/exenatide group as compared to -0.4 kg (95% CI=-2.0 to 1.3) in the placebo group.

There was a corresponding statistically significant difference compared to placebo for the PPAS at week 24 (LS estimate: -3.7 kg [95% CI=-6.2 to -1.3]; p=0.0036), see Section 14.2.2 (Table 86).

Table 17 **Mixed model for repeated measures of change from baseline in body weight (kg) at week 24. Alternative model. Full analysis set**

Body weight (kg)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Number of subjects included in analysis	25	24
Adjusted mean change (95% CI)	-4.50 (-6.11, -2.90)	-0.35 (-2.03, 1.32)
Difference (95% CI)	-4.15 (-6.47, -1.84)	
p-value	0.0008	

A mixed model for repeated measures (MMRM) adjusted for treatment, week, the interaction between treatment and week, gender, baseline body weight and the interaction between baseline body weight and week was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.

11.4.2 Secondary Efficacy Variable

11.4.2.1 Mean Percentage Change in Body Weight (%) from Baseline to Week 24

The combined treatment effect of dapagliflozin/exenatide compared to placebo on percentage mean change in body weight (%) from baseline to week 24 was estimated using the same method as for the primary efficacy variable.

A statistically significant reduction in mean body weight based on percentage change from baseline (week 0) to week 24 was observed for the dapagliflozin/exenatide group compared to the placebo group (p=0.0006; Table 18). The LS estimate of the difference in percentage weight reduction between the treatment groups was -4.2% (95% CI=-6.5 to -1.9) at week 24.

The adjusted mean percentage change in body weight from baseline to week 24 was -4.5% (95% CI=-6.0 to -2.9) in the dapagliflozin/exenatide group as compared to -0.3% (95% CI=-1.9 to 1.4) in the placebo group.

There was a corresponding statistically significant difference compared to placebo for the PPAS at week 24 (LS estimate: -3.7% [95% CI=-6.1 to -1.4]; p=0.0026), see Section 14.2.1 (Table 87).

Table 18 Mixed model for repeated measures of percentage change from baseline in Body weight at week 24. Full analysis set

Body weight (%)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Number of subjects included in analysis	25	24
Adjusted mean change (95% CI)	-4.47 (-6.04, -2.89)	-0.27 (-1.92, 1.37)
Difference (95% CI)	-4.19 (-6.47, -1.92)	
p-value	0.0006	

A mixed model for repeated measures (MMRM) adjusted for treatment, week, treatment*week, gender and baseline body weight was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.

11.4.3 Exploratory Efficacy Variables

Descriptive data and the results of the statistical analyses for the FAS are presented in Section 11.4.3.1 (Proportion of subjects with at least 5% and 10% weight reduction), Section 11.4.3.2 (Mean change in body weight), Section 11.4.3.3 (Percentage change in body weight), Section 11.4.3.4 (Body fat composition), Section 11.4.3.5 (3h-OGTT results), Section 11.4.3.6 (Blood lipid profile), Section 11.4.3.7 (Vital signs), Section 11.4.3.8 (Other anthropometric measurements), Section 11.4.3.9 (UGE), Section 11.4.3.10 (eGFR) and Section 11.4.3.11 (Model building of potential covariates).

The corresponding tables for the PPAS are provided in Section 14.2.2. Individual data pertaining to this section are provided in Appendix 16.2.6.

11.4.3.1 Proportion of Subjects with at least 5% and 10% Reduction of Body Weight at Week 24

The proportion of subjects with at least 5% and 10% reduction of body weight from baseline (week 0) was calculated for both the FAS (Table 19) and the PPAS (Table 88 in Section 14.2.2.1). The proportion of subjects with at least 5% or 10% reduction of body weight at week 24 was too low for any statistical analyses to be performed (see Section 9.8.2, Changes to the planned analyses).

In the dapagliflozin/exenatide group, 9 of 25 subjects (36.0%) had more than, or equal to, 5% weight loss and 3 of 25 subjects (12.0%) had more than, or equal to, 10% weight loss at week 24 (Table 19). None of the subjects in the placebo group exhibited a weight reduction of 5% or more (Table 19).

Corresponding results were obtained for the PPAS (Table 88 in Section 14.2.2.1).

Table 19 At least 5% and 10% weight reduction at week 24. Full analysis set

	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
At least 5%	9 (36.0%)	0
At least 10%	3 (12.0%)	0

The percentage was based on N for the FAS.
Baseline = randomization (week 0)
At least 5% = more than or equal to 5%
At least 10% = more than or equal to 10%

11.4.3.2 Mean Change in Body Weight (kg) Between Screening and Week 24

A statistically significant reduction in body weight between screening and week 24 was observed in the dapagliflozin/exenatide group compared to the placebo group (p=0.0003; Table 20 and Table 89). The LS estimate of the difference in weight reduction between treatment groups was -4.5 kg (95% CI=-6.9 to -2.2) at week 24.

The adjusted mean change from screening in body weight at week 24 was -4.8 kg (95% CI=-6.4 to -3.2) in the dapagliflozin/exenatide group as compared to -0.2 kg (95% CI=-1.9 to 1.5) in the placebo group.

There was a corresponding statistically significant difference compared to placebo for the PPAS at week 24 (LS estimate: -4.4 kg [95% CI=-6.9 to -1.9]; p=0.0010), see Section 14.2.2.2 (Table 90).

Table 20 Mixed model for repeated measures of change from screening in body weight (kg) at week 24. Full analysis set

Body weight (kg)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Week -2-(-1) (Baseline)		
n/nmiss	25/0	24/0
Mean (SD)	106.82 (15.67)	102.61 (16.96)
Median	110.10	97.90
Q1, Q3	92.00, 116.30	93.30, 111.95
Min, Max	82.0, 143.2	73.7, 144.9
Week 24		
n/nmiss	23/2	20/4
Mean (SD)	101.84 (17.36)	104.86 (17.38)
Median	98.50	96.05
Q1, Q3	85.30, 112.10	94.05, 116.10
Min, Max	75.0, 141.9	83.3, 150.2
Number of subjects included in analysis	25	24
Adjusted mean change (95% CI)	-4.75 (-6.36, -3.15)	-0.23 (-1.91, 1.46)
Difference (95% CI)	-4.53 (-6.85, -2.21)	
p-value	0.0003	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
A mixed model for repeated measures (MMRM) adjusted for treatment, week, treatment*week, gender and screening body weight was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.

11.4.3.3 Percentage Change in Body Weight (%) Between Screening and Week 24

A statistically significant reduction in body weight based on percentage change from screening to week 24 was observed in the dapagliflozin/exenatide group compared to the placebo group (p=0.0002; Table 21 and Table 91). The LS estimate of the difference in percentage weight reduction between treatment groups was -4.5% (95% CI=-6.8 to -2.2) at week 24.

The adjusted percentage mean change from screening in body weight to week 24 was -4.7% (95% CI=-6.2 to -3.1) in the dapagliflozin/exenatide group as compared to -0.2% (95% CI=-1.8 to 1.4) in the placebo group.

There was a corresponding statistically significant difference compared to placebo for the PPAS at week 24 (LS estimate: -4.3% [95% CI=-6.7 to -1.9]; p=0.0009), see Section 14.2.2.3 (Table 92).

Table 21 Mixed model for repeated measures of percentage change from screening in body weight (kg) at week 24. Full analysis set

Body weight (kg)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Week -2-(-1) (Baseline)		
n/nmiss	25/0	24/0
Mean (SD)	106.82 (15.67)	102.61 (16.96)
Median	110.10	97.90
Q1, Q3	92.00, 116.30	93.30, 111.95
Min, Max	82.0, 143.2	73.7, 144.9
Week 24		
n/nmiss	23/2	20/4
Mean (SD)	101.84 (17.36)	104.86 (17.38)
Median	98.50	96.05
Q1, Q3	85.30, 112.10	94.05, 116.10
Min, Max	75.0, 141.9	83.3, 150.2
Number of subjects included in analysis	25	24
Adjusted mean change (95% CI)	-4.68 (-6.24, -3.11)	-0.19 (-1.83, 1.44)
Difference (95% CI)	-4.48 (-6.75, -2.22)	
p-value	0.0002	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
A mixed model for repeated measures (MMRM) adjusted for treatment, week, treatment*week, gender and screening body weight was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.

11.4.3.4 Body Fat Composition

Descriptive data and the results of the statistical analyses for the FAS are presented in Section 11.4.3.4.1 (total adipose tissue, visceral adipose tissue, abdominal subcutaneous adipose tissue and total lean tissue), Section 11.4.3.4.2 (percentage liver fat, liver volume and total liver fat) and Section 11.4.3.4.3 (percentage body fat as measured by bioimpedance). A summary table is provided in Section 11.4.3.4.4.

The corresponding tables for the PPAS are provided in Section 14.2.2.5. Individual data pertaining to this section are provided in Appendix 16.2.6.

11.4.3.4.1 Total, Subcutaneous and Visceral Adipose Tissue and Total Lean Tissue

A statistically significant reduction of total adipose tissue between baseline and week 24 was observed for the dapagliflozin/exenatide group compared to the placebo group (p=0.0004; Table 22). The LS estimate of the difference in reduction of total adipose tissue between treatment groups was -4.09 L (95% CI=-6.23 to -1.94) at week 24.

The adjusted mean change from baseline to week 24 in total adipose tissue was -4.22 L (95% CI=-5.69 to -2.76) in the dapagliflozin/exenatide group as compared to -0.14 L (95% CI=-1.72 to 1.45) in the placebo group.

The reduction in total adipose tissue was attributed to statistically significant reductions in both visceral adipose tissue (p=0.0005) and abdominal subcutaneous adipose tissue (p=0.0003) compared to placebo (Table 23 and Table 24). The LS estimates of the difference between treatment groups were -0.62 L (95% CI=-0.95 to -0.29) for visceral adipose tissue and -1.44 L (95% CI=-2.16 to -0.71) for abdominal subcutaneous adipose tissue at week 24.

The adjusted mean change from baseline to week 24 in visceral adipose tissue was -0.40 L (95% CI=-0.63 to -0.16) in the dapagliflozin/exenatide group as compared to 0.22 L (95% CI=-0.02 to 0.46) in the placebo group (Table 23). The adjusted mean change from baseline in abdominal subcutaneous adipose tissue at week 24 was -1.31 L (95% CI=-1.80 to -0.81) in the dapagliflozin/exenatide group as compared to 0.13 L (95% CI=-0.40 to 0.67) in the placebo group (Table 24).

There were corresponding statistically significant differences compared to placebo for the PPAS at week 24 (LS estimates: -4.07 L [95%CI=-6.27 to -1.87], p=0.0006 for total adipose tissue. -0.61 L [95%CI=-0.94 to -0.27], p=0.0008 for visceral adipose tissue and -1.45 L [95%CI=-2.19 to -0.71], p=0.0003 for abdominal subcutaneous adipose tissue), see Section 14.2.2.5.1 (Table 93 to Table 95).

Total lean tissue was reduced in both treatment groups between baseline and week 24 but there was no statistically significant difference between the groups in either FAS or PPAS, see Section 14.2.2.5.1 (Table 96 and Table 97).

Table 22 Analysis of covariance of change from baseline to week 24 in Total adipose tissue (L). Full analysis set

Total adipose tissue (L)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Week 0		
n/nmiss	24/1	22/2
Mean (SD)	57.06 (9.70)	53.35 (7.02)
Median	56.54	54.55
Q1, Q3	48.78, 64.84	48.39, 56.35
Min, Max	42.3, 76.1	41.3, 70.6
Week 24		
n/nmiss	23/2	19/5
Mean (SD)	52.69 (12.36)	53.75 (7.27)
Median	51.34	52.92
Q1, Q3	42.64, 62.19	49.86, 57.62
Min, Max	33.1, 76.0	39.0, 71.4
Number of subjects included in analysis	22	19
Adjusted mean change (95% CI)	-4.222 (-5.688, -2.755)	-0.137 (-1.724, 1.451)
Difference (95% CI)	-4.085 (-6.232, -1.938)	
p-value	0.0004	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.

Table 23 Analysis of covariance of change from baseline to week 24 in Visceral adipose tissue (L). Full analysis set

Visceral adipose tissue (L)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Week 0		
n/nmiss	24/1	23/1
Mean (SD)	6.31 (3.09)	5.66 (2.44)
Median	5.92	4.78
Q1, Q3	3.73, 8.90	4.09, 7.16
Min, Max	2.0, 12.5	2.7, 11.0
Week 24		
n/nmiss	23/2	20/4
Mean (SD)	5.93 (3.05)	6.07 (2.58)
Median	5.00	5.29
Q1, Q3	3.54, 8.97	4.30, 7.68
Min, Max	1.8, 11.9	2.9, 11.7
Number of subjects included in analysis	22	20
Adjusted mean change (95% CI)	-0.396 (-0.630, -0.163)	0.223 (-0.015, 0.462)
Difference (95% CI)	-0.620 (-0.949, -0.291)	
p-value	0.0005	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.

Table 24 Analysis of covariance of change from baseline to week 24 in Subcutaneous adipose tissue (L). Full analysis set

Subcutaneous adipose tissue (L)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Week 0		
n/nmiss	24/1	22/2
Mean (SD)	14.35 (3.82)	14.01 (2.45)
Median	13.59	13.44
Q1, Q3	11.71, 16.68	12.98, 14.47
Min, Max	8.2, 25.7	9.4, 19.6
Week 24		
n/nmiss	23/2	19/5
Mean (SD)	12.75 (4.48)	14.18 (2.63)
Median	12.35	13.32
Q1, Q3	9.03, 16.60	12.53, 15.24
Min, Max	7.2, 25.0	9.2, 19.5
Number of subjects included in analysis	22	19
Adjusted mean change (95% CI)	-1.306 (-1.801, -0.810)	0.131 (-0.407, 0.668)
Difference (95% CI)	-1.436 (-2.158, -0.714)	
p-value	0.0003	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.

11.4.3.4.2 Percentage Liver Fat, Liver Volume and Total Liver Fat

No statistically significant changes in percentage liver fat (Table 25), liver volume (Table 98 in Section 14.2.2.5.2) or total liver fat (Table 99 in Section 14.2.2.5.2) between baseline and week 24 were observed for the dapagliflozin/exenatide group compared to the placebo group.

Similar results were obtained for the PPAS, see Section 14.2.2.5.2 (Table 100 to Table 102).

Table 25 Analysis of covariance of change from baseline to week 24 in Liver fat (%) Full analysis set

Liver fat (%)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Week 0		
n/nmiss	25/0	23/1
Mean (SD)	10.85 (10.63)	10.00 (8.48)
Median	7.60	7.50
Q1, Q3	2.90, 14.70	2.40, 15.70
Min, Max	0.9, 45.3	0.9, 26.5
Week 24		
n/nmiss	22/3	20/4
Mean (SD)	10.04 (10.59)	9.95 (9.39)
Median	6.10	6.15
Q1, Q3	2.80, 15.90	2.15, 16.95
Min, Max	1.2, 45.4	1.0, 33.0
Number of subjects included in analysis	22	20
Adjusted mean change (95% CI)	-1.41 (-2.75, -0.08)	-0.31 (-1.71, 1.08)
Difference (95% CI)	-1.10 (-3.01, 0.82)	
p-value	0.2537	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.

11.4.3.4.3 Body Fat as Measured by Bioimpedance

Body fat percentage (%) was analysed with the same method (MMRM) as the primary efficacy variable including the continuous fixed covariate of percentage baseline body fat (%) instead of body weight (kg).

No statistically significant changes in percentage total body fat between baseline and week 24 were observed in the dapagliflozin/exenatide group compared to the placebo group (Table 103 in Section 14.2.2.5.3). Similar results were obtained for the PPAS (Table 104 in Section 14.2.2.5.3).

11.4.3.4.4 Summary - Body Fat Composition

Statistically significant treatment effects of dapagliflozin/exenatide were observed on the change from baseline in total adipose tissue (-4.09 L; p=0.0004), visceral adipose tissue (-0.62 L; p=0.0005) and abdominal subcutaneous adipose tissue (-1.44 L; p=0.0003) following 24 weeks of treatment compared to placebo (Table 26). There were no statistically significant differences between treatment groups with regard to percentage liver fat, liver volume, total liver fat, total lean tissue or percentage body fat as measured by bioimpedance.

Table 26 Summary table of treatment differences at week 24 in change from baseline in body fat composition. Full analysis set

Variable[a]	Unit	Treatment difference at week 24[b]	(95% CI)	p-value
Total adipose tissue	**L**	**-4.085**	**(-6.232 to -1.938)**	**p=0.0004**
Visceral adipose tissue	**L**	**-0.620**	**(-0.949 to -0.291)**	**p=0.0005**
Subcutaneous adipose tissue	**L**	**-1.436**	**(-2.158 to -0.714)**	**p=0.0003**
Total lean tissue	L	-0.188	(-0.939 to 0.562)	p=0.6137
Body fat	%	-0.96	(-2.21 to 0.29)	p=0.1283
Liver fat	%	-1.10	(-3.01 to 0.82)	p=0.2537
Liver volume	L	0.056	(-0.030 to 0.142)	p=0.1964
Total liver fat	L	-0.006	(-0.056 to 0.044)	p=0.8119

[a] All variables were measured by MRI except percentage body fat which was assessed by bioimpedance.

[b] Least square estimate of the treatment difference at week 24 with 95% CI and corresponding p-value.

Source: Table 22 to Table 26 and Table 93 to Table 104.

11.4.3.5 HbA1c, Glucose Tolerance, Insulin Secretion, Insulin Sensitivity and Lipolysis Regulation

Descriptive data and the results of the statistical analyses for the FAS are presented in Section 11.4.3.5.1 (HbA1c), Section 11.4.3.5.2 (Glucose), Section 11.4.3.5.3 (IFG), Section 11.4.3.5.4 (IGT), Section 11.4.3.5.5 (IFG and/or IGT), Section 11.4.3.5.6 (Insulin), Section 11.4.3.5.7 (QUICKI index), Section 11.4.3.5.8 (Revised QUICKI index), Section 11.4.3.5.9 (weighted Matsuda index adjusted for UGE), Section 11.4.3.5.10 (Insulinogenic index), Section 11.4.3.5.11 (C-peptide), Section 11.4.3.5.12 (Glucagon), Section 11.4.3.5.13 (Glycerol), Section 11.4.3.5.14 (FFA) and Section 11.4.3.5.15 (Ketones).

A summary table is provided in Section 11.4.3.5.16. The corresponding tables for the PPAS are provided in Section 14.2.2.6. Individual data pertaining to this section are provided in Appendix 16.2.6.

11.4.3.5.1 Haemoglobin A1c

A statistically significant reduction in mean HbA1c levels between baseline (screening) and week 24 was observed for the dapagliflozin/exenatide group compared to the placebo group (p=0.0004; Table 27 and Table 105). The LS estimate of the difference in HbA1c reduction between treatment groups was -2.3 mmol/mol (95% CI=-3.5 to -1.1) at week 24.

The adjusted mean change from baseline to week 24 in HbA1c levels was -3.9 mmol/mol (95%CI=-4.7 to -3.1) in the dapagliflozin/exenatide group as compared to -1.6 mmol/mol (95%CI= -2.5 to -0.7) in the placebo group. The mean HbA1c levels during the 24-week treatment period are presented in Figure 4 (FAS) and Figure 22 (PPAS).

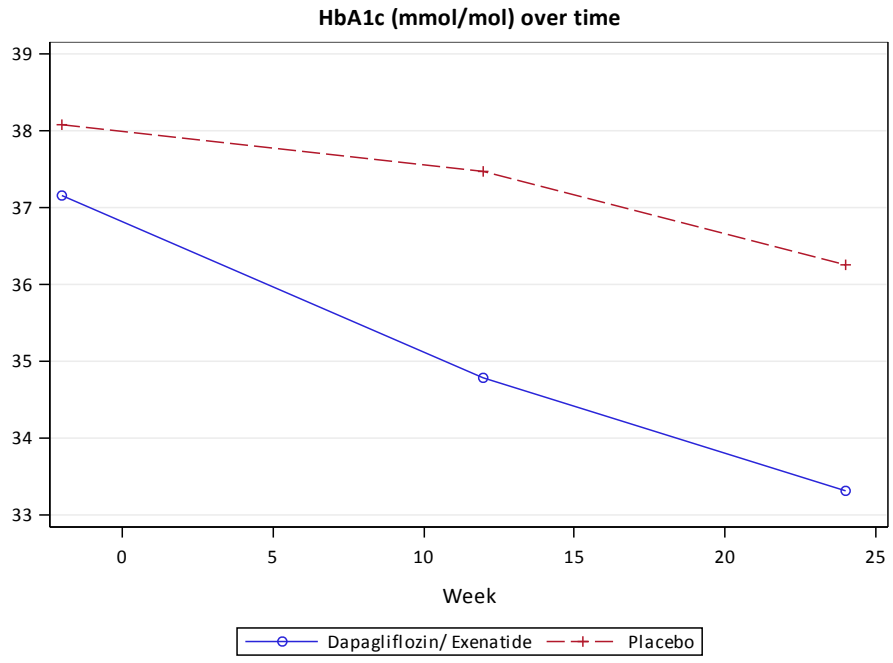
There was a corresponding statistically significant difference compared to placebo for the PPAS at week 24 (LS estimate: -2.4 mmol/mol [95% CI=-3.6 to -1.1); p=0.0004), see Section 14.2.2.6.1 (Table 106 and Table 107).

Table 27 Mixed model for repeated measures of change from baseline in HbA1c (mmol/mol) at week 24. Full analysis set

HbA1c (mmol/mol)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Screening		
n/nmiss	25/0	24/0
Mean (SD)	37.16 (3.87)	38.08 (3.32)
Median	37.00	37.50
Q1, Q3	35.00, 40.00	36.00, 40.00
Min, Max	29.0, 47.0	33.0, 49.0
Week 12		
n/nmiss	23/2	21/3
Mean (SD)	34.78 (3.34)	37.48 (3.39)
Median	34.00	37.00
Q1, Q3	32.00, 37.00	36.00, 39.00
Min, Max	28.0, 42.0	32.0, 47.0
Week 24		
n/nmiss	22/3	20/4
Mean (SD)	33.32 (4.02)	36.25 (3.55)
Median	33.00	36.00
Q1, Q3	31.00, 36.00	33.00, 38.00
Min, Max	27.0, 43.0	32.0, 47.0
Number of subjects included in analysis	25	24
Adjusted mean change (95% CI)	-3.9 (-4.7, -3.1)	-1.6 (-2.5, -0.7)
Difference (95% CI)	-2.3 (-3.5, -1.1)	
p-value	0.0004	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
A mixed model for repeated measures (MMRM) adjusted for treatment, week, treatment*week, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

Figure 4 HbA1c (mmol/mol) series plot by week. Full analysis set



11.4.3.5.2 Glucose

Fasting plasma glucose

A statistically significant reduction in fasting plasma glucose (FPG) between baseline (screening) and week 24 was observed for the dapagliflozin/exenatide group compared to the placebo group (p<0.0001; Table 28 and Table 109). The LS estimate of the difference in FPG reduction between treatment groups was -0.7 mmol/L (95% CI=-0.9 to -0.4) at week 24.

The adjusted mean change from baseline to week 24 in FPG levels was -0.4 mmol/L (95% CI=-0.6 to -0.2) in the dapagliflozin/exenatide group as compared to 0.3 mmol/L (95% CI=0.1 to 0.5) in the placebo group (Table 28). Mean FPG levels at screening, week 12 and week 24 are presented in Figure 5 (FAS) and Figure 23 (PPAS).

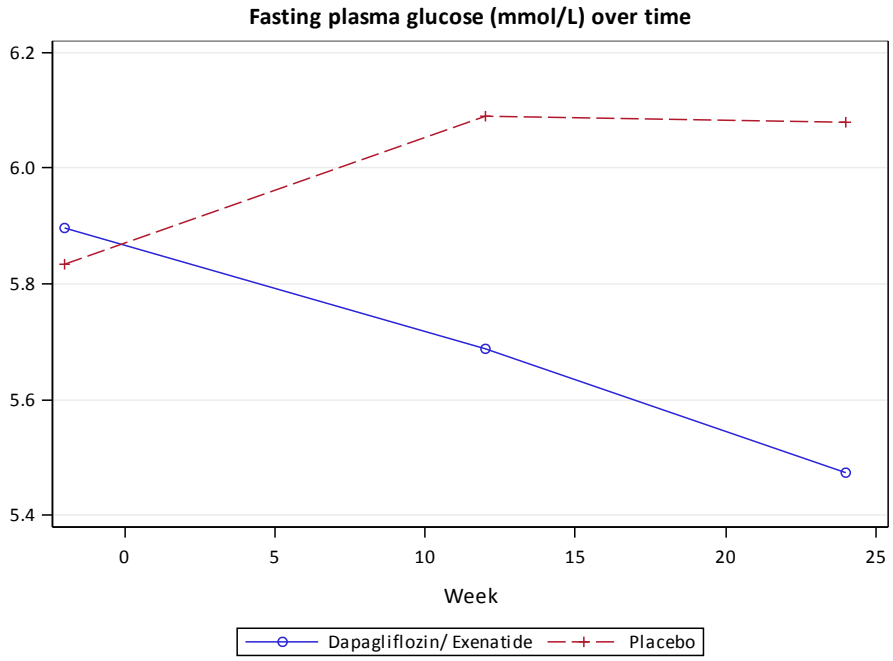
There was a corresponding statistically significant difference compared to placebo for the PPAS at week 24 (LS estimate: -0.7 mmol/L [95%CI=-1.0 to -0.4], p<0.0001), see Section 14.2.2.6.2 (Table 108, Table 110).

Table 28 Analysis of covariance of change from baseline to week 24 of Glucose (mmol/L) at time 0 min during the OGTT. Full analysis set

Glucose (mmol/L)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Screening		
n/nmiss	25/0	24/0
Mean (SD)	5.90 (0.63)	5.83 (0.43)
Median	5.80	5.75
Q1, Q3	5.40, 6.10	5.50, 6.10
Min, Max	5.0, 7.2	5.1, 6.6
Week 24		
n/nmiss	23/2	20/4
Mean (SD)	5.47 (0.52)	6.08 (0.69)
Median	5.40	5.95
Q1, Q3	5.20, 5.70	5.70, 6.40
Min, Max	4.7, 7.1	5.1, 8.3
Number of subjects included in analysis	23	20
Adjusted mean change (95% CI)	-0.41 (-0.61, -0.22)	0.25 (0.05, 0.46)
Difference (95% CI)	-0.66 (-0.94, -0.39)	
p-value	<.0001	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

Figure 5 **Fasting plasma glucose (mmol/L) series plot by week. Full analysis set**



120 min post-prandial plasma glucose

There was a statistically significant reduction in 120 minutes postprandial plasma glucose levels for the dapagliflozin/exenatide group compared to the placebo group at week 24 (p=0.0131, Table 29). The LS estimate of the difference in glucose reduction between treatment groups was -1.5 mmol/L (95% CI=-2.7 to -0.3) at week 24.

The adjusted mean change from baseline to week 24 in postprandial glucose levels was -1.6 mmol/L (95%CI= -2.4 to -0.8) in the dapagliflozin/exenatide group as compared to -0.1 mmol/L (95%CI=-0.9 to 0.8) in the placebo group (Table 29).

There was a corresponding statistically significant difference compared to placebo for the PPAS at week 24 (LS estimate: -1.5 mmol/L [95%CI= -2.7 to -0.3], p=0.0145), see Section 14.2.2.6.2 (Table 111).

Table 29 Analysis of covariance of change from baseline to week 24 of Glucose (mmol/L) at time 120 min during the OGTT. Full analysis set

Glucose (mmol/L)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Screening		
n/nmiss	25/0	24/0
Mean (SD)	7.99 (2.25)	7.10 (1.12)
Median	7.40	7.10
Q1, Q3	6.30, 10.00	6.45, 7.90
Min, Max	4.3, 12.8	4.8, 9.4
Week 24		
n/nmiss	23/2	20/4
Mean (SD)	6.07 (1.74)	7.42 (1.91)
Median	5.70	6.90
Q1, Q3	4.70, 7.00	6.10, 8.50
Min, Max	3.8, 10.8	4.3, 12.5
Number of subjects included in analysis	23	20
Adjusted mean change (95% CI)	-1.57 (-2.36, -0.78)	-0.08 (-0.93, 0.76)
Difference (95% CI)	-1.49 (-2.65, -0.33)	
p-value	0.0131	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

AUC $_{0\text{-}3h}$ (Plasma glucose)

A statistically significant reduction in mean $AUC_{0\text{-}3h}$ for plasma glucose between baseline (screening) and week 24 was observed in the dapagliflozin/exenatide group compared to the placebo group during the 3h-OGTT (p=0.0032, Table 30). The LS estimate of the difference in glucose mean $AUC_{0\text{-}3h}$ reduction between treatment groups was -223.1 mmol/L x 180 min (95% CI=-366.6 to -79.7) at week 24.

The adjusted mean change from baseline to week 24 in $AUC_{0\text{-}3h}$ for plasma glucose was -186.5 mmol/L x 180 min (95%CI=-287.0 to – 86.1) in the dapagliflozin/exenatide group as compared to 36.6 mmol/L x 180 min (95%CI=-65.3 to 138.5) in the placebo group (Table 30). The mean glucose levels during the 3h-OGGT at baseline and week 24 is presented per treatment group in Figure 6 (FAS) and Figure 24 (PPAS).

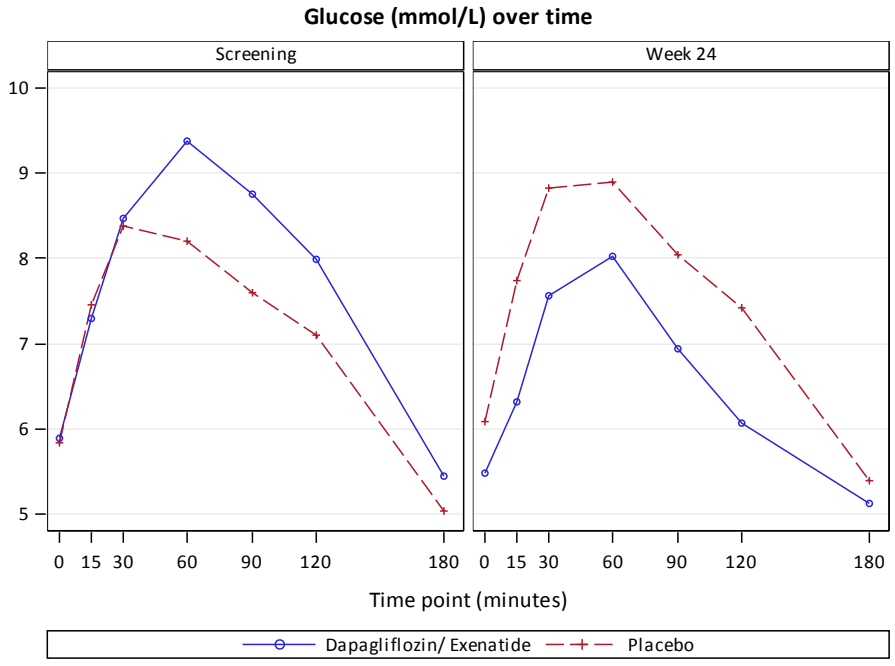
There was a corresponding statistically significant difference compared to placebo for the PPAS at week 24 (LS estimate: -225.3 mmol/L x 180 min [95%CI=-374.1 to -76.6], p=0.0040), see Section 14.2.2.6.2 (Table 112).

Table 30 Analysis of covariance of change from baseline to week 24 in Glucose AUC (mmol/L x 180 min). Full analysis set

Glucose AUC (mmol/L x 180 min)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Screening		
n/nmiss	24/1	24/0
Mean (SD)	1426.53 (310.00)	1288.53 (163.93)
95% CI for the mean	(1295.63, 1557.43)	(1219.31, 1357.75)
Geometric mean	1392.510	1278.670
%CV	21.7%	12.7%
Median	1515.75	1270.88
Q1, Q3	1179.00, 1644.38	1159.50, 1383.38
Min, Max	851.3, 1936.5	992.3, 1606.5
Week 24		
n/nmiss	22/3	20/4
Mean (SD)	1186.23 (230.48)	1364.03 (271.32)
95% CI for the mean	(1084.04, 1288.42)	(1237.04, 1491.01)
Geometric mean	1166.270	1341.280
%CV	19.4%	19.9%
Median	1139.63	1299.75
Q1, Q3	1011.00, 1357.50	1191.00, 1468.13
Min, Max	899.3, 1674.8	995.3, 2193.8
Number of subjects included in analysis	21	20
Adjusted mean change (95% CI)	-186.54 (-287.02, -86.07)	36.60 (-65.31, 138.50)
Difference (95% CI)	-223.14 (-366.63, -79.65)	
p-value	0.0032	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
CV = coefficient of variation.
CI = Confidence interval.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
Screening = week -2-(-1)

Figure 6 Glucose (mmol/L) series plots during the OGTTs. Full analysis set



11.4.3.5.3 Impaired Fasting Glucose

Impaired fasting glucose (IFG) was assessed at Time 0 of the 3h-OGTT at screening and at week 24. The threshold for IFG was categorized as FPG levels ≥5.6 mmol/L (*i.e.,* subjects with fasting FPG <5.6 mmol/L were categorized as having a normal FPG).

At week 24, there was a statistically significant difference in the proportion of subjects with IFG between the dapagliflozin/exenatide group and the placebo group (p=0.0009; Table 31). The proportion of subjects with IFG was lower in the dapagliflozin/exenatide group (34.8%) than in the placebo group (85.0%), see Table 31.

Within the dapagliflozin/exenatide group, there was a statistically significant reduction in the proportion of subjects with IFG, 30.4% shifted from raised to normal and 0% shifted from normal to raised between baseline (screening) and week 24 (p=0.0082), see Table 31. Within the placebo group, there was no statistically significant difference between baseline and week 24 (Table 31).

Similar results were obtained for the PPAS (p=0.0011 [Cochran-Mantel-Haenszel] and p=0.0082 [McNemar]), see Section 14.2.2.6.3 (Table 113).

Table 31 IFG category. Full analysis set

IFG	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Screening		
Normal	9 (36.0%)	7 (29.2%)
Raised	16 (64.0%)	17 (70.8%)
Week 24		
Normal	15 (65.2%)	3 (15.0%)
Raised	8 (34.8%)	17 (85.0%)
Shift from screening to week 24		
Normal, no change	8 (34.8%)	2 (10.0%)
Normal to raised	0	3 (15.0%)
Raised to normal	7 (30.4%)	1 (5.0%)
Raised, no change	8 (34.8%)	14 (70.0%)
p-value[1]	0.0082	0.3173
p-value[2]	0.0009	

[1]P-value of difference between baseline and week 24 based on a paired McNemar test.
[2]P-value of difference between treatments at week 24 based on a Cochran-Mantel-Haenszel test adjusted for baseline IFG category.
Screening = baseline

11.4.3.5.4 Impaired Glucose Tolerance

Impaired glucose tolerance (IGT) was assessed at Time 120 minutes during the 3h-OGTT at screening and at week 24. The threshold for IGT was categorized as FPG at Time 120 min ≥7.8 mmol/L (*i.e.*, subjects with IGT <7.8 mmol/L were categorized as having a normal glucose tolerance).

There was no statistically significant difference between treatment groups with regard to the proportion of subjects with IGT at week 24 (Table 32).

Within the dapagliflozin/exenatide group, there was a statistically significant reduction in the proportion of subjects with IGT, 34.8% shifted from raised to normal and 4.3% shifted from normal to raised between baseline and week 24 (p=0.0196),see Table 32. Within the placebo group, there was no statistically significant difference between baseline and week 24 (Table 32).

Similar results were obtained for the PPAS, see Section 14.2.2.6.4 (Table 114).

Table 32 IGT category. Full analysis set

IGT	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Screening		
Normal	13 (52.0%)	16 (66.7%)
Raised	12 (48.0%)	8 (33.3%)
Week 24		
Normal	19 (82.6%)	12 (60.0%)
Raised	4 (17.4%)	8 (40.0%)
Shift from screening to week 24		
Normal, no change	11 (47.8%)	9 (45.0%)
Normal to raised	1 (4.3%)	4 (20.0%)
Raised to normal	8 (34.8%)	3 (15.0%)
Raised, no change	3 (13.0%)	4 (20.0%)
p-value[1]	0.0196	0.7055
p-value[2]	0.0656	

[1]P-value of difference between baseline and week 24 based on a paired McNemar test.
[2]P-value of difference between treatments at week 24 based on a Cochran-Mantel-Haenszel test adjusted for baseline IGT.
Screening = baseline

11.4.3.5.5 Impaired Fasting Glucose and/or Impaired Glucose Tolerance

The number of subjects with IFG and/or IGT as defined in Section 11.4.3.5.3 and 11.4.3.5.4 was summarized in order to estimate the proportion of subjects who were prediabetic at baseline and at week 24.

At week 24, there was a statistically significant difference in the proportion of subjects with IFG and/or IGT for the dapagliflozin/exenatide group compared to the placebo group (p=0.0017; Table 33). The proportion of subjects with IFG and/or IGT was lower in the dapagliflozin/exenatide group (34.8%) than in the placebo group (85.0%), see Table 33.

Within the dapagliflozin/exenatide group, there was a statistically significant reduction in the proportion of subjects with IFG and/or IGT, 34.8% shifted from raised to normal and 0% shifted from normal to raised (p=0.0047), see Table 33. Within the placebo group there was no statistically significant difference (Table 33).

Similar results were obtained for the PPAS (p=0.0019 [Cochran-Mantel-Haenszel] and p=0.0047[McNemar]), see Section 14.2.2.6.5 (Table 115).

Table 33 Any IFG and/or IGT category. Full analysis set

Any IFG/IGT	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Screening		
Normal	8 (32.0%)	5 (20.8%)
Raised	17 (68.0%)	19 (79.2%)
Week 24		
Normal	15 (65.2%)	3 (15.0%)
Raised	8 (34.8%)	17 (85.0%)
Shift from screening to week 24		
Normal, no change	7 (30.4%)	2 (10.0%)
Normal to raised	0	1 (5.0%)
Raised to normal	8 (34.8%)	1 (5.0%)
Raised, no change	8 (34.8%)	16 (80.0%)
p-value[1]	0.0047	1.0000
p-value[2]	0.0017	

[1]P-value of difference between baseline and week 24 based on a paired McNemar test.
[2]P-value of difference between treatments at week 24 based on a Cochran-Mantel-Haenszel test adjusted for baseline IFG/IGT category.
Screening = baseline

11.4.3.5.6 Insulin

3h-OGTT Time 0 and 120 minutes (Insulin)

There was no statistically significant treatment effect of dapagliflozin/exenatide on insulin levels between baseline (screening) and week 24 at either Time 0 or at 120 minutes of the 3h-OGTT compared to placebo, see Table 38 and Section 14.2.2.6.6 (Table 116 and Table 117).

Similar results were obtained for the PPAS, see Section 14.2.2.6.6 (Table 118 and Table 119).

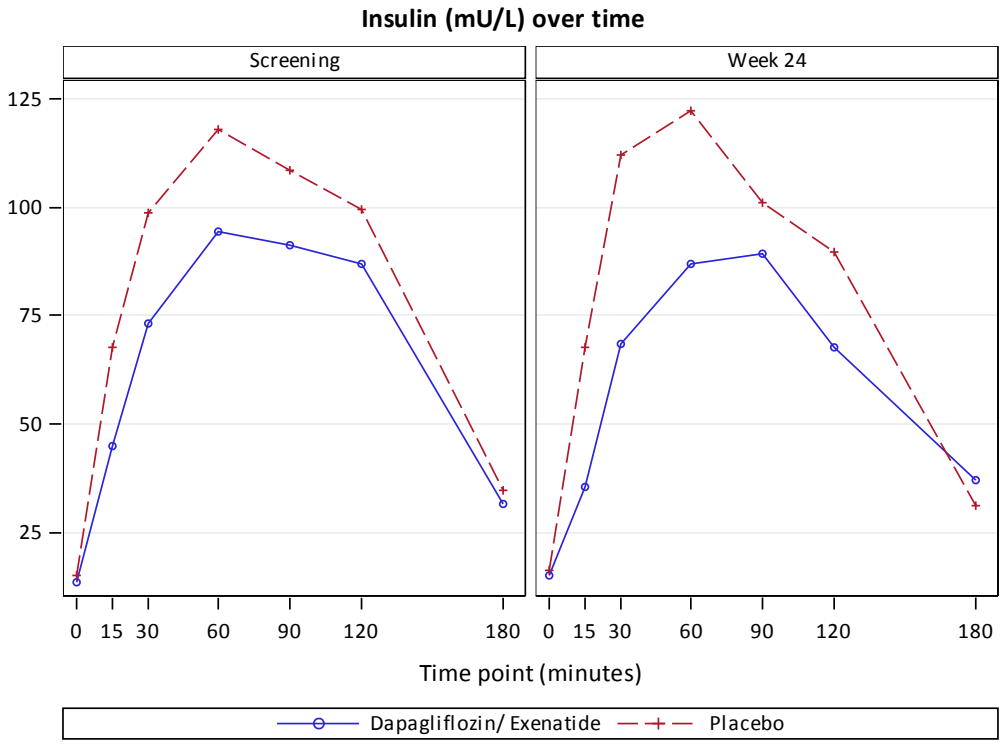
AUC $_{0\text{-}3h}$ (Insulin)

There was no statistically significant change in mean $AUC_{0\text{-}3h}$ for serum insulin between baseline (screening) and week 24 for the dapagliflozin/exenatide group compared to placebo, see Table 38 and Section 14.2.2.6.6 (Table 120).

The mean insulin levels during the 3h-OGGT at baseline and week 24 is presented per treatment group in Figure 7 (FAS) and Figure 25 (PPAS).

Similar results were obtained for the PPAS, see Section 14.2.2.6.6 (Table 121).

Figure 7 Insulin (mU/L) series plots during the OGTTs. Full analysis set



11.4.3.5.7 Quantitative Insulin Sensitivity Check Index

There was no statistically significant change in QUICKI index between baseline (screening) and week 24 in the dapagliflozin/exenatide group compared to the placebo group, see Table 38 and Section 14.2.2.6.7 (Table 122).

Within both groups, the QUICKI index was stable between baseline and week 24, suggesting that the insulin sensitivity was unaffected over the 24-week treatment period.

Similar results were obtained for the PPAS, see Section 14.2.2.6.7 (Table 123).

11.4.3.5.8 Revised Quantitative Insulin Sensitivity Check Index

There was no statistically significant change in the revised QUICKI index between baseline (screening) and week 24 for the dapagliflozin/exenatide group compared to the placebo group, see Table 38 and Section 14.2.2.6.8 (Table 124).

Within both groups, the revised QUICKI index was stable between baseline and week 24, suggesting that the insulin sensitivity was unaffected over the 24-week treatment period.

Similar results were obtained for the PPAS, see Section 14.2.2.6.8 (Table 125).

11.4.3.5.9 Weighted Matsuda Index Adjusted for Urinary Glucose Excretion

There was no statistically significant change in the weighted Matsuda index adjusted for UGE between baseline (screening) and week 24 in the dapagliflozin/exenatide group compared to the placebo group, see Table 38 and Section 14.2.2.6.9 (Table 126).

Similar results were obtained for the PPAS, see Section 14.2.2.6.9 (Table 127).

11.4.3.5.10 Insulinogenic Index

There was no statistically significant change in Insulinogenic index between baseline (screening) and week 24 for the dapagliflozin/exenatide group compared to placebo, see Table 38 and Section 14.2.2.6.10 (Table 128).

Similar results were obtained for the PPAS, see Section 14.2.2.6.10 (Table 129).

11.4.3.5.11 C-peptide

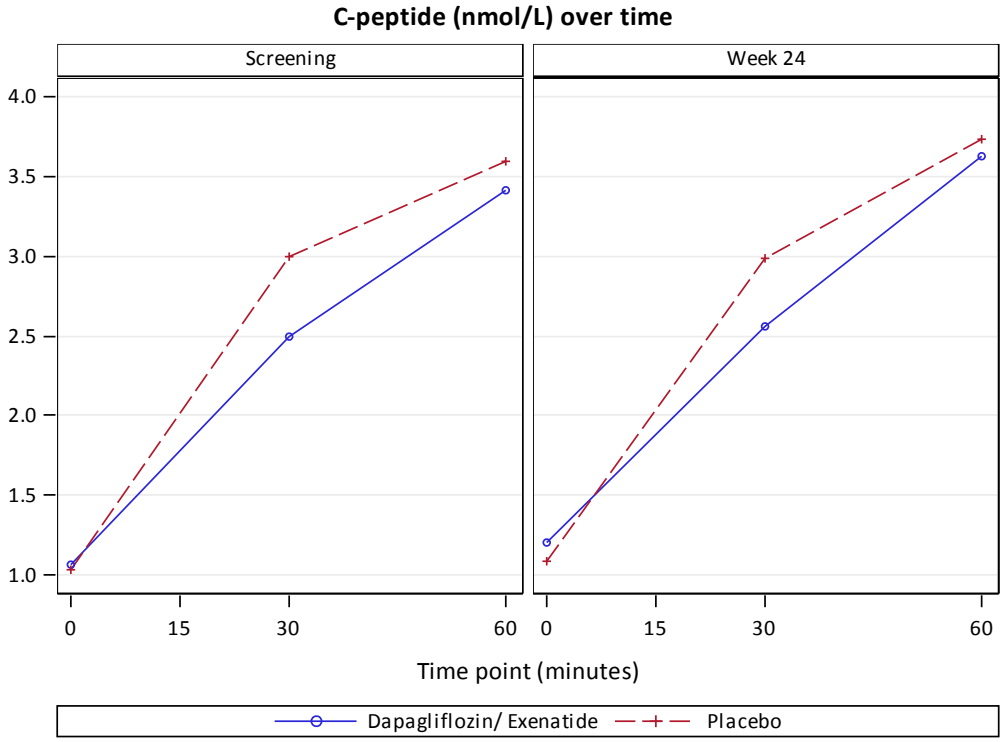
3h-OGTT Time 0, 30 and 60 minutes (C-peptide)

There was no statistically significant treatment effect of dapagliflozin/exenatide on C-peptide levels between baseline (screening) and week 24 at either Time 0, at 30 minutes or at 60 minutes compared to placebo, see Table 38 and Section 14.2.2.6.11 (Table 130 to Table 132).

The mean C-peptide levels during the first 60 minutes of the 3h-OGTT at baseline and week 24 are shown in Figure 8 (PPAS) and Figure 26 (FAS).

Similar results were obtained for the PPAS, see Section 14.2.2.6.11 (Table 133 to Table 135).

Figure 8 C-peptide (nmol/L) series plots during the OGTTs. Full analysis set



11.4.3.5.12 Glucagon

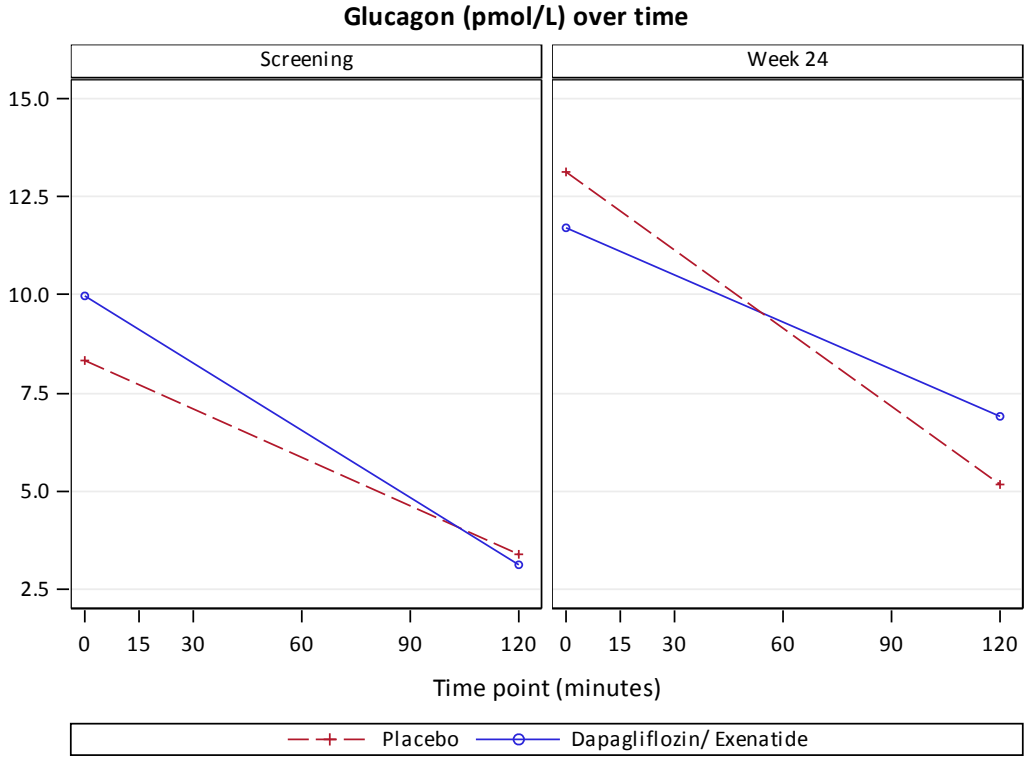
3h-OGTT Time 0 and Time 120 (Glucagon)

There was no statistically significant treatment effect of dapagliflozin/exenatide on mean glucagon levels between baseline (screening) and week 24 at either Time 0 or at 120 minutes compared to placebo, see Table 38 and Section 14.2.2.6.12 (Table 136 and Table 137).

The mean glucagon levels at 0 and 120 minutes of the 3h-OGTT at baseline and week 24 are shown in Figure 9 (FAS) and Figure 27(PPAS).

Similar results were obtained for the PPAS, see Section 14.2.2.6.12 (Table 138 to Table 139).

Figure 9 Glucagon (pmol/L) series plots during the OGTTs. Full analysis set



11.4.3.5.13 Glycerol

3h-OGTT Time 0, 30, 60 and 120 minutes (Glycerol)

There was no statistically significant treatment effect of dapagliflozin/exenatide on mean glucagon levels between baseline (screening) and week 24 at either Time 0, 30, 60 or 120 minutes compared to placebo, see Table 38 and Section 14.2.2.6.13 (Table 140 to Table 143).

The mean glycerol levels during the first 120 minutes of the 3h-OGTT at baseline and week 24 are shown in Figure 10 (FAS) and Figure 28 (PPAS).

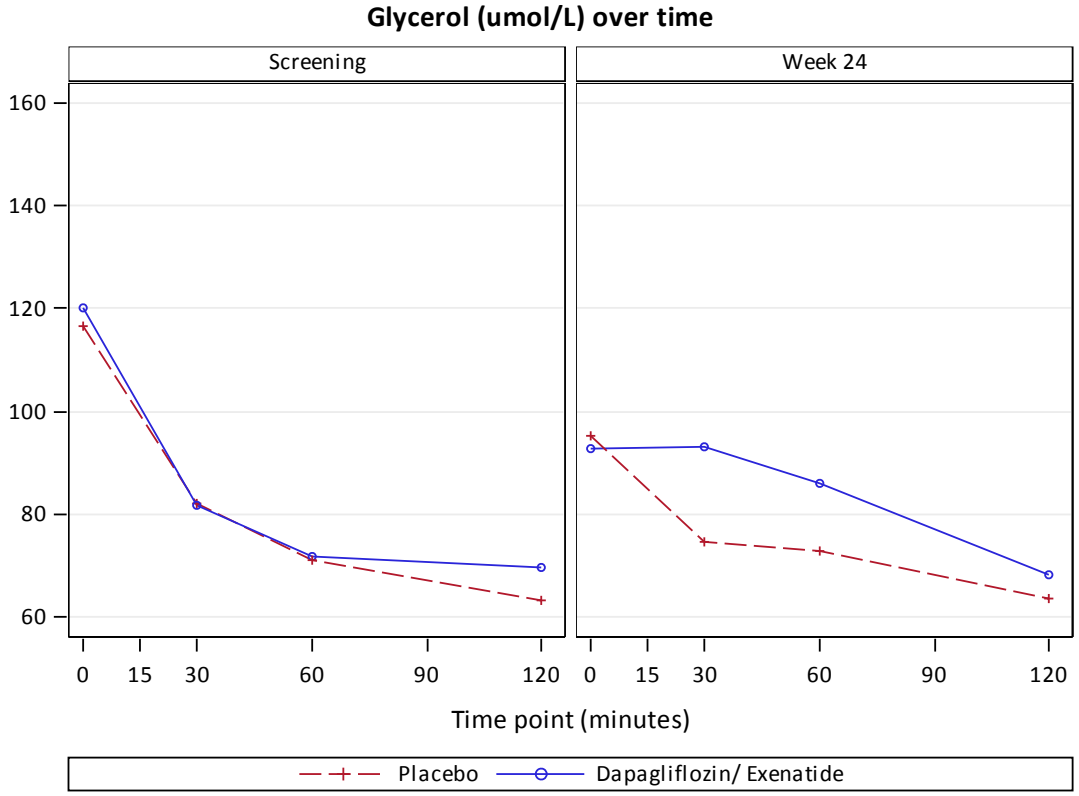
Similar results were obtained for the PPAS, see Section 14.2.2.6.13 (Table 144 to Table 147).

AUC $_{0\text{-}2h}$ (Glycerol)

There was no statistically significant treatment effect of dapagliflozin/exenatide on mean $AUC_{0\text{-}2h}$ for plasma glycerol between baseline (screening) and week 24 compared to placebo, see Section 14.2.2.6.13 (Table 148).

Similar results were obtained for the PPAS, see Section 14.2.2.6.13 (Table 149).

Figure 10 Glycerol (µmol/L) series plots during the OGTTs. Full analysis set



Incremental AUC $_{0\text{-}2h}$ (Glycerol)

There was no statistically significant treatment effect of dapagliflozin/exenatide on mean $iAUC_{0\text{-}2h}$ for plasma glycerol between baseline (screening) and week 24 compared to placebo, see Table 38 and Section 14.2.2.6.13 (Table 150).

Similar results were obtained for the PPAS, see Section 14.2.2.6.13 (Table 151).

11.4.3.5.14 Free Fatty Acids

3h-OGTT Time 0, 30, 60 and 120 minutes (FFA)

There was no statistically significant treatment effect of dapagliflozin/exenatide on plasma FFA levels between baseline and week 24 compared to placebo at Time 0 of the 3h-OGTT, see Table 38 and Section 14.2.2.6.14 (Table 152).

At 30, 60 and 120 minutes there were, on the other hand, statistically significant increases in FFA levels between baseline (screening) and week 24 in the dapagliflozin/exenatide group compared to the placebo group (p=0.0355, p=0.0033 and p=0.0129 at 30, 60 and 120 minutes, respectively; Table 34 to Table 36).

The LS estimates of the difference between treatment groups at week 24 were 25.3 µmol/L (95% CI=1.8 to 48.8) at 30 minutes (Table 34), 31.8 µmol/L (95% CI=11.3 to 52.4) at 60 minutes (Table 35) and 21.9 µmol/L (95% CI=4.9 to 39.0) at 120 minutes (Table 36).

The mean FFA levels during the first 120 minutes of the 3h-OGTT at baseline and week 24 are shown in Figure 11 (FAS) and Figure 29 (PPAS).

There was a corresponding statistically significant difference compared to placebo for the PPAS at week 24 at 60 minutes (LS estimate: 24.9 µmol/L [95%CI=8.9 to 50.0], p=0.0061) and at 120 minutes (LS estimate: 20.4 µmol/L [95%CI=3.2 to 37.5], p=0.0212), see Section 14.2.2.6.14 (Table 155 and Table 156). No other statistically significant differences were obtained in the PPAS, see Section 14.2.2.6.14 (Table 153 to Table 154).

Table 34 Analysis of covariance of change from baseline to week 24 of FFA (µmol/L) at time 30 min during the OGTT. Full analysis set

Free fatty acid (FFA) (µmol/L)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Screening		
n/nmiss	23/2	20/4
Mean (SD)	171.30 (80.02)	142.00 (52.45)
Median	177.00	133.50
Q1, Q3	100.00, 233.00	109.50, 185.50
Min, Max	61.0, 326.0	54.0, 243.0
Week 24		
n/nmiss	23/2	20/4
Mean (SD)	189.57 (59.09)	149.80 (37.67)
Median	192.00	149.50
Q1, Q3	144.00, 230.00	129.50, 175.50
Min, Max	79.0, 305.0	81.0, 235.0
Number of subjects included in analysis	23	20
Adjusted mean change (95% CI)	24.0 (8.0, 40.0)	-1.3 (-18.6, 15.9)
Difference (95% CI)	25.3 (1.8, 48.8)	
p-value	0.0355	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

Table 35 Analysis of covariance of change from baseline to week 24 of FFA (µmol/L) at time 60 min during the OGTT. Full analysis set

Free fatty acid (FFA) (µmol/L)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Screening		
n/nmiss	23/2	20/4
Mean (SD)	82.61 (50.48)	72.65 (46.61)
Median	79.00	64.00
Q1, Q3	40.00, 114.00	38.00, 95.50
Min, Max	19.0, 205.0	14.0, 191.0
Week 24		
n/nmiss	23/2	20/4
Mean (SD)	107.65 (49.48)	69.60 (37.04)
Median	98.00	51.00
Q1, Q3	73.00, 139.00	42.50, 97.50
Min, Max	26.0, 222.0	25.0, 140.0
Number of subjects included in analysis	23	20
Adjusted mean change (95% CI)	26.5 (12.4, 40.7)	-5.3 (-20.4, 9.8)
Difference (95% CI)	31.8 (11.3, 52.4)	
p-value	0.0033	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

Table 36 Analysis of covariance of change from baseline to week 24 of FFA (µmol/L) at time 120 min during the OGTT. Full analysis set

Free fatty acid (FFA) (µmol/L)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Screening		
n/nmiss	23/2	20/4
Mean (SD)	31.78 (22.24)	27.55 (23.38)
Median	24.00	21.00
Q1, Q3	17.00, 42.00	11.50, 30.00
Min, Max	1.0, 96.0	5.0, 99.0
Week 24		
n/nmiss	23/2	20/4
Mean (SD)	50.13 (36.49)	26.05 (18.69)
Median	35.00	19.00
Q1, Q3	24.00, 71.00	13.50, 31.50
Min, Max	4.0, 148.0	7.0, 70.0
Number of subjects included in analysis	23	20
Adjusted mean change (95% CI)	19.8 (8.1, 31.6)	-2.1 (-14.6, 10.4)
Difference (95% CI)	21.9 (4.9, 39.0)	
p-value	0.0129	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

AUC $_{0\text{-}2h}$ (FFA)

A statistically significant increase in mean $AUC_{0\text{-}2h}$ for plasma FFA between baseline (screening) and week 24 was observed in the dapagliflozin/exenatide group compared to the placebo group during the 3h-OGTT (p=0.0016, Table 37). The LS estimate of the difference in mean FFA $AUC_{0\text{-}2h}$ between treatment groups was 2871.5 µmol/L x 120 min (95% CI=1156.0 to 4586.9) at week 24.

The adjusted mean change from baseline to week 24 in $AUC_{0\text{-}2h}$ for plasma FFA was 2432.6 µmol/L x 120 min (95%CI= 1257.3 to 3607.9) in the dapagliflozin/exenatide group as compared to -438.9 µmol/L x 120 min (95%CI= -1697.2 to 819.4) in the placebo group (Table 37). The mean FFA levels during the 3h-OGGT at baseline and week 24 is presented per treatment group in Figure 11.

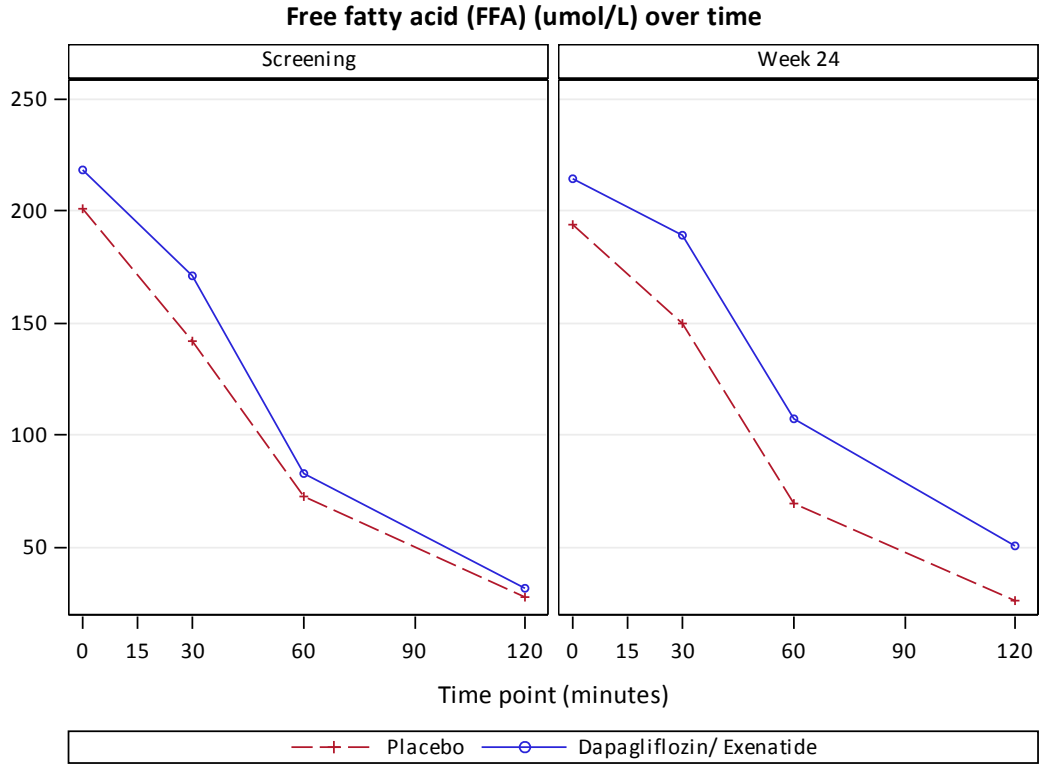
There was a corresponding statistically significant difference compared to placebo for the PPAS at week 24 (LS estimate: 2649.3 µmol/L x 120 min [95%CI=945.7 to 4352.8], p=0.0032), see Section 14.2.2.6.14 (Table 157).

Table 37 Analysis of covariance of change from baseline to week 24 in FFA AUC (µmol/L x 120 min). Full analysis set

FFA AUC (umol/L x 120 min)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Screening		
n/nmiss	23/2	20/4
Mean (SD)	13086.52 (5636.88)	11370.00 (4233.28)
95% CI for the mean	(10648.95, 15524.09)	(9388.76, 13351.24)
Geometric mean	11896.470	10704.680
%CV	43.1%	37.2%
Median	12705.00	10740.00
Q1, Q3	8760.00, 16515.00	8197.50, 13177.50
Min, Max	4425.0, 26025.0	6120.0, 20820.0
Week 24		
n/nmiss	23/2	20/4
Mean (SD)	15256.96 (4747.11)	11315.25 (3240.50)
95% CI for the mean	(13204.15, 17309.76)	(9798.65, 12831.85)
Geometric mean	14499.930	10919.870
%CV	31.1%	28.6%
Median	14460.00	10237.50
Q1, Q3	11130.00, 19020.00	9202.50, 13080.00
Min, Max	6630.0, 25440.0	6900.0, 18660.0
Number of subjects included in analysis	23	20
Adjusted mean change (95% CI)	2432.60 (1257.33, 3607.87)	-438.87 (-1697.16, 819.42)
Difference (95% CI)	2871.47 (1156.02, 4586.93)	
p-value	0.0016	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
CV = coefficient of variation.
CI = Confidence interval.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
Screening = week -2-(-1)

Figure 11 FFA (µmol/L) series plots during the OGTTs. Full analysis set



Incremental AUC $_{0\text{-}2h}$ (Free fatty acids)

There was no statistically significant treatment effect of dapagliflozin/exenatide on mean $iAUC_{0\text{-}2h}$ for plasma FFA between baseline (screening) and week 24 compared to placebo, see Table 38 and Section 14.2.2.6.14 (Table 158).

Similar results were obtained for the PPAS, see Section 14.2.2.6.14 (Table 159).

11.4.3.5.15 Ketones

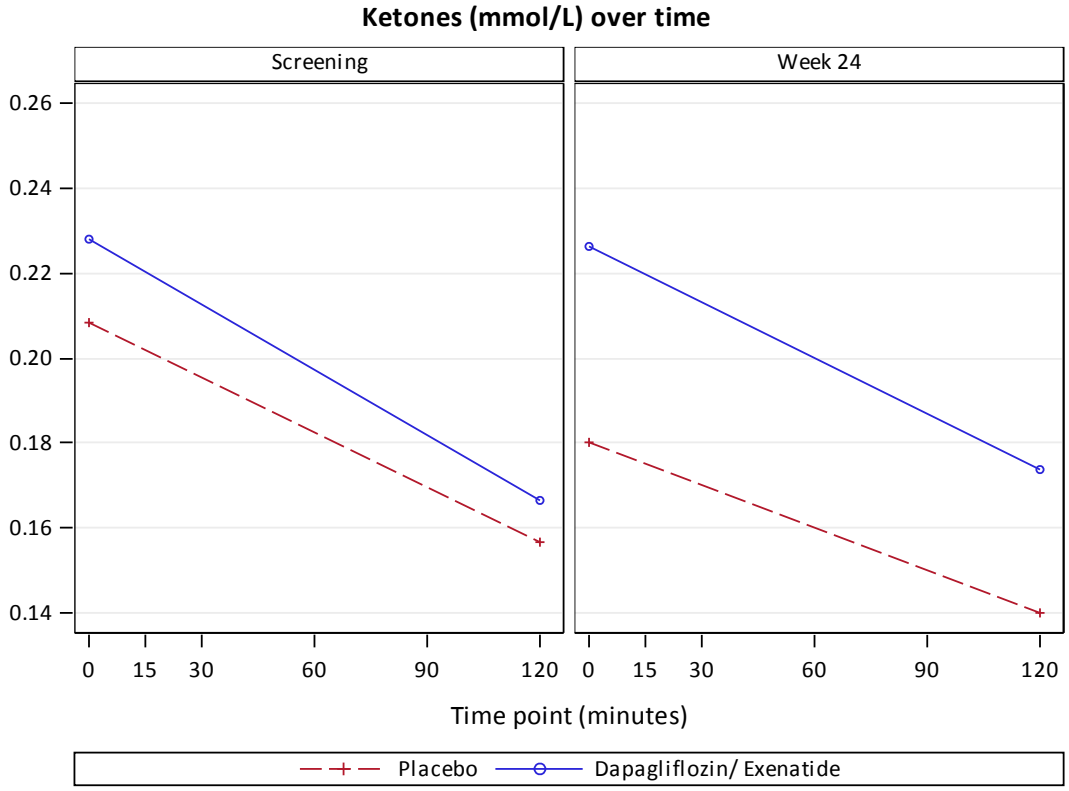
OGTT Time 0 and Time 120 minutes

There was no statistically significant treatment effect of dapagliflozin/exenatide on ketone levels between baseline and week 24 at either Time 0 or at 120 minutes compared to placebo, see Table 38 and Section 14.2.2.6.15 (Table 160 and Table 161).

The mean ketone levels at 0 and 120 minutes of the 3h-OGTT at baseline and week 24 are shown in Figure 12 (FAS) and in Figure 30 (PPAS).

Similar results were obtained for the PPAS, see Section 14.2.2.6.15 (Table 162 and Table 163).

Figure 12 Ketones (mmol/L) series plots during the OGTTs. Full analysis set



Suppression of ketones during OGTT

No statistically significant difference between treatment groups were observed in terms of suppression of blood ketones during the 3h-OGTT from screening to week 24, see Table 38 and Section 14.2.2.6.15 (Table 164).

Similar results were obtained for the PPAS, see Section 14.2.2.6.15 (Table 165).

11.4.3.5.16 Summary – Results from the 3h-OGTT

A statistically significant treatment effect of dapagliflozin/exenatide on the change from baseline in HbA1c (decrease), glucose (decrease) and FFA (increase) were observed following 24 weeks of treatment compared to placebo (Table 38).

There were no statistically significant differences between treatment groups in either glucose tolerance, insulin secretion or insulin sensitivity as measured by QUICKI index, Revised QUICKI index, weighted Matsuda index adjusted for UGE, Insulinogenic index or in blood levels of C-peptide, glucagon, glycerol or ketones over the 24-week treatment period compared to placebo.

Table 38 Summary table of treatment differences in glucose tolerance, insulin secretion, insulin sensitivity and lipolysis regulation at week 24. Full analysis set

Variable	Unit	Treatment difference at week 24[a]	(95% CI)	p-value
HbA1c	**mmol/L**	**-2.3**	**(-3.5 to -1.1)**	**p=0.0004**
Glucose 0 min (FPG)	**mmol/L**	**-0.66**	**(-0.94 to -0.39)**	**p<0.0001**
Glucose 120 min	**mmol/L**	**-1.49**	**(-2.65 to -0.33)**	**p=0.0131**
Glucose AUC_{0-3h}	**mmol/L x 180 min**	**-223.14**	**(-366,63 to -79.65)**	**p=0.0032**
Insulin 0 min	mU/L	0.37	(-5.78 to 6.52)	p=0.9039
Insulin 120 min	mU/L	-17.29	(-49.48 to 14.89)	p=0.2837
Insulin AUC_{0-3h}	mU/L x 180 min	-1904.77	(-5270.66 to 1461.13)	p=0.2587
QUICKI index	-	0.007	(-0.010 to 0.024)	p=0.4323
Revised QUICKI index	-	-0.001	(-0.007 to 0.005)	p=0.7378
Matsuda index[b]	-	0.61	(-0.48 to 1.70)	p=0.2658
Insulinogenic index	-	-7.431	(-21.497 to 6.636)	p=0.2916
C-peptide 0 min	nmol/L	0.050	(-0.110 to 0.210)	p=0.5288
C-peptide 30 min	nmol/L	-0.144	(-0.667 to 0.380)	p=0.5809
C-peptide 60 min	nmol/L	-0.104	(-0.617 to 0.408)	p=0.6829
Glucagon 0 min	pmol/L	-2.288	(-5.959 to 1.384)	p=0.2147
Glucagon 120 min	pmol/L	1.807	(-1.297 to 4.911)	p=0.2457
Glycerol 0 min	µmol/L	-4.1	(-23.0 to 14.7)	p=0.6605
Glycerol 30 min	µmol/L	18.9	(-0.2 to 38.1)	p=0.0524
Glycerol 60 min	µmol/L	12.7	(-17.0 to 42.5)	p=0.3927
Glycerol 120 min	µmol/L	2.2	(-15.1 to 19.5)	p=0.7978
Glycerol AUC_{0-2h}	µmol/L x 120 min	1074.66	(-1247.60 to 3396.92)	p=0.3550
Glycerol $iAUC_{0-2h}$	µmol/L/min	1595.4	(-334.2 to 3525.0)	p=0.1025
FFA 0 min	µmol/L	12.8	(-15.2 to 40.7)	p=0.3607
FFA 30 min	**µmol/L**	**25.3**	**(1.8 to 48.8)**	**p=0.0355**
FFA 60 min	**µmol/L**	**31.8**	**(11.3 to 52.4)**	**p=0.0033**
FFA 120 min	**µmol/L**	**21.9**	**(4.9 to 39.0)**	**p=0.0129**
FFA AUC_{0-2h}	**µmol/L x 120 min**	**2871.47**	**(1156.02 to 4586.93)**	**p=0.0016**
FFA $iAUC_{0-2h}$	µmol/L/min	1491.0	(-1041.1 to 4023.1)	p=0.2408
Ketones 0 min	mmol/L	0.05	(-0.02 to 0.11)	p=0.1488
Ketones 120 min	mmol/L	0.02	(-0.02 to 0.07)	p=0.2841
Ketones delta-delta	mmol/L	-0.010	(-0.084 to 0.065)	p=0.7930

[a] Least square estimates of the treatment difference at week 24 with 95% CI and corresponding p-value were calculated for all variables except IFG, IGT and IFG/IGT for which the treatment difference at week 24 was tested using a Cochran-Mantel-Haenszel test.

[b] The weighted Matsuda index was adjusted for UGE.

Source: Table 27 to Table 37 and FAS tables among Table 116 to Table 165.

11.4.3.6 Blood Lipid Profile

The blood lipid profile was assessed at screening (baseline), weeks 12 and 24.

Descriptive data and results of the statistical analyses of the FAS are presented in Section 11.4.3.6.1 (TC, LDL-C and HDL-C) and Section 11.4.3.6.2 (TG). A summary table is provided in Section 11.4.3.6.3. The corresponding tables for the PPAS are provided in Section 14.2.2.7. Individual data pertaining to this section are provided in Appendix 16.2.6.

11.4.3.6.1 Total Cholesterol, low-density Lipoprotein Cholesterol and high-density Lipoprotein Cholesterol

There was no statistically significant treatment effect of dapagliflozin/exenatide on mean serum TC levels, mean serum LDL-C levels or mean serum HDL-C levels between baseline and week 24 compared to placebo, see Table 39 and Section 14.2.2.7.1 (Table 166, Table 168 and Table 170).

Similar results were obtained for the PPAS, see Section 14.2.2.7.1 (Table 167, Table 169 and Table 171).

11.4.3.6.2 Triglycerides

There was no statistically significant treatment effect of dapagliflozin/exenatide on mean serum TG levels between baseline and week 24 compared to placebo, see Table 39 and Section 14.2.2.7.2 (Table 172).

Similar results were obtained for the PPAS, see Section 14.2.2.7.2 (Table 173).

11.4.3.6.3 Summary – Blood Lipid Profile

No statistically significant treatment effect of dapagliflozin/exenatide on the blood lipid profile was observed following 24 weeks of treatment compared to placebo (Table 39).

Table 39 Summary table of treatment differences at week 24 in blood lipid profile. Full analysis set

Variable	Unit	Treatment difference at week 24[a]	(95% CI)	p-value
TC	mmol/L	0.10	(-0.27 to 0.47)	p=0.5955
LDL-C	mmol/L	0.05	(-0.25 to 0.35)	p=0.7266
HDL-C	mmol/L	0.089	(-0.018 to 0.196)	p=0.1005
TG	mmol/L	-0.090	(-0.367 to 0.187)	p=0.5158

[a] Least squares estimate of the treatment difference at week 24 with 95% CI and corresponding p-value.

Source: Table 166 to Table 173.

11.4.3.7 Vital Signs

Vital signs (blood pressure and pulse) were assessed at screening, week 0 (baseline), weeks 4, 8, 12 and 24. A summary table is provided in Section 11.4.3.7.1. The corresponding tables for the PPAS are provided in Section 14.2.2.8. Individual data pertaining to this section are provided in Appendix 16.2.6.

Systolic blood pressure

A statistically significant reduction in mean systolic blood pressure between baseline and week 24 was observed in the dapagliflozin/exenatide group compared to placebo (p=0.0220; Table 40). The LS estimate of the difference between treatment groups was -6.7 mmHg (95% CI=-12.4 to -1.0) at week 24.

A statistically significant reduction in mean systolic blood pressure was observed in the dapagliflozin/exenatide group also at week 8 (-8.7 mmHg [95% CI=-14.4 to -3.1]; p=0.0032) compared to placebo (Table 40).

There were corresponding statistically significant differences compared to placebo for the PPAS at week 8 (LS estimate – 7.0 mmHg [95%CI=-12.5 to -1.53]; p=0.0136) and at week 24 (LS estimate -6.3 mmHg [95%CI=-12.6 to -0.1]; p=0.0470), see Section 14.2.2.8 (Table 174).

Table 40 Mixed model for repeated measures of change from baseline in Systolic blood pressure (mmHg). Full analysis set

Systolic blood pressure (mmHg)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Week -2(-1)		
n/nmiss	25/0	24/0
Mean (SD)	135.98 (17.65)	136.15 (15.46)
Median	136.00	135.75
Q1, Q3	121.50, 145.00	122.00, 148.75
Min, Max	108.0, 171.0	111.0, 167.5
Week 0 (Baseline)		
n/nmiss	25/0	24/0
Mean (SD)	133.68 (12.66)	133.81 (17.50)
Median	136.50	135.00
Q1, Q3	122.50, 144.50	119.50, 146.50
Min, Max	114.0, 162.5	95.0, 161.0
Week 4		
n/nmiss	25/0	24/0
Mean (SD)	129.02 (15.61)	136.17 (16.81)
Median	128.00	135.00
Q1, Q3	118.50, 140.00	123.00, 142.00
Min, Max	102.5, 159.0	115.0, 190.0
Adjusted mean change (95% CI)	-4.93 (-9.94, 0.07)	2.15 (-2.97, 7.27)
Difference (95% CI)	-7.08 (-14.20, 0.03)	
p-value	0.0511	
Week 8		
n/nmiss	24/1	23/1
Mean (SD)	124.48 (13.65)	134.20 (15.08)
Median	124.00	132.00
Q1, Q3	114.00, 135.25	122.00, 146.00
Min, Max	100.0, 150.0	110.0, 163.0
Adjusted mean change (95% CI)	-9.46 (-13.43, -5.48)	-0.71 (-4.80, 3.37)
Difference (95% CI)	-8.74 (-14.39, -3.09)	
p-value	0.0032	

Systolic blood pressure (mmHg)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Week 12		
n/nmiss	23/2	21/3
Mean (SD)	124.85 (15.50)	132.86 (12.59)
Median	123.50	133.00
Q1, Q3	110.00, 133.50	128.00, 142.00
Min, Max	105.0, 167.0	100.0, 155.0
Adjusted mean change (95% CI)	-8.59 (-12.98, -4.20)	-3.01 (-7.57, 1.56)
Difference (95% CI)	-5.58 (-11.87, 0.71)	
p-value	0.0806	
Week 24		
n/nmiss	23/2	20/4
Mean (SD)	124.07 (10.99)	133.33 (12.86)
Median	121.00	133.50
Q1, Q3	117.00, 133.00	125.25, 142.50
Min, Max	97.0, 142.5	111.0, 156.5
Adjusted mean change (95% CI)	-9.64 (-13.58, -5.70)	-2.95 (-7.09, 1.20)
Difference (95% CI)	-6.69 (-12.37, -1.01)	
p-value	0.0220	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
A mixed model for repeated measures (MMRM) adjusted for treatment, week, treatment*week, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.

Diastolic blood pressure and pulse

There was no statistically significant treatment effect of dapagliflozin/exenatide on either mean diastolic blood pressure or pulse between baseline and week 24 compared to placebo, see Table 41 and Section 14.2.2.8 (Table 175 and Table 177).

Similar results were obtained for the PPAS, see Section 14.2.2.8 (Table 176 and Table 178).

11.4.3.7.1 Summary – Vital Signs

A statistically significant treatment effect of dapagliflozin/exenatide on reduction of the change from baseline in mean systolic blood pressure was observed following 24 weeks of treatment compared to placebo (treatment difference -6.7 mmHg; p=0.0220). There were no statistically significant differences between treatment groups with regard to diastolic blood pressure or pulse (Table 41).

Table 41 Summary table of treatment differences at week 24 in vital signs

Variable	Unit	Treatment difference at week 24[a]	(95% CI)	p-value
Diastolic blood pressure	mm Hg	-0.48	(-7.06 to 6.10)	p=0.8827
Systolic blood pressure	**mm Hg**	**-6.69**	**(-12.37 to -1.01)**	**p=0.0220**
Pulse	beats/min	2.1	(-1.8 to 6.1)	p=0.2812

[a] Least squares estimate of the treatment difference at week 24 with 95% CI and corresponding p-value.

Source: Table 40 and Table 175 to Table 177.

11.4.3.8 Other Anthropometric Measurements

Measurements of waist and hip circumference (cm) were assessed at screening, week 0 (baseline), and weeks 4, 8, 12 and 24.

A summary table is provided in Section 11.4.3.8.4. The corresponding tables for the PPAS are provided in Section 14.2.2.9. Individual data pertaining to this section are provided in Appendix 16.2.4.

11.4.3.8.1 Waist Circumference

No statistically significant treatment effect of dapagliflozin/exenatide on mean waist circumference between baseline and week 24 was observed compared to placebo, see Table 43 and Section 14.2.2.9.1 (Table 179).

Similar results were obtained for the PPAS, see Section 14.2.2.9.1 (Table 180).

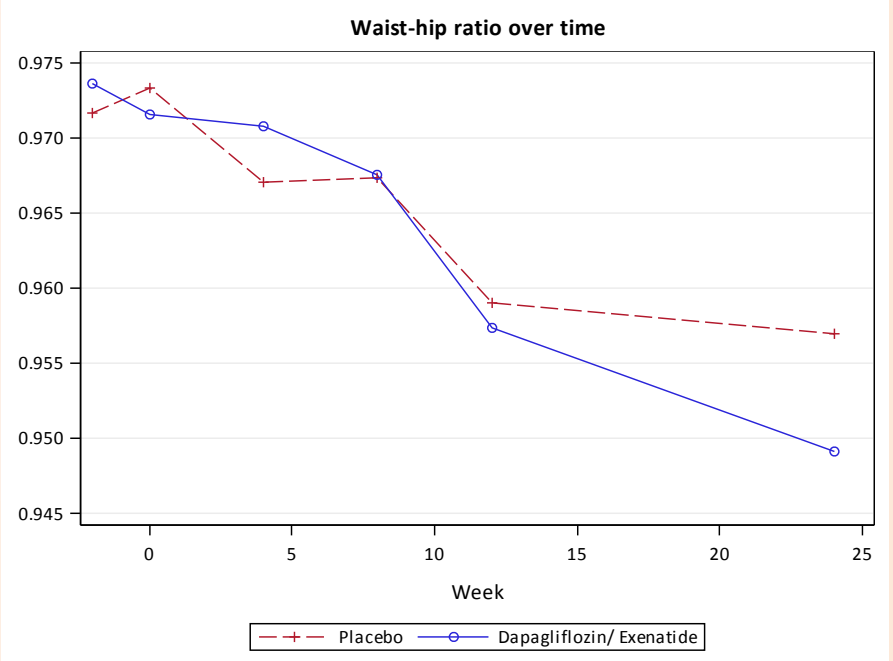
11.4.3.8.2 Waist-hip Ratio

No statistically significant treatment effect of dapagliflozin/exenatide on the mean WHR between baseline and week 24 was observed compared to placebo, see Table 43 and Section 14.2.2.9.2 (Table 181).

The mean WHR over time is displayed in Figure 13 (FAS) and in Figure 15 (PPAS).

Similar results were obtained for the PPAS, see Section 14.2.2.9.2 (Table 182).

Figure 13 Waist-hip ratio series plot by week. Full analysis set



11.4.3.8.3 Body Mass Index

A statistically significant treatment effect of dapagliflozin/exenatide on mean BMI between baseline and week 24 was observed compared to placebo (p=0.0008; Table 42 and Table 183). The LS estimate of the difference between treatment groups at week 24 was -1.4 kg/m^2 (95% CI=-2.2 to -0.6).

There was a corresponding statistically significant difference compared to placebo for the PPAS at week 24 (LS estimate -1.3 kg/m^2 [95%CI=-2.1 to -0.5]; p=0.0034), see Section 14.2.2.9.3 (Table 184).

Table 42 Mixed model for repeated measures of change in Body mass index (BMI) (kg/m^2) from baseline to week 24. Full analysis set

Body mass index (BMI) (kg/m2)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Week 0 (Baseline)		
n/nmiss	25/0	24/0
Mean (SD)	35.82 (2.88)	34.98 (3.69)
Median	36.13	33.92
Q1, Q3	33.74, 37.55	32.98, 35.95
Min, Max	30.9, 44.1	30.6, 44.8
Week 24		
n/nmiss	23/2	20/4
Mean (SD)	34.40 (4.01)	35.31 (4.05)
Median	35.05	34.14
Q1, Q3	30.82, 36.60	32.47, 37.50
Min, Max	26.1, 43.8	31.2, 45.3
Number of subjects included in analysis	25	24
Adjusted mean change (95% CI)	-1.501 (-2.043, -0.958)	-0.092 (-0.660, 0.475)
Difference (95% CI)	-1.408 (-2.192, -0.624)	
p-value	0.0008	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
A mixed model for repeated measures (MMRM) adjusted for treatment, week, treatment*week, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.

11.4.3.8.4 Summary - Other Anthropometric Measurements

A statistically significant treatment effect of dapagliflozin/exenatide on the change from baseline in BMI was observed following 24 weeks of treatment compared to placebo (treatment difference -1.4 kg/m^2; p=0.0008). There were no statistically significant differences between treatment groups with regard to waist circumference or WHR (Table 43).

Table 43 Summary table of treatment differences at week 24 in other anthropometric measurements. Full analysis set

Variable	Unit	Treatment difference at week 24[a]	(95% CI)	p-value
Waist circumference	cm	-2.77	(-5.91 to 0.37)	p=0.0827
WHR	-	-0.005	(-0.033 to 0.022)	p=0.7104
BMI	**(kg/m^2)**	**-1.408**	**(-2.192 to -0.624)**	**p=0.0008**

[a] Least squares estimate of the treatment difference at week 24 with 95% CI and corresponding p-value.

Source: Table 42, Table 179 and Table 181.

11.4.3.9 Urinary Glucose Excretion

Urine was collected for measurement of glucose excretion into the urine (U-glucose) during the 3h-OGTT at week 24. The data are presented as summary statistics in Table 44.

At week 24, the mean value of U-glucose was 189.5 mmol/L (SD=107.3) in the dapagliflozin/exenatide as compared to 0.95 mmol/L (SD=2.1) in the placebo group, i.e. 24 weeks of exposure to dapagliflozin/exenatide increased the excretion of glucose into the urine during the 3h-OGTT compared to placebo treatment.

Similar results were obtained for the PPAS, see Section 14.2.2.10 (Table 185).

Table 44 U-glucose (mmol/L). Full analysis set

Glucose (mmol/L)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Week 24		
n/nmiss	23/2	20/4
Mean (SD)	189.47 (107.28)	0.95 (2.05)
Median	188.00	0.30
Q1, Q3	112.00, 311.00	0.20, 0.65
Min, Max	45.8, 387.0	0.1, 9.4

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.

11.4.3.10 Estimated Glomerular Filtration Rate

No statistically significant treatment effect of dapagliflozin/exenatide on mean eGFR between baseline and week 24 was observed compared to placebo, see Section 14.2.2.11 (Table 186).

Similar results were obtained for the PPAS, see Section 14.2.2.11 (Table 187).

11.4.3.11 Model Building for Identification of Potential Covariates

Exploratory model building of potential covariates for the primary and secondary variables (weight change [kg] and percentage weight change [%]) was performed as described in detail in Section 9.7.10.3.14.

Baseline BMI and baseline WHR were identified as significant covariates for prediction of the outcome of the primary variable (Table 46). This means that the higher the BMI at baseline, the lower the weight reduction was observed at week 24. Conversely, a greater WHR at baseline is associated with a greater loss of weight after 24 weeks. As both BMI and WHR are measures of obesity the contradicting results should be interpreted with caution.

In line with the MMRM results of the primary variable presented in Section 11.4.1, the ANCOVA analysis used for the model building revealed a statistically significant treatment effect of dapagliflozin/exenatide on body weight (kg) compared to placebo following 24 weeks of treatment (Table 45). The LS estimate of the treatment difference was -4.0 kg (95% CI=-6.2 to -1.9; p=0.0005) at week 24.

In addition, no statistically significant treatment effects of dapagliflozin/exenatide on waist circumference or WHR were achieved which may be explained by methodological limitations, e.g. difficulties in measuring the waist and hip circumference consistently throughout the study.

Similar results were obtained for the secondary variable (percentage weight change [%]), see Table 47 and Table 48.

The corresponding tables for the PPAS are provided in Section 14.2.2.12 (Table 188 to Table 191).

Table 45 Analysis of covariance of change from baseline to week 24 in Body weight (kg). Full analysis set

Weight	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Number of subjects included in analysis	23	20
Adjusted mean change (95% CI)	-4.46 (-5.92, -3.00)	-0.46 (-2.02, 1.11)
Difference (95% CI)	-4.00 (-6.15, -1.86)	
p-value	0.0005	

CI = Confidence interval.
An analysis of covariance (ANCOVA) model adjusted for treatment, baseline WHR and baseline BMI was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 46 Analysis of covariance of change from baseline to week 24 in body weight (kg). Full analysis set

Effect	Levels	Reference	Estimate	Standard error	t-value	p-value
Treatment	Dapagliflozin/ Exenatide	No	-4	1.06	-3.78	0.0005
	Placebo	Yes				
Baseline BMI		No	0.65	0.18	3.54	0.0011
Baseline WHR		No	-14.64	6.22	-2.36	0.0236

Estimates based on an analysis of covariance (ANCOVA) model.

Table 47 Analysis of covariance of percentage change from baseline to week 24 in body weight (%). Full analysis set

Weight	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Number of subjects included in analysis	23	20
Adjusted mean change (95% CI)	-4.45 (-5.87, -3.04)	-0.46 (-1.97, 1.06)
Difference (95% CI)	-4.00 (-6.07, -1.92)	
p-value	0.0004	

CI = Confidence interval.
An analysis of covariance (ANCOVA) model adjusted for treatment, baseline WHR and baseline BMI was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 48 Analysis of covariance of percentage change from baseline to week 24 in body weight (%). Full analysis set

Effect	Levels	Reference	Estimate	Standard error	t-value	p-value
Treatment	Dapagliflozin/ Exenatide	No	-4	1.03	-3.89	0.0004
	Placebo	Yes				
Baseline BMI		No	0.66	0.18	3.70	0.0007
Baseline WHR		No	-13.63	6.03	-2.26	0.0295

Estimates based on an analysis of covariance (ANCOVA) model.

11.4.4 Statistical/Analytical Issues

11.4.4.1 Adjustments for Covariates

The mixed model for repeated measures (MMRM) was adjusted for treatment, week, treatment-by-week, gender and baseline value as covariates. In addition, the MMRM for the alternative analysis of the primary variable was adjusted for the interaction between baseline and week.

The covariance analysis (ANCOVA) was adjusted for treatment, gender and baseline value.

11.4.4.2 Handling of Dropouts or Missing Data

No imputations of missing data were performed for the FAS, PPAS and Safety analysis set.

For continuous variables for which analyses were performed using mixed-effects models for repeat measures (MMRM), missing values were handled by means of built-in maximum-likelihood based methods in the SAS procedures used for the analysis.

11.4.4.3 Interim Analyses and Data Monitoring

An interim safety evaluation, blinded to the whole study team and principal Investigator, was performed after all subjects had conducted 12 weeks of treatment. The objective of the interim analysis was to enable planning of future studies by AstraZeneca and was not part of the scientific and statistical evaluation of the study data.

During the evaluation, subject data and randomization codes were only made available to firewalled AstraZeneca staff, a statistician and a physician who performed the safety evaluation based on unblinded data, as this was found to exclude any major safety issue. No statistical analyses were performed with regard to the primary or secondary objectives of the study. The persons performing the safety evaluation were not involved in analysing the final data from the study, and did not have any contact with the statisticians doing so.

No formal statistical evaluation or summary from the safety evaluation were made or spread beyond the AstraZeneca statistician and physician performing the evaluation. No information from the evaluation was available for anyone at AstraZeneca included in the conduct of the study or for anyone involved with study activities at the site. No decision regarding study conduct (such as stopping the trial) was to be taken as a result of this administrative evaluation. Thus, no adjustments of the p-values or confidence intervals were needed when analysing the data after completion of the study as a result of this administrative action.

11.4.4.4 Multiple Comparison/Multiplicity

No control for multiplicity of endpoints was performed.

11.4.4.5 Examination of Subgroups

No subgroup analyses were performed in the study.

11.4.5 Tabulation of Individual Response

Individual subject data listings (efficacy response data) are provided in Appendix 16.2.4 and 16.2.6.

11.4.6 By-Patient Displays

Individual body weight curves between screening and week 24 are presented in Section 14.2.2.4 (Figure 16 to Figure 19).

11.4.7 Efficacy Conclusions

Primary Efficacy Variable

Mean Change in Body Weight (kg)

- A statistically significant treatment effect of dapagliflozin/exenatide on the mean change from baseline to week 24 in body weight (kg) was observed compared to placebo. Twenty-four weeks of treatment with dapagliflozin/exenatide reduced the mean body weight by -4.1 kg (95% CI=-6.4 to -1.8; p=0.0008) compared to placebo.

  Similar results were obtained for the PPAS: -3.7 kg (95% CI=-6.1 to -1.3; p=0.0036).

- A statistically significant dapagliflozin/exenatide-induced reduction of body weight compared to placebo was observed at weeks 8 and 12 (-1.7 kg [95% CI=-3.0 to -0.4; p=0.0136] and -3.5 kg [95% CI=-5.2 to -1.8; p=0.0002], respectively).

- A majority of the weight loss in the dapagliflozin/exenatide group occurred during the first 12 weeks of the 24-week treatment period. After week 12, the weight reduction diminished.

Alternative Primary Efficacy Model

Mean Change in Body Weight (kg)

- A statistically significant treatment effect of dapagliflozin/exenatide on the mean change from baseline to week 24 in body weight (kg) was observed compared to placebo. Twenty-four weeks of treatment with dapagliflozin/exenatide reduced the mean body weight by -4.2 kg (95% CI=-6.5 to -1.8; p=0.0008) compared to placebo.

  Similar results were obtained for the PPAS: -3.7 kg (95% CI=-6.2 to -1.3; p=0.0036).

Secondary Efficacy Variable

Percentage Change in Body Weight

- A statistically significant treatment effect of dapagliflozin/exenatide on the mean percentage change from baseline to week 24 in body weight (%) was observed compared to placebo. Twenty-four weeks of treatment with dapagliflozin/exenatide reduced the mean body weight by -4.2% (95% CI=-6.5 to -1.9; p=0.0006) compared to placebo.

  Similar results were obtained for the PPAS: -3.7% (95% CI=-6.1 to -1.4; p=0.0026).

Exploratory Variables

Proportion of subjects with at least 5% and 10% reduction of body weight at week 24

- The proportion of subjects with more than or equal to 5% weight loss at week 24 was 36.0% vs 0.0% in the dapagliflozin/exenatide and placebo group, respectively (FAS). Similar results were obtained for the PPAS (40.9% vs 0.0%).

- The proportion of subjects with more than or equal to 10% weight loss at week 24 was 12.0% vs 0.0% in the dapagliflozin/exenatide and placebo group, respectively. Similar results were obtained for the PPAS (13.6% vs 0.0%).

Mean change in body weight (kg) between screening and week 24

- A statistically significant treatment effect of dapagliflozin/exenatide on the mean change from screening to week 24 in body weight (kg) was observed compared to placebo. Twenty-four weeks of treatment with dapagliflozin/exenatide reduced the mean body weight by -4.5 kg (95% CI=-6.9 to -2.2; p=0.0003) compared to placebo.

  Similar results were obtained for the PPAS: -4.4 kg (95% CI=-6.9 to -1.9; p=0.0010).

Percentage change in body weight (%) between screening and week 24

- A statistically significant treatment effect of dapagliflozin/exenatide on the mean percentage change from screening to week 24 in body weight (%) was observed compared to placebo. Twenty-four weeks of treatment with dapagliflozin/exenatide reduced the mean body weight by -4.5% (95% CI=-6.8 to -2.2; p=0.0002) compared to placebo.

  Similar results were obtained for the PPAS: -4.3% (95% CI=-6.7 to -1.9; p=0.0009).

Body fat composition

- Statistically significant treatment effects of dapagliflozin/exenatide on the mean change from baseline to week 24 in total adipose tissue (L), visceral adipose tissue (L) and abdominal subcutaneous adipose tissue (L) were observed compared to placebo. Twenty-four weeks of treatment with dapagliflozin/exenatide reduced the mean volume of total adipose tissue by -4.09 L (95% CI=-6.23 to -1.94; p=0.0004), visceral adipose tissue by -0.62 L (95% CI=-0.95 to -0.29; p=0.0005) and abdominal subcutaneous adipose tissue by -1.44 L (95% CI=-2.16 to -0.71; p=0.0003) compared to placebo.
- No statistically significant treatment effect of dapagliflozin/exenatide on the mean change from baseline to week 24 in percentage liver fat (%), liver volume (L), total liver fat (L) or total lean tissue (L) were observed compared to placebo.
- A discrepancy between whole body MRI and bioimpedance for assessment of total body fat was observed. MRI data revealed a statistically significant reduction of total adipose tissue (L) in the dapagliflozin/exenatide group compared to placebo. In contrast, no statistically significant difference between treatment groups was achieved when bioimpedance was used for assessment of the percentage total body fat (%).

Haemoglobin A1c

- A statistically significant treatment effect of dapagliflozin/exenatide was observed on the mean change from baseline to week 24 in plasma HbA1c levels compared to placebo. Twenty-four weeks of treatment with dapagliflozin/exenatide significantly reduced the mean levels of HbA1c by -2.3 mmol/mol (95% CI=-3.5 to -1.1; p=0.0004) compared to placebo.

Fasting plasma glucose

- In response to a glucose challenge (3h-OGTT, 75 g glucose), a statistically significant treatment effect of dapagliflozin/exenatide was observed on the mean change from baseline to week 24 in both preprandial (Time 0) and 120 min postprandial plasma glucose levels compared to placebo. Twenty-four weeks of treatment with dapagliflozin/exenatide reduced the preprandial plasma glucose levels by -0.7 mmol/L (95% CI=-0.9 to -0.4; p<0.0001), the 2h-postprandial plasma glucose levels by -1.5 mmol/L (95% CI=-2.7 to -0.3; p=0.0131) and the mean AUC_{0-2h} by -223.1 mmol/L x 180 min (95% CI=-366.6 to -79.7; p=0.0032) compared to placebo.

Impaired fasting plasma glucose and impaired glucose tolerance

- The proportion of subjects with IFG (FPG ≥5.6 mmol/L) was significantly lower in the dapagliflozin/exenatide group compared to the placebo group (34.8% vs 85.0%; p=0.0009) at week 24. Within the dapagliflozin/exenatide group, but not within the placebo group, there was a statistically significant reduction in the proportion of subjects with IFG between baseline and week 24; 30.4% shifted from raised to normal and 0% shifted from normal to raised (p=0.0082).

- No statistically significant difference between treatment groups was observed with regard to the proportion of subjects with IGT (postprandial plasma glucose ≥7.8 mmol/L at Time 120 minutes during the 3h-OGTT) at week 24. Within the dapagliflozin/exenatide group, but not within the placebo group, there was a statistically significant reduction in the proportion of subjects with IGT between baseline and week 24; 34.8% shifted from raised to normal and 4.3% shifted from normal to raised (p=0.0196).
- The proportion of subjects with IFG and/or IGT was significantly lower in the dapagliflozin/exenatide group compared to the placebo group (34.8% vs 85.0%; p=0.0017) at week 24. Within the dapagliflozin/exenatide group, but not within the placebo group, there was a statistically significant reduction in the proportion of subjects with IFG and/or IGT between baseline and week 24; 34.8% shifted from raised to normal and 0% shifted from normal to raised (p=0.0047).

Insulin secretion and insulin sensitivity

- No statistically significant treatment effect of dapagliflozin/exenatide on the mean change from baseline to week 24 in either preprandial, 2h-postprandial serum insulin levels, or AUC_{0-3h} during the 3h-OGTT was observed compared to placebo.
- No statistically significant treatment effect of dapagliflozin/exenatide on the mean change from baseline to week 24 in insulin sensitivity, as estimated by the QUICKI index, the Revised QUICKI index or the weighted Matsuda index adjusted for UGE, was observed compared to placebo.
- No statistically significant treatment effect of dapagliflozin/exenatide on the mean change from baseline to week 24 in insulin secretion as estimated by the Insulinogenic index was observed compared to placebo.

Lipolysis regulation

- A statistically significant treatment effect of dapagliflozin/exenatide was observed on the mean change from baseline to week 24 in postprandial (but not preprandial) plasma FFA levels. Exposure to dapagliflozin/exenatide increased the postprandial plasma FFA levels during the 3h-OGTT at Time 30, 60 and 120 minutes and the treatment difference in mean change from baseline in AUC_{0-2h} was 2871.5 µmol/L x 120 min (95% CI=1156.0 to 4586.9; p=0.0016) compared to placebo.

  No statistically significant treatment effect of dapagliflozin/exenatide was observed on the mean change from baseline in $iAUC_{0-2h}$ for plasma FFA at week 24 compared to placebo.

Other variables

- No statistically significant treatment effects of dapagliflozin/exenatide on the mean change from baseline to week 24 in preprandial or postprandial blood levels of glucagon, glycerol, ketones or C-peptide during the 3h-OGTT were observed compared to placebo.

Blood lipid profile

- No statistically significant treatment effects of dapagliflozin/exenatide on the mean change from baseline to week 24 in the blood lipid profile, as estimated by serum levels of TC, LDL-C, HDL-C and TG, were observed compared to placebo.

Vital signs

- A statistically significant treatment effect of dapagliflozin/exenatide on the mean change from baseline to week 24 in systolic blood pressure (mm Hg) was observed compared to placebo. Exposure to dapagliflozin/exenatide lowered the mean systolic blood pressure by -6.7 mmHg (95% CI=-12.4 to -1.0; p=0.0220) compared to placebo.

  Also, at week 8, a statistically significant reduction of systolic blood pressure was observed in the dapagliflozin/exenatide group (-8.7 mmHg [95% CI=-14.4 to -3.1]; p=0.0032) compared to placebo.

- No statistically significant treatment effects of dapagliflozin/exenatide on the mean change from baseline to week 24 in diastolic blood pressure or pulse were observed compared to placebo.

Other anthropometric measurements

- A statistically significant treatment effect of dapagliflozin/exenatide on the mean change from baseline to week 24 in BMI (kg/m^2) was observed compared to placebo. Exposure to dapagliflozin/exenatide reduced the mean BMI by -1.4 kg/m^2 (95% CI=-2.2 to -0.6; p=0.0008) compared to placebo.

- No statistically significant treatment effect of dapagliflozin/exenatide on the mean change from baseline to week 24 of waist circumference or WHR were observed compared to placebo, possibly due to limited precision in the measurement of waist and hip circumference throughout the study.

Urinary excretion of glucose

- Twenty-four weeks of exposure to dapagliflozin/exenatide increased the excretion of glucose into the urine compared to placebo (189.5 mmol [SD=107.3] vs 0.95 mmol [SD=2.1]) during the 3h-OGTT.

Estimated glomerular filtration rate

- No statistically significant treatment effect of dapagliflozin/exenatide on the mean change from baseline to week 24 in eGFR was observed compared to placebo.

Model building to identify potential covariates

- Baseline BMI and baseline WHR were identified as significant covariates (p=0.0011 and p=0.0236) for prediction of the outcome of the primary variable. This means that the higher BMI at baseline, the lower weight reduction was observed at week 24. Conversely, a greater WHR at baseline is associated with a greater loss of weight after 24 weeks. As both BMI and WHR are measures of obesity the contradicting results should be interpreted with caution.

12. SAFETY EVALUATION

Safety data in this report are presented as extent of exposure (Section 12.1), clinical laboratory evaluation (Section 12.2), vital signs and other physical findings (Section 12.3), AEs (Section 12.4), and deaths, other SAEs, and other significant AEs (Section 12.5).

The safety conclusions are presented in Section 12.6.

Vital signs were both part of the safety evaluation and listed as one of the exploratory efficacy variables and data on mean change from baseline to week 24 are presented, per treatment group, in Section 11.4.3.7.

12.1 EXTENT OF EXPOSURE

The extent of exposure to IP is expressed as duration of exposure to exenatide injections (weekly) and duration of exposure to dapagliflozin tablets (daily), and is summarized for each treatment group in Table 49 and Table 50. Individual data are listed by subject in Appendix 16.2.5. For measurements of treatment compliance, refer to Section 11.3.

Based on data from all subjects, the mean duration of treatment with exenatide/matching placebo (weekly injections) was 22.7 weeks (SD=5.5) and 21.2 weeks (SD=6.2) in the dapagliflozin/exenatide and placebo group, respectively. The median duration of exposure was 24.0 weeks in both groups (range: 4.1 to 26.9 weeks in the dapagliflozin/exenatide group and 4.3 to 24.7 weeks in the placebo group), see Table 49.

The mean duration of treatment with dapagliflozin/matching placebo (daily administration) was 159 days (SD=38.5) versus 148 days (SD=43.2) in the dapagliflozin/exenatide and placebo group, respectively. The median duration of exposure was 168 days (24 weeks) in both groups (range 29 to 188 days in the dapagliflozin/exenatide group and 30 to 173 days in the placebo group), see Table 50.

Thus, there was a minor difference of approximately 11 days in mean duration of exposure between the groups: 22.7 vs 21.2 weeks for exenatide or matching placebo and 159 vs 148 days for dapagliflozin or matching placebo. This difference in duration of exposure reflects the lower drop-out rate in dapagliflozin/exenatide group (8.0%), compared to the placebo group (20.0%), as presented in Section 10.1.

Table 49 Duration of exposure to Exenatide injections (weekly). Safety analysis set

	Dapagliflozin/ Exenatide (N=25)	Placebo (N=25)
Duration of exposure (weeks)		
n/nmiss	25/0	25/0
Mean (SD)	22.71 (5.50)	21.17 (6.17)
Median	24.00	24.00
Q1, Q3	23.86, 24.43	23.86, 24.14
Min, Max	4.1, 26.9	4.3, 24.7

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.

Table 50 Duration of exposure to Dapagliflozin tablets (daily). Safety analysis set

	Dapagliflozin/ Exenatide (N=25)	Placebo (N=25)
Duration of exposure (days)		
n/nmiss	25/0	25/0
Mean (SD)	158.96 (38.52)	148.20 (43.20)
Median	168.00	168.00
Q1, Q3	167.00, 171.00	167.00, 169.00
Min, Max	29.0, 188.0	30.0, 173.0

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.

12.2 CLINICAL LABORATORY EVALUATION

12.2.1 Listing of Individual Laboratory Measurements by Patient

Listings of individual laboratory data for haematology and clinical chemistry are provided in Appendix 16.2.8. No data listing presenting each abnormal laboratory value is included in the report. Abnormalities assessed as clinically significant were instead reported as AEs in this study (see Section 12.2.3).

12.2.2 Laboratory Values Over Time

Haematology data (B-haemoglobin) and clinical chemistry data (creatinine, total bilirubin, ALP, AST, ALT, albumin, potassium, total calcium, sodium, CK and CRP) are summarised in Section 14.3.1 (Table 192 to Table 203).

Haematology and clinical chemistry data are presented as summary statistics and change from baseline to weeks 12 and 24 for all variables and the baseline samples were collected at screening.

No apparent differences between the treatment groups, or clinically significant changes in mean values from screening to week 24, were observed for any of the clinical chemistry laboratory variables.

An increase in mean and median haemoglobin values between screening and week 24 was indicated based on descriptive data, which is consistent with previous findings following dapagliflozin administration (Table 192).

A transient elevation of the mean CRP levels was observed at week 12 in the dapagliflozin/exenatide group (9.5 mg/L [SD=19.5] vs 3.4 mg/L [SD=2.3] in the placebo group), see Table 203 in Section 14.3.1. This transient increase in the mean CRP value was solely due to subject E135 who displayed elevated CRP levels (84 mg/L) following an incident involving head trauma which was reported as an SAE (PT injury) (see Section 12.5.1.2 for more details). The head trauma occurred on 19 May 2015 and the elevated CRP levels were measured 3 days later on 22 May 2015 (Visit 6). At Visit 7, the CRP levels were normalised (1.6 mg/L). For all other subjects, CRP levels were considered normal at all time points.

12.2.3 Individual Clinically Significant Abnormalities

The following subjects had an abnormal clinically significant laboratory finding reported as AE, assessed as related to IP:

- Subject E121 (placebo): Progression of hyperlipidaemia (PT hyperlipidaemia) was reported 13 weeks after start of treatment. The AE was assessed by the Investigator as mild and possibly related to IP. Atorvastatin (10 mg daily) was given as treatment for the AE but no action with the study treatment was taken. The subject completed the study, but had not

recovered from the AE at the last visit (Visit 7, week 24) (eCRF, Table 207, Table 208, Appendix 16.2.7).

- Subject E129 (placebo): Elevated levels of ketones (P-bOH-butyrate 2.3 mmol/L; PT blood ketone body increased) were observed for subject E129 at week 12 but was normalized 14 days later. The AE was assessed by the Investigator as possibly related to IP leading to premature withdrawal of the subject from the study (see also Section 12.4.4). The main reason for withdrawal of subject E129 was however not the elevated levels of ketones but rather severe non-compliance with the protocol and diet instructions. The subject was following an LCHF diet and not a 'balanced' diet as indicated in the study protocol. According to the Investigator, it is likely that a strict LCHF diet combined with dapagliflozin treatment contributed to the elevated levels of ketones (see also Section 10.2.1).

12.2.4 Creatinine Clearance

At baseline (screening), the mean value of creatinine clearance was similar in both treatment groups (146.0 mL/min [SD=43.0] vs 145.9 mL/min [SD=41.1]). Twenty-four weeks of exposure to dapagliflozin/exenatide led to a reduction of the creatinine clearance rate compared to placebo. The mean change from baseline to week 24 was -8.4 mL/min (SD=18.6) and 1.4 mL/min (SD=17.1) in the dapagliflozin/exenatide and placebo group, respectively, see Section 14.3.1 (Table 204.

As body weight is included as one of the variables in the formula for calculation of creatinine clearance, the reduced creatinine clearance observed in the dapagliflozin/exenatide group is probably attributable to the reduced mean body weight in this group.

Besides body weight, serum creatinine is a variable in the formula by Cockcroft-Gault (increased serum creatinine leads to a reduction in creatinine clearance rate). Data on serum creatinine levels at baseline, week 12 and week 24 are presented in Section 14.3.1 (see Table 193).

12.3 VITAL SIGNS, PHYSICAL FINDINGS, AND OTHER OBSERVATIONS RELATED TO EXPLORATORY EFFICACY

Vital signs (diastolic/systolic blood pressure and pulse) were assessed at baseline (screening), week 0 and weeks 4 to 24. Vital signs were included as an exploratory efficacy variable and data are presented as mean change from baseline to week 24, per treatment group, in Section 11.4.3.7. Individual data of vital signs are provided in Appendix 16.2.6.

A statistically significant treatment effect of dapagliflozin/exenatide was observed on systolic blood pressure following 24 weeks of treatment compared to placebo. Exposure to dapagliflozin/exenatide during 24 weeks lowered the mean systolic blood pressure by -6.7 mmHg (95% CI=-12.4 to -1.0; p=0.0220) compared to placebo (Section 11.4.3.7). No statistically significant treatment effects of dapagliflozin/exenatide on diastolic blood pressure or pulse were observed at week 24 compared to placebo (Section 11.4.3.7).

Occasional abnormal clinically significant findings related to vital signs and physical status were reported as AEs in the study (Section 9.7.11.4).

12.4 ADVERSE EVENTS

Additional summary tables pertaining to this section can be found in Section 14.3.2 (Table 205 to Table 208). Individual AE listings by subject are provided in Appendix 16.2.7 and individual laboratory measurements by subject are provided in Appendix 16.2.8.

12.4.1 Brief Summary of Adverse Events

An overview of the AEs, including intensity, relationship to IP, SAEs and AEs leading to withdrawal, is presented by treatment group in Table 51.

All 50 randomized subjects (100.0%) reported AEs during the study period. There were in total 281 AEs reported; 168 in the dapagliflozin/exenatide group and 113 in the placebo group.

Two subjects had SAEs during the study; 1 SAE (head trauma/injury) was reported by 1 subject in the dapagliflozin/exenatide group (4.0%) and 2 concomitant SAEs (dyspnoea and fatigue) were reported by 1 subject in the placebo group (4.0%). All SAEs were assessed by the Investigator as unlikely related to IP (for details, see Section 12.5.1.2).

Four subjects (16.0%) in the placebo group (of which one had non-compliance to the protocol as primary reason for withdrawal) and 2 subjects (8.0%) in the dapagliflozin/exenatide group were withdrawn due to AEs (for details, see Section 12.4.4).

Most AEs were mild in both treatment groups (206 AEs in total; 125 AEs reported by 23 subjects [92.0%] in the dapagliflozin/exenatide group and 81 AEs reported by 25 subjects [100.0%] in the placebo group). Moderate AEs (71 in total) were reported by 17 and 12 subjects in the dapagliflozin/exenatide and placebo groups, respectively. Thus, the proportion of subjects reporting moderate AEs was higher in the dapagliflozin/exenatide group compared to placebo (68.0% vs 48.0%). Severe AEs (4 in total) were reported by 1 subject (4.0%) in the dapagliflozin/exenatide group and by 2 subjects (8.0%) in the placebo group.

In both treatment groups, most AEs were assessed as possibly related to treatment (174 AEs in total; 107 in the dapagliflozin/exenatide group and 67 in the placebo group) or to have an unlikely relationship to treatment (100 AEs in total; 57 in the dapagliflozin/exenatide group and 43 in the placebo group). AEs assessed as related to treatment (7 AEs in total; 4 in the dapagliflozin/exenatide group and 3 in the placebo group) were reported at a comparable frequency in both treatment groups.

Overall, there were no major differences in AE severity or relationship to IP between the groups.

Table 51 Overview of adverse events. Safety analysis set

	Dapagliflozin/ Exenatide (N=25)		Placebo (N=25)	
	n (%)	m	n (%)	m
Any adverse events	25 (100.0%)	168	25 (100.0%)	113
Any serious adverse events	1 (4.0%)	1	1 (4.0%)	2
Adverse events leading to withdrawal	2 (8.0%)	3	4 (16.0%)[a]	6
Severity of adverse events				
Mild	23 (92.0%)	125	25 (100.0%)	81
Moderate	17 (68.0%)	42	12 (48.0%)	29
Severe	1 (4.0%)	1	2 (8.0%)	3
Causality of adverse events				
Unlikely related	19 (76.0%)	57	20 (80.0%)	43
Possibly related	23 (92.0%)	107	23 (92.0%)	67
Related	4 (16.0%)	4	3 (12.0%)	3

n is the number of subjects, m is the number of events.
Percentages are based on the number of subjects in the Safety analysis set.

[a] Includes subject E129 for whom the primary reason for discontinuation was non-compliance with diet instructions. However, the AE "blood ketone body increased" (potentially caused by the dietary non-compliance) contributed to the withdrawal.

12.4.2 Display of Adverse Events

All AEs are presented in Section 14.3.2; the incidence of AEs by SOC and PT, in Table 205, by severity in Table 206 (dapagliflozin/exenatide) and Table 207 (placebo), and by relationship to IP in Table 208.

The incidence of AEs, by SOC and PT, are summarized in Section 12.4.3.1, by severity in Section 12.4.3.2 and by relationship to IP in Section 12.4.3.3.

AEs of special interest for dapagliflozin and exenatide are presented in Section 12.4.3.1.1 (dapagliflozin) and Section 12.4.3.1.2 (exenatide).

Adverse events related to appetite regulation are presented in Section 12.4.3.1.3.

12.4.3 Analysis of Adverse Events

12.4.3.1 Adverse events by System Organ Class and Preferred term

The most common SOCs (reported by ≥20% of the subjects in any group) are summarized in Table 52 and the most common PTs (reported by ≥10% of the subjects in any group) are summarized in Table 53. All reported AEs are summarized by SOC and PT by treatment group, in Table 205 in Section 14.3.2.

The most common SOCs were:

- Gastrointestinal disorders: 18 subjects (72.0%) vs 13 subjects (52.0%) in the dapagliflozin/exenatide and placebo group, respectively.
- General disorders and administration site conditions: 16 subjects (64.0%) vs 17 subjects (68.0%) in the dapagliflozin/exenatide and placebo group, respectively.
- Nervous system disorders: 12 subjects (48.0%) vs 6 subjects (24.0%) in the dapagliflozin/exenatide group and placebo group, respectively.

The most common PTs were:

- Nasopharyngitis: 9 events reported by 9 subjects (36.0%) vs 4 events reported by 4 subjects (16.0%) in the dapagliflozin/exenatide and placebo group, respectively.
- Headache: 12 events reported by 8 subjects (32.0%) vs 4 events reported by 4 subjects (16.0%) in the dapagliflozin/exenatide and placebo group, respectively.
- Decreased appetite: 8 events reported by 8 subjects (32.0%) vs 3 events reported by 3 subjects (12.0%) in the dapagliflozin/exenatide and placebo group, respectively.

There was 1 subject (E114; 50-year old male), in the placebo group who was diagnosed with diabetes (PT *diabetes mellitus*) based on high FPG and high postprandial plasma glucose levels during the 3h-OGTT at the final study visit (Visit 7, week 24). The event, reported as an AE of moderate intensity, was assessed by the Investigator as unlikely related to study treatment.

Table 52 Most common adverse event system organ classes, reported by ≥20% of the subjects in any treatment group. Safety analysis set.

	Dapagliflozin/ Exenatide (N=25)		Placebo (N=25)	
System organ class/Preferred term	**n (%)**	**m**	**n (%)**	**m**
Gastrointestinal disorders	18 (72.0%)	37	13 (52.0%)	15
General disorders and administration site conditions	16 (64.0%)	36	17 (68.0%)	30
Nervous system disorders	12 (48.0%)	21	6 (24.0%)	12
Infections and infestations	11 (44.0%)	15	9 (36.0%)	12
Musculoskeletal and connective tissue disorders	11 (44.0%)	15	5 (20.0%)	9
Metabolism and nutrition disorders	10 (40.0%)	11	5 (20.0%)	5
Skin and subcutaneous tissue disorders	7 (28.0%)	9	3 (12.0%)	3
Renal and urinary disorders	5 (20.0%)	5	6 (24.0%)	6
Vascular disorders	2 (8.0%)	2	5 (20.0%)	5

Adverse events are coded according to MedDRA version 18.0E.
n is the number of subjects, m is the number of events
Percentages are based on the number of subjects in the Safety analysis set
Source: Based on Table 205 in Section 14.3.2

Table 53 Most common adverse event preferred terms reported by ≥10% of the subjects in any treatment group. Safety analysis set.

	Dapagliflozin/ Exenatide (N=25)		Placebo (N=25)	
System organ class/Preferred term	n (%)	m	n (%)	m
Nasopharyngitis	9 (36.0%)	9	4 (16.0%)	4
Headache	8 (32.0%)	12	4 (16.0%)	4
Decreased appetite	8 (32.0%)	8	3 (12.0%)	3
Injection site mass	7 (28.0%)	7	5 (20.0%)	5
Nausea	7 (28.0%)	8	3 (12.0%)	3
Injection site pruritus	7 (28.0%)	7	2 (8.0%)	2
Pollakiuria	5 (20.0%)	5	5 (20.0%)	5
Dizziness	5 (20.0%)	5	3 (12.0%)	4
Back pain	4 (16.0%)	4	2 (8.0%)	3
Fatigue	3 (12.0%)	3	6 (24.0%)	6
Arthralgia	3 (12.0%)	3	3 (12.0%)	3
Diarrhoea	3 (12.0%)	3	3 (12.0%)	3
Abdominal distension	3 (12.0%)	3	2 (8.0%)	2
Abdominal pain upper	3 (12.0%)	4	2 (8.0%)	2
Gastrooesophageal reflux disease	3 (12.0%)	3	1 (4.0%)	1
Vomiting	3 (12.0%)	4	1 (4.0%)	1
Hyperhidrosis	3 (12.0%)	3	1 (4.0%)	1
Injection site erythema	3 (12.0%)	3	1 (4.0%)	1
Oropharyngeal pain	3 (12.0%)	4	0	0
Cold sweat	3 (12.0%)	3	0	0
Hunger	1 (4.0%)	1	3 (12.0%)	3

Adverse events are coded according to MedDRA version 18.0E.
n is the number of subjects, m is the number of events
Percentages are based on the number of subjects in the Safety analysis set
Source: Based on Table 205 in Section 14.3.2

12.4.3.1.1 Adverse Events of Special Interest for Dapagliflozin

Given the mode of action of dapagliflozin, the AEs of special interest monitored in this study were genital infections, urinary tract infections, volume depletion-related events and renal impairment-related events. Reference listings of PTs, grouped into these 4 different categories, were provided by AstraZeneca and are included in Appendix 16.2.7.

Summary tables of reported AEs of special interest are presented by PT in Table 54 (urinary tract infections), Table 55 (genital infections) and Table 56 (volume depletion).

There were no reported AEs related to renal impairment.

Urinary tract infections

Urinary tract infections were reported by 2 subjects (8.0%) in the dapagliflozin/exenatide group (PT urinary tract infection fungal and PT pyelonephritis acute) and by 1 subject (4.0%) in the placebo group (PT urinary tract infection) (Table 54).

Genital infections

Genital infection was reported by 1 subject (4.0%) in the dapagliflozin/exenatide group (PT vaginal infection) (Table 55).

Events possibly related to volume depletion

The PT hypotension, which could be a sign of a volume depletion, was reported by 1 subject (4.0%) in the placebo group (Table 59).

In summary, the frequency of genital and urinary tract infections and events possibly related to volume depletion was low in both treatment groups and all events were of mild to moderate intensity (Table 206 and Table 207). There were no reported events related to renal impairment. Thus, there were no signs of a different AE pattern in this study than previously reported.

Table 54 Adverse events related to urinary infections

	Dapagliflozin/ Exenatide (N=25)		Placebo (N=25)	
Preferred term	**n (%)**	**m**	**n (%)**	**m**
Total subjects with an event	2 (8.0%)		1 (4.0%)	
Urinary tract infection	0	0	1 (4.0%)	1
Urinary tract infection fungal	1 (4.0%)	1	0	0
Pyelonephritis acute	1 (4.0%)	1	0	0

Adverse events are coded according to MedDRA version 18.0E.
n is the number of subjects, m is the number of events
Percentages are based on the number of subjects in the Safety analysis set
Source: Table 205 in Section 14.3.2 and listings of dapagliflozin-related side-effects in Appendix 16.2.7.

Table 55 Adverse events related to genital infections

	Dapagliflozin/ Exenatide (N=25)		Placebo (N=25)	
Preferred term	**n (%)**	**m**	**n (%)**	**m**
Total subjects with an event	1 (4.0%)		0	
Vaginal infection	1 (4.0%)	1	0	0

Adverse events are coded according to MedDRA version 18.0E.
n is the number of subjects, m is the number of events
Percentages are based on the number of subjects in the Safety analysis set
Source: Table 205 in Section 14.3.2 and listings of dapagliflozin-related side-effects in Appendix 16.2.7.

Table 56 Adverse events possibly related to volume depletion

	Dapagliflozin/ Exenatide (N=25)		Placebo (N=25)	
Preferred term	**n (%)**	**m**	**n (%)**	**m**
Total subjects with an event	0		1 (4.0%)	
Hypotension	0	0	1 (4.0%)	1

Adverse events are coded according to MedDRA version 18.0E.
n is the number of subjects, m is the number of events
Percentages are based on the number of subjects in the Safety analysis set
Source: Table 205 in Section 14.3.2 and listings of dapagliflozin-related side-effects in Appendix 16.2.7.

12.4.3.1.2 Adverse Events of Special Interest for Exenatide

AEs of special interest with regard to the mode of action of exenatide are gastrointestinal symptoms and injection site-related events. A reference listing of the gastrointestinal symptoms frequently observed in response to exenatide treatment was provided by AstraZeneca and is included in Appendix 16.2.7. This predefined list of MedDRA preferred terms consisted of a subset of relevant terms out of the full SOC Gastrointestinal disorders. The terms were judged to be of high interest in relation to previously observed AE patterns in GLP1 receptor agonist trials. Summary tables of reported AEs of special interest in relation to exenatide are presented by PT in Table 57 (gastrointestinal AEs) and Table 58 (injection site-related AEs).

Gastrointestinal adverse events

In the dapagliflozin/exenatide group, 16 of 25 subjects (64.0%) reported in total 26 gastrointestinal AEs based on a predefined list of MedDRA terms (Table 57). In the placebo group, 10 of 25 subjects (40.0%) reported in total 11 such AEs. Thus, the AEs of gastrointestinal nature were more frequently observed in the dapagliflozin/exenatide group compared to the placebo group.

The 3 most common gastrointestinal AEs were: nausea (28.0% vs 12.0%), diarrhoea (12.0% vs 12.0%) and abdominal distension (12.0% vs 8.0%).

Injection site-related adverse events

Injection site reactions were evaluated based on all injection site-related terms under the SOC General disorders and administration site conditions. In the dapagliflozin/exenatide group, 11 of 25 subjects (44.0%) reported in total 21 injection site-related AEs (Table 58). In the placebo group, 8 of 25 subjects (32.0%) reported in total 12 AEs injection site-related AEs. Thus, injection site-related AEs were also more frequently observed in the dapagliflozin/exenatide group compared to the placebo group.

The 3 most common injection site-related AEs were: injection site mass (28.0% vs 20.0%), injection site pruritus (28.0% vs 8.0%) and injection site erythema (12.0% vs 4.0%).

In conclusion, gastrointestinal symptoms and injection site-related events were more frequently observed in the group receiving active treatment compared to placebo and all events were of mild to moderate intensity (Table 57, Table 58, Table 206 and Table 207).

Table 57 Adverse events related to gastrointestinal symptoms

	Dapagliflozin/ Exenatide (N=25)		Placebo (N=25)	
Preferred term	n (%)	m	n (%)	m
Total subjects with an event	16 (64.0%)	26	10 (40.0%)	11
Nausea	7 (28.0%)	8	3 (12.0%)	3
Diarrhoea	3 (12.0%)	3	3 (12.0%)	3
Abdominal distension	3 (12.0%)	3	2 (8.0%)	2
Vomiting	3 (12.0%)	4	1 (4.0%)	1
Gastrooesophageal reflux disease	3 (12.0%)	3	1 (4.0%)	1
Constipation	2 (8.0%)	2	1 (4.0%)	1
Dyspepsia	2 (8.0%)	2	0	0
Abdominal pain	1 (4.0%)	1	0	0

Adverse events are coded according to MedDRA version 18.0E.
n is the number of subjects, m is the number of events
Percentages are based on the number of subjects in the Safety analysis set
Source: Table 205 in Section 14.3.2 and a listing of exenatide-related side-effects of gastrointestinal character in Appendix 16.2.7.

Table 58 Adverse events related to injection

	Dapagliflozin/ Exenatide (N=25)		Placebo (N=25)	
Preferred term	n (%)	m	n (%)	m
Total subjects with an event	11 (44.0%)	21	8 (32.0%)	12
Injection site mass	7 (28.0%)	7	5 (20.0%)	5
Injection site pruritus	7 (28.0%)	7	2 (8.0%)	2
Injection site erythema	3 (12.0%)	3	1 (4.0%)	1
Injection site nodule	2 (8.0%)	2	1 (4.0%)	1
Injection site swelling	0	0	2 (8.0%)	2
Injection site pain	1 (4.0%)	1	0	0
Injection site cyst	1 (4.0%)	1	0	0
Injection site rash	0	0	1 (4.0%)	1

Adverse events are coded according to MedDRA version 18.0E.
n is the number of subjects, m is the number of events
Percentages are based on the number of subjects in the Safety analysis set
Source: Table 205 in Section 14.3.2 and a listing of exenatide-related AEs of gastrointestinal character in Appendix 16.2.7.

12.4.3.1.3 Adverse Events Related to Regulation of Appetite

A small difference between treatment groups with regard to AEs related to appetite regulation was observed: decreased appetite (32.0% vs 12.0% in the dapagliflozin/exenatide and placebo group, respectively) vs hunger/increased appetite (8.0% vs 12.0%), see Table 205 in Section 14.3.2.

12.4.3.2 Adverse Events by Severity

All reported AEs are summarized by SOC, PT and severity (mild, moderate and severe) in Table 206 (dapagliflozin/exenatide group) in Section 14.3.2.2 and in Table 207 (placebo group) in Section 14.3.2.3.

The majority of the reported AEs were mild in both treatment groups: 125 of 168 reported AEs (74.4%) in the dapagliflozin/exenatide group and 81 of 113 reported AEs (71.7%) in the placebo group (Table 51, Table 206 and Table 207).

There were 71 AEs of moderate severity: 42 of 168 reported AEs (25.0%) in the dapagliflozin/exenatide group and 29 of 113 reported AEs (25.7%) in the placebo group (Table 51).

Four AEs were of severe intensity: 1 (PT injury) was reported by 1 subject in the dapagliflozin/exenatide group and 3 (PTs fatigue, dyspnoea and meniscus operation) were reported by 2 subjects in the placebo group (Table 51 and individual AE listings in Appendix 16.2.7).

Two subjects reported SAEs during the study; 1 SAE (head trauma/injury) was reported by 1 subject in the dapagliflozin/exenatide group (4.0%) and 2 concomitant SAEs (dyspnoea and fatigue) were reported by 1 subject in the placebo group (4.0%). All SAEs were of severe intensity and assessed by the Investigator as unlikely related to IP (for details, see Section 12.5.1.2).

In conclusion, there were no apparent differences in the severity of the AEs between the treatment groups.

12.4.3.3 Adverse Events by Relationship to IP

All reported AEs are summarized by SOC, PT and relationship to IP (not related and related) in Table 208, in Section 14.3.2.4.

The majority of the reported AEs were assessed as possibly related to the IP: 107 of 168 reported AEs (63.7%) in the dapagliflozin/exenatide group and 67 of 113 reported AEs (59.3%) in the placebo group (Table 51).

Seven AEs were assessed as related to IP: 4 AEs (2.4% of reported AEs) in the dapagliflozin/exenatide group and 3 AEs (2.7% of reported AEs) in the placebo group.

AEs assessed as unlikely related to treatment were also reported at a similar frequency in both groups: 57 AEs (33.9%) in the dapagliflozin/exenatide and 43 AEs (38.1%) in the placebo group.

In conclusion, there were no apparent differences in the relationship to IP of the AEs between the treatment groups.

12.4.4 Withdrawals due to Adverse Events

Six subjects were prematurely withdrawn from the study due to the occurrence of AEs or SAEs, 2 subjects in the dapagliflozin/exenatide group reporting 3 AEs and 4 subjects in the placebo group, reporting 6 AEs (the primary reason for withdrawal for one placebo subject, E129, was non-compliance to the study protocol), see Table 59 (overview) and Table 60 (detailed summary).

In the dapagliflozin/exenatide group, subject E145 was withdrawn after Visit 4, due to abdominal pain (PT abdominal pain), assessed as moderate and possibly related to IP and subject E156 was withdrawn after Visit 5, due to itching lump at injection site (PTs injection site mass and injection site pruritus, both moderate, possibly related to IP, see eCRF and Appendix 16.2.7.

In the placebo group, subject E103 was withdrawn after Visit 5, due to reported foot ulcer and suspected recurrence of vasculitis (PTs skin ulcer and vasculitis, both moderate and possibly related to IP), subject E115 was withdrawn after Visit 6, due to "not feeling well" (PT malaise, mild, possibly related to IP) and subject E153 was withdrawn after Visit 4 due to dyspnoea and fatigue (PTs dyspnoea and fatigue, SAEs, severe, unlikely related to IP), see eCRF and Appendix 16.2.7.
Subject E129 was withdrawn after Visit 6 due to high blood ketone levels (PT blood ketone body increased, moderate, possibly related), however the primary reason for discontinuation was "Severe non-compliance with the study protocol" (see Sections 10.1.2, 10.2.1 and 11.1).

Table 59 Adverse events leading to withdrawal of IP. Safety analysis set.

	Dapagliflozin/ Exenatide (N=25)		Placebo (N=25)	
System organ class/Preferred term	**n (%)**	**m**	**n (%)**	**m**
Vascular disorders	0	0	1 (4.0%)	1
Vasculitis	0	0	1 (4.0%)	1
Respiratory, thoracic and mediastinal disorders	0	0	1 (4.0%)	1
Dyspnoea	0	0	1 (4.0%)	1
Gastrointestinal disorders	1 (4.0%)	1	0	0
Abdominal pain	1 (4.0%)	1	0	0
Skin and subcutaneous tissue disorders	0	0	1 (4.0%)	1
Skin ulcer	0	0	1 (4.0%)	1
General disorders and administration site conditions	1 (4.0%)	2	2 (8.0%)	2
Fatigue	0	0	1 (4.0%)	1
Injection site mass	1 (4.0%)	1	0	0
Injection site pruritus	1 (4.0%)	1	0	0
Malaise	0	0	1 (4.0%)	1
Investigations	0	0	1 (4.0%)	1
Blood ketone body increased	0	0	1 (4.0%)	1

Adverse events are coded according to MedDRA version 18.0E.
n is the number of subjects, m is the number of events
Percentages are based on the number of subjects in the Safety analysis set

Table 60 Detailed summary of premature withdrawals due to adverse events. Safety analysis set.

Treatment group	Subject ID	AE (SOC/ PT)	Start date	Stop date	Onset after first dose (days)	Intensity/ Relationship	Action taken	Concom-itant treatment given	Outcome	Date of withdrawal	Concomitant AEs (PT)
Placebo	E103	Skin ulcer/ Skin and subcutaneous tissue disorders/ Vasculitis/ Vascular disorders	03 Feb 2015	Ongoing	46	Moderate/ Possibly related	Drug withdrawn	Heracillin	Not recovered/Not resolved	20 Feb 2015	Injection site swelling
Placebo	E115	Malaise/ General disorders and administration site conditions	13 Feb 2015	Ongoing	1	Mild/ Possibly related	Dose not changed	-	Recovering/ Resolving	06 May 2015	Dizziness, Tremor, Head discomfort
Placebo	E129[a]	Blood ketone body increased/Investigations	20 May 2015	04 Jun 2015	83	Moderate/ Possibly related	Drug withdrawn	-	Recovered/ Resolved	04 Jun 2015	-
Dapagliflozin/ exenatide	E145	Abdominal pain/ Gastrointestinal disorders	18 Mar 2015	24 Mar 2015	8	Moderate/ Possibly related	Drug withdrawn	-	Recovering/ Resolving	08 Apr 2015	-
Placebo	E153	Dyspnoea (SAE)/ Respiratory, thoracic and administration site conditions Fatigue (SAE)/ General disorders and administration site conditions	01 Apr 2015	Ongoing	22	Severe/ Unlikely related	Drug withdrawn	Cortisone Kåvepenin	Recovering/ Resolving	09 Apr 2015	Hunger
Dapagliflozin/ exenatide	E156	Injection site pruritus/ General disorders and administration site conditions Injection site mass/ General disorders and administration site conditions	26 Mar 2015	23 Apr 2015	15	Moderate/ Possibly related	Drug withdrawn	Hydro-cortisone, Miconazole, Clemastine	Recovered/ Resolved	15 Apr 2015	Headache, Pain in extremity, Injection site erythema, Pollakiuria, Decreased appetite, Diarrhoea

[a] The primary reason for withdrawal of subject E129 was severe non-compliance to the protocol, see Sections 10.1.2, 10.2.1 and 11.1. However, the AE "blood ketone body increased" (potentially caused by the dietary non-compliance) contributed to the withdrawal.
Source: Based on e-CRF data and individual subject listings in Appendix 16.2.7.

12.4.5 Listing of Adverse Events by Subject

AEs are listed by subject in Appendix 16.2.7.

12.5 DEATHS, OTHER SERIOUS ADVERSE EVENTS, AND OTHER SIGNIFICANT ADVERSE EVENTS

12.5.1 Listing of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

All individual data on SAEs are included in the AE listing in Appendix 16.2.7.

12.5.1.1 Deaths

No deaths occurred in the study.

12.5.1.2 Other Serious Adverse Events

Three SAEs (PTs dyspnoea and fatigue reported for subject E153 and PT *injury* reported for subject E135) occurred in the study. A summary is provided in Table 61.

Subject E135 (dapagliflozin/exenatide group) experienced one SAE; head trauma (PT injury). The SAE criterion was hospitalisation. Briefly, subject E135 was on vacation in Greece when developing nausea and fever. The subject got up during the night to take paracetamol and probably fainted. The subject went to the hospital (19 May 2015) for face and thorax x-ray, the head was sutured and she was transferred to another hospital for a CT scan with no findings. The subject was administered i.v. antibiotics (unknown type and dose, 19 May 2015) and was discharged from the hospital in the evening 20 May 2015. The subject was prescribed amoxicillin (daily dose 1500 mg, 21 – 31 May 2015) and returned to Sweden (as planned) 21 May 2015. The subject attended study visit 6 (22 May 2015) and a neurological examination was performed: cranial nerves, balance and coordination, upper and lower body strength, reflexes and higher functions were tested without pathological findings. Also heart and lung function were examined without any findings. The injury, head trauma after fainting, was judged by the Investigator to be due to dehydration and low blood pressure.

The event was assessed by the Investigator as severe in intensity and unlikely related to treatment. The subject temporarily stopped with the study treatment (for unknown number of days), but completed the study. The subject recovered from the event (end date: 13 Aug 2015, duration: 86 days; eCRF and Appendix 16.2.7).

Subject E153 (placebo group) experienced 2 concomitant SAEs; dyspnoea and fatigue (PTs dyspnoea and fatigue). The SAE criterion was hospitalisation. Briefly, the subject's medical history included asthma, sleep apnoea, pituitary insufficiency affecting thyroid and gonadal axis, stented coronary artery due to myocardial infarction, hypertension. At study visit 4 (07 Apr 2015), subject E153 reported dyspnoea, fatigue, possibly fever and productive green and brown cough, aspiration of reflux acid and common cold symptoms, causing the subject to stay home from work. Dyspnoea and fatigue were reported as AEs, with start date 01 Apr 2015. The subject was prescribed prophylactic antibiotics (Kåvepenin, daily dose 3 g, unknown duration) but laboratory results later showed normal CRP which ruled out bacterial infection. The subject was sent to Huddinge medical emergency unit on 07 Apr 2015, to rule out cardiopulmonary event. Cardiopulmonary event was ruled out and the subject received cortisone (daily dose 30 mg, ongoing at the subject's last visit) with good effect. The subject was still dyspnoeic but was recovering at the last study visit 09 Apr 2015.

The events were assessed by the Investigator as severe in intensity and as unlikely related to treatment. Due to the subject's condition, the subject stopped treatment with IP and was withdrawn from the study (09 Apr 2015), after study visit 4. The Investigator judgement was that the subject's original condition (*i.e.*, progress of known pituitary insufficiency) might have contributed to the events (eCRF and Appendix 16.2.7).

Table 61 Serious adverse events. Safety analysis set

System organ class/Preferred term	Dapagliflozin/ Exenatide (N=25) n (%)	m	Placebo (N=25) n (%)	m
Respiratory, thoracic and mediastinal disorders	0	0	1 (4.0%)	1
Dyspnoea[a]	0	0	1 (4.0%)	1
General disorders and administration site conditions	0	0	1 (4.0%)	1
Fatigue[a]	0	0	1 (4.0%)	1
Injury, poisoning and procedural complications	1 (4.0%)	1	0	0
Injury[b]	1 (4.0%)	1	0	0

Adverse events are coded according to MedDRA version 18.0E.
n is the number of subjects, m is the number of events
Percentages are based on the number of subjects in the Safety analysis set
[a] The PTs dyspnoea and fatigue refer to subject E153.
[b] The PT injury refers to subject E135.

12.5.1.3 Other Significant Adverse Events

No other significant AEs occurred in the study. No pregnancies were reported.

12.5.2 Narratives of Deaths, Other Serious Adverse Events, and Certain Other Significant Adverse Events

Not applicable since all SAEs were assessed by the Investigator as unlikely related to IP (for details, see Section 12.5.1.2).

12.5.3 Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

All SAEs were assessed by the Investigator as unlikely related to IP (for details, see Section 12.5.1.2).

12.6 SAFETY CONCLUSIONS

- No safety concerns were identified for the combined treatment with dapagliflozin (10 mg once daily) and exenatide (2 mg weekly injections) during 24 weeks in obese otherwise healthy subjects based on clinical laboratory tests, creatinine clearance, vital signs and AEs/SAEs.
- The mean duration of exposure and treatment compliance was largely similar in both treatment groups.
- There were no major changes in mean laboratory values during the study and no apparent differences between treatment groups.
- All 50 randomized subjects reported AEs (281 AEs in total, 168 AEs in the dapagliflozin/exenatide group and 113 AEs in the placebo group). Thus, the total number of AEs reported in the dapagliflozin/exenatide group was approximately 20 percentage points higher compared to the total number of AEs reported in the placebo group.
- A majority of the AEs (206 of 281 AEs in total; 73.3%) were of mild intensity. Most AEs were assessed as related or possibly related to treatment (181 of 281 AEs in total; 64.4%). There were no apparent differences in AE severity or relationship to IP between the groups.
- Six subjects were prematurely withdrawn from the study due to the occurrence of AEs or SAEs; 2 subjects in the dapagliflozin/exenatide group and 4 subjects in the placebo group. The primary reason for withdrawal of one of these subjects (E129, placebo) was non-compliance to the study protocol.
- The most common SOCs, reported by >50% of subjects in any group, were: gastrointestinal disorders (72.0% vs 52.0% of all subjects in the dapagliflozin/exenatide and placebo group, respectively) and general disorders and administration site conditions (64.0% vs 68.0%).
- The most common PTs were: nasopharyngitis (36.0% vs 16.0%), headache (32.0% vs 16.0%), decreased appetite (32.0% vs 12.0%) and injection site mass (28.0% vs 20.0%).
- Few AEs of special interest with regard to the mode of action of dapagliflozin (urinary tract infections, genital infections, volume depletion-related events or renal impairment-related events) were reported in the study and there was no major difference in reporting frequency between treatment groups.
- Gastrointestinal AEs of special interest with regard to the mode of action of exenatide treatment were more frequently reported in the dapagliflozin/exenatide group compared to the placebo group: 64.0% vs 40.0% of all subjects in the dapagliflozin/exenatide and placebo group, respectively. The 3 most common gastrointestinal symptoms were: nausea (28.0% vs 12.0%), diarrhoea (12.0% vs 12.0%) and abdominal distension (12.0% vs 8.0%).
- Injection site-related AEs were more frequently reported in the dapagliflozin/exenatide group compared to the placebo group: 44.0% vs 32.0% of all subjects in the dapagliflozin/exenatide and placebo group, respectively, experienced injection site-related AEs. The 3 most common injection site-related AEs were: injection site mass (28.0% vs 20.0%), injection site pruritus (28.0% vs 8.0%) and injection site erythema (12.0% vs 4.0%).
- The combined treatment with dapagliflozin/exenatide was not associated with any signs indicative of hypoglycaemia.

13. DISCUSSION AND OVERALL CONCLUSIONS

13.1 DISCUSSION

13.1.1 Efficacy

This study was designed to investigate the combined effect of dapagliflozin and exenatide on weight reduction when co-administered in obese, otherwise healthy subjects. The study used a randomized, double-blind and placebo-controlled design with 2 treatment arms, the combined active treatment (dapagliflozin/exenatide) vs placebo. Throughout the study, subjects received dietary and life style counselling at the clinic. The subjects were instructed to follow a balanced diet according to general national diet guidelines and to modestly increase physical activity, e.g. by walking 30 minutes most days of the week.

In the original protocol, the study duration was 24 weeks. During the course of the study, the 24-week double-blind treatment period was extended with a 28-week open-label treatment period for those subjects who were eligible and willing to continue treatment with study medication for an additional 28 weeks. The aim of the extension study was to demonstrate maintained, or additional, weight reduction by active treatment up to 12 months. This report describes the results obtained during the initial 24-week double-blind study period.

A total of 50 subjects were treated with either dapagliflozin/exenatide (25 subjects) or matching placebo (25 subjects) during 24 weeks. In total, 43 subjects (86.0%) completed the study: 23 subjects (92.0%) in the dapagliflozin/exenatide group and 20 subjects (80.0%) in the placebo group. Treatment compliance was equally high in both groups and for both IPs, only 2 subjects took less than 80% of the planned doses and were excluded from the PPAS.

The treatment groups were well balanced at baseline with regard to demographics, prior medical procedures and prior medications. Slightly higher baseline mean values of body weight, other anthropometric measurements (waist and hip circumference and BMI) and obesity history were observed in the dapagliflozin/exenatide group compared to placebo. However, the small differences between treatment groups in baseline body weight and other anthropometric measurements had no impact on the reported study outcomes as all statistical analyses were adjusted for baseline values.

The primary endpoint was change in body weight (kg) from baseline to week 24. Besides an incremental change in body weight, measures of body fat composition (total adipose tissue, visceral adipose tissue and liver fat) together with measures of glucose, insulin and other variables were included as exploratory outcome measures to further clarify the effects of the combined treatment with dapagliflozin and exenatide. The study was powered to detect a change in body weight of 4.0 kg between active treatment and placebo.

Between baseline and week 24, the mean body weight was reduced by 4.1 kg in the dapagliflozin/exenatide group compared to placebo (p=0.0008; FAS). Similar results were obtained for the PPAS (-3.7 kg; p=0.0036).

Thirty-six percent (36.0%) of all subjects in the FAS had more than or equal to 5% weight loss and 12% had more than or equal to 10% weight loss at week 24 in the dapagliflozin/exenatide group whereas no subject in the placebo group had a weight reduction of 5% or more.

A majority of the total weight loss in the dapagliflozin/exenatide group occurred during the first 12 weeks of the 24-week treatment period. This trend may reflect the subjects' inability of adhering to diet instructions and to sustain increased physical activity for more than 8 to 12 weeks. The weight-reducing effects of dapagliflozin and exenatide may also diminish with time.

In a recent publication, data were pooled from 7 different studies evaluating dapagliflozin as mono- or combination therapy in T2DM. The results showed a mean weight loss of 2 kg following 24 weeks of treatment with dapagliflozin.[5] In the current study, the combined treatment with

dapagliflozin and exenatide induced a statistically significant weight loss of approximately 4 kg which suggests that exenatide increased the total weight loss of 4 kg with approximately 2 kg. This is in agreement with previous studies reporting a mean weight loss of approximately 2 kg in response to long-term exenatide treatment.[9] Thus, the total weight loss of approximately 4 kg observed in the current study is compatible with additive effects of co-administration of dapagliflozin and exenatide based on their individual effects in previous studies in T2DM. Besides body weight, additional anthropometric measurements including waist circumference, WHR and BMI were also assessed. In agreement with the body weight data, a statistically significant reduction of the mean BMI was observed in the dapagliflozin/exenatide group compared to placebo (p=0.0008). In contrast to the BMI data, no statistically significant treatment effects on the waist circumference or WHR were achieved which might be due to a limited precision in the measurements of waist and hip circumference throughout the study.

Measurements of body composition by whole body MRI revealed that the dapagliflozin/exenatide-induced reduction of body weight was essentially accounted for by a loss of adipose tissue. Treatment with dapagliflozin and exenatide during 24 weeks significantly reduced the volume of total adipose tissue by -4.1 L (p=0.0004), visceral adipose tissue by -0.6 L (p=0.0005) and abdominal subcutaneous adipose tissue by -1.4 L (p=0.0003) compared to placebo. There were no statistically significant differences between treatment groups in percentage liver fat, liver volume, total liver fat or total lean tissue at week 24. These findings are in line with a previous study demonstrating that the dapagliflozin-induced weight loss in patients with T2DM was mainly attributable to loss of adipose tissue, with significant loss both in the subcutaneous and visceral adipose depots.[5]

In this study, a discrepancy between the methods used for assessment of total body fat was observed. A statistically significant treatment effect of dapagliflozin/exenatide on total body fat was achieved when whole body MRI was used to measure total adipose tissue (L) whereas no statistically significant treatment effect was observed when bioimpedance was used for assessment of the percentage total body fat (%). As the MRI data correlate with body weight and BMI data, it appears that whole body MRI is a more precise and accurate method for measuring total body fat in obese subjects (BMI>30kg/m^2) compared to bioimpedance.

Dapagliflozin, an SGLT-2 inhibitor, lowers plasma glucose by inhibiting the renal reabsorption of glucose and thereby promotes its urinary excretion. Thus, dapagliflozin is associated with body weight reduction via a continuous loss of energy (up to 300 kcal/day) via the urine. In the current study, a near 200-fold higher excretion of glucose into the urine was indicated during the 3h-OGTT at week 24 in the dapagliflozin/exenatide group compared to placebo.

Exenatide is a subcutaneously injected GLP-1 receptor agonist which increases insulin secretion from the β-cells in the pancreas in individuals with elevated levels of plasma glucose. Although the mechanisms of weight loss with exenatide are not fully understood, several clinical trials in diabetic patients have reported consistent weight loss associated with exenatide treatment.[9] The mechanisms of weight loss with exenatide may include decreased energy intake (loss of appetite).[14] Preclinical studies suggest that exenatide may reduce appetite by promoting satiety via hypothalamic receptors.[15] Nausea, the most common adverse effect of exenatide, may also contribute to the observed weight loss, but mainly in the beginning of the treatment period since the severity of nausea usually decreases over time.

Being developed for T2DM, both dapagliflozin and exenatide have demonstrated robust glucose-lowering effects, albeit via different mechanisms, and lead to reduction in FPG, postprandial plasma glucose and HbA1c with no clear signs of hypoglycaemia.[4,5,6,9] Improved glycaemic control was anticipated due to dapagliflozin through glucosuria and exenatide via increased glucose-dependent insulin secretion. Exenatide has been shown to enhance both insulin sensitivity and insulin secretion (β-cell function) in diabetic subjects.[9]

In the current study, 24 weeks of treatment with dapagliflozin/exenatide in obese non-diabetic subjects significantly reduced both HbA1c (p=0.0004), FPG (p<0.0001) and postprandial plasma glucose levels (p=0.0131) with no clear signs of hypoglycaemia. Impaired fasting glucose (defined as FPG≥5.6 mmol/L) is considered a pre-diabetic state and is associated with insulin resistance. In this study, combined treatment with dapagliflozin and exenatide significantly reduced the proportion of subjects with IFG at week 24 (p=0.0009) compared to placebo.

Although no statistically significant differences between treatment groups were observed in either pre- or postprandial insulin levels, insulin sensitivity or insulin secretion at week 24, combined active treatment significantly reduced the proportion of subjects with IGT within the dapagliflozin/exenatide group (p=0.0196) but not in the placebo group. The proportion of subjects who shifted from IGT to normal postprandial glucose levels between screening and week 24 in the dapagliflozin/exenatide group was 34.8% compared to 15.0% in the placebo group.

Besides the lowering effects on HbA1c and plasma glucose, a statistically significant increase in plasma FFA levels during the glucose challenge at week 24 were observed in the dapagliflozin/exenatide group compared to placebo ($AUC_{0\text{-}2h}$; p=0.0016). In contrast, there were no statistically significant differences between treatment groups with regard to blood levels of glucagon, glycerol, ketones, C-peptide, cholesterol and triglycerides.

Finally, 24 weeks of treatment with dapagliflozin/exenatide significantly lowered the mean systolic blood pressure by -6.7 mmHg (p=0.0220) compared to placebo with no effect on diastolic blood pressure or pulse. In fact, a statistically significant reduction of systolic blood pressure was observed in the dapagliflozin/exenatide group already at week 8 (-8.7 mmHg; p=0.0032) compared to placebo.

Previous studies have reported a blood pressure-lowering effect of both dapagliflozin and exenatide when administered alone, but not to the same degree as observed in this study.[4,5,6,9] Thus, combined treatment with dapagliflozin and exenatide appears to display additive effects on the reduction of systolic blood pressure in obese subjects. The blood pressure reduction is likely to be explained by both decreased adiposity and by an SGLT2-mediated mild diuretic effect.

In summary, 24 weeks of combined treatment with dapagliflozin and exenatide in obese, otherwise healthy subjects resulted in a statistically significant weight loss of 4.1 kg compared to placebo. The weight loss was essentially accounted for by a loss of adipose tissue. In addition to its weight-reducing effect, the combined treatment with dapagliflozin and exenatide significantly lowered both HbA1c, FPG and postprandial glucose levels without any clear signs of hypoglycaemia. No statistically significant differences between treatment groups were observed with regard to pre- and postprandial insulin levels, insulin sensitivity, insulin secretion, C-peptide, glucagon, glycerol, ketones or blood lipids. Finally, 24 weeks of combined treatment with dapagliflozin and exenatide led to a statistically significant reduction of systolic blood pressure compared to placebo.

13.1.2 Safety

The safety results indicated no safety or tolerability concerns for combined treatment with dapagliflozin and exenatide in obese subjects during 24 weeks of treatment. There were no major changes in mean laboratory values during the study and no apparent differences between treatment groups except a numerical decrease in the creatinine clearance rate (-8.4 mL/min) in the dapagliflozin/exenatide group between baseline and week 24. The reduction in estimated creatinine clearance rate observed at week 24 in the group receiving active treatment is probably at least partly attributable to the reduced mean body weight in this group. Body weight is one of the variables in the Cockcroft-Gault formula for calculation of creatinine clearance. On the contrary, eGFR calculated according to the MDRD equation[16] did not show any clinically significant reduction following either treatment, and thus there was no sign of treatment-related renal impairment.

The reported AEs in the study were well tolerated and did not indicate any major safety issues for the combined treatment of dapagliflozin and exenatide. In brief, the total number of AEs reported in the

dapagliflozin/exenatide group was approximately 20 percentage points higher compared to the total number of AEs reported in the placebo group. Most AEs were of mild intensity and most were assessed as possibly related to treatment. There were no apparent differences in AE severity or relationship to IP between the groups. Relatively few subjects were withdrawn from the study due to AEs; 2 subjects in the dapagliflozin/exenatide group and 4 subjects in the placebo group. Importantly, there were no reported AEs that could be confirmed as hypoglycaemia.

Despite increased glucosuria in dapagliflozin/exenatide-treated subjects, no apparent increase in symptoms of urinary tract infection or genital infection, frequently noted in dapagliflozin arms in previous studies, were observed.[13] In fact, very few AEs of special interest with regard to the mode of action of dapagliflozin, including urinary tract infections, genital infections, volume depletion-related events and renal impairment-related events were reported in the study. Volume depletion could, at least theoretically, occur as a consequence of increased vomiting due to exenatide and increased diuresis due to dapagliflozin. However, vomiting occurred at a very low frequency (5 events in total, reported by 4 subjects). Moreover, there was no increase in AEs from the cardiovascular system including hypotension, syncope or orthostatic reactions which may also be indicative of volume depletion.

Adverse events of special interest with regard to the mode of action of exenatide include gastrointestinal symptoms and injection site-related AEs and were more frequently reported in the dapagliflozin/exenatide group compared to the placebo group.[12] In total 64.0% of all subjects in the dapagliflozin/exenatide group reported gastrointestinal AEs known as potential side-effects of exenatide treatment compared to 40.0% of all subjects in the placebo group. The most frequently reported gastrointestinal AEs (reported by >10% of the subjects in the dapagliflozin/exenatide group) were nausea, diarrhoea, abdominal distension, vomiting and gastroesophageal reflux disease, which are well-known side-effects of treatment with GLP-1 receptor agonists.[12] Likewise, 44.0% of all subjects in the dapagliflozin/exenatide group reported injection site-related AEs compared to 32.0% of all subjects in the placebo group. The most frequently reported injection site-related events related to exenatide treatment (reported by >10% of the subjects in the dapagliflozin/exenatide group) were injection site mass, injection site pruritus and injection site erythema.

Finally, it was observed that AEs reported as appetite changes differed somewhat between the treatment groups. Decreased appetite was more frequently reported in the group receiving active treatment compared to placebo (32.0% vs 12.0% of all subjects in the dapagliflozin/exenatide and placebo group, respectively). In line with that, hunger/increased appetite was reported by 8.0% in the dapagliflozin/exenatide as compared to 12.0% in the placebo group.

In summary, no safety issues were raised with regard to the combined dapagliflozin/exenatide treatment in obese subjects without diabetes during 24 weeks of treatment based on laboratory measurements, creatinine clearance, vital signs or reported AEs during the study.

13.2 OVERALL CONSLUSIONS

13.2.1 Efficacy

- 24 weeks of combined treatment with dapagliflozin and exenatide in obese, otherwise healthy subjects resulted in a statistically significant weight loss of 4.1 kg compared to placebo (p=0.0008). The weight loss was essentially accounted for by a loss of adipose tissue (-4.1L; p=0.0004). In addition to its weight-reducing effect, the combined treatment with dapagliflozin and exenatide significantly lowered the plasma levels of both HbA1c (p=0.0004) and FPG (p<0.0001) with no clear signs of hypoglycaemia.
- In response to a glucose challenge at week 24, both postprandial plasma glucose levels (p=0.0131) and $AUC_{0\text{-}3h}$ (p=0.0032) were significantly reduced in the dapagliflozin/exenatide group compared to placebo. A statistically significant reduction of the proportion of subjects with IFG and IFG and/or IGT (p=0.0009 and p=0.0017) was observed in the dapagliflozin/exenatide group compared to placebo at week 24. No statistically significant differences between treatment groups were observed with regard to pre- and postprandial insulin levels, insulin sensitivity, insulin secretion, C-peptide, glucagon, glycerol, ketones or blood lipids. Finally, 24 weeks of combined treatment with dapagliflozin and exenatide led to a statistically significant reduction of mean systolic blood pressure (-6.7 mmHg; p=0.0220) compared to placebo.

13.2.2 Safety

- No major safety issues were identified for the combined treatment with dapagliflozin (10 mg once daily) and exenatide (2 mg weekly injections) during 24 weeks of treatment in obese, otherwise healthy, subjects based on clinical laboratory tests, creatinine clearance, vital signs and AEs/SAEs.

- The AE reporting did not reveal any sign of new patterns not previously noted for the individual drugs. Importantly there were no signs of an increased frequency of events related to hypovolemia or impaired renal function when patients were given the combination of dapagliflozin and exenatide.

14. TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

14.1 DEMOGRAPHIC DATA

14.1.1 Disposition of Subjects

Table 62 Disposition of subjects

	Dapagliflozin/ Exenatide	Placebo	Total
Enrolled[a]			61
Eligible			53
Not eligible			8
Screening failures			8
Randomized[b]	25	25	50
Randomized and not taken any study medication	0	0	0
Randomized and taken study medication	25 (100.0%)	25 (100.0%)	50 (100.0%)
Completed trial	23 (92.0%)	20 (80.0%)	43 (86.0%)
Prematurely withdrawn	2 (8.0%)	5 (20.0%)	7 (14.0%)
Analysis datasets			
Safety analysis set	25 (100.0%)	25 (100.0%)	50 (82.0%)
Full analysis set	25 (100.0%)	24 (96.0%)	49 (80.3%)
Per-protocol analysis set	22 (88.0%)	20 (80.0%)	42 (68.9%)

Percentages are based on the number of randomized subjects.

[a] All subjects who gave their written informed consent to participate in the study were enrolled for screening.

[b] In total 11 of 61 enrolled subjects were screening failures and never randomized in the study: 8 of these were not eligible at screening and 3 were eligible at screening but were classified as screening failures prior to randomization for other reasons, see Section 10.1 and Table 8).

14.1.2 Protocol Deviations

Table 63 Protocol deviations. Randomized subjects

	Dapagliflozin/ Exenatide (N=25)		Placebo (N=25)		Total (N=50)	
	n (%)	m	n (%)	m	n (%)	m
Major	0	0	1 (4.0%)	1	1 (2.0%)	1
Minor	11 (44.0%)	14	5 (20.0%)	6	16 (32.0%)	20

Percentages are based on the number of randomised subjects.
n is the number of subjects, m is the number of deviations.

14.1.3 Demographics

Table 64 Demographics. Safety analysis set

	Dapagliflozin/ Exenatide (N=25)	Placebo (N=25)	Total (N=50)
Age (years)			
n/nmiss	25/0	25/0	50/0
Mean (SD)	53.48 (13.48)	49.28 (12.13)	51.38 (12.87)
Median	53.00	50.00	51.00
Q1, Q3	48.00, 65.00	43.00, 57.00	43.00, 62.00
Min, Max	20.0, 69.0	23.0, 68.0	20.0, 69.0
Gender			
Female	15 (60.0%)	15 (60.0%)	30 (60.0%)
Male	10 (40.0%)	10 (40.0%)	20 (40.0%)
Race			
Asian	1 (4.0%)	0	1 (2.0%)
Other	1 (4.0%)	0	1 (2.0%)
White	23 (92.0%)	25 (100.0%)	48 (96.0%)
Childbearing potential			
Yes	4 (26.7%)	6 (40.0%)	10 (33.3%)
No	11 (73.3%)	9 (60.0%)	20 (66.7%)
Reason			
Postmenopausal	8 (72.7%)	8 (88.9%)	16 (80.0%)
Surgically sterile	1 (9.1%)	1 (11.1%)	2 (10.0%)
Premenarcheal[a]	1 (9.1%)	0	1 (5.0%)
Other	1 (9.1%)	0	1 (5.0%)

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
Percentages are based on the number of subjects in the applicable analysis set.
[a] One female subject (E144) in the dapagliflozin/exenatide group was erroneously registered in the eCRF as being of no child-bearing potential due to premenarcheal state but the true reason was due to koriocarcinoma.

14.1.4 Anthropometrics

14.1.4.1 Body Weight and Other Anthropometric Measures

Table 65 Body weight and other anthropometric measures. Full analysis set

	Week -2-(-1)	Week 0 (Baseline)	Week 4	Week 8	Week 12	Week 24
Height (cm)						
Dapagliflozin/ Exenatide (N=25)						
n/nmiss	25/0					
Mean (SD)	171.98 (8.87)					
Median	171.00					
Q1, Q3	166.50, 179.00					
Min, Max	156.0, 191.5					
Placebo (N=24)						
n/nmiss	24/0					
Mean (SD)	170.94 (9.59)					
Median	171.75					
Q1, Q3	164.25, 177.25					
Min, Max	155.0, 190.0					
Total (N=49)						
n/nmiss	49/0					
Mean (SD)	171.47 (9.15)					
Median	171.50					
Q1, Q3	165.00, 179.00					
Min, Max	155.0, 191.5					
Body weight (kg)						
Dapagliflozin/ Exenatide (N=25)						
n/nmiss	25/0	25/0	25/0	24/1	23/2	23/2
Mean (SD)	106.82 (15.67)	106.43 (15.55)	105.51 (15.79)	104.93 (15.63)	102.37 (16.05)	101.84 (17.36)
Median	110.10	108.10	105.70	106.30	98.70	98.50
Q1, Q3	92.00, 116.30	93.60, 116.30	92.20, 116.10	92.25, 116.00	87.90, 113.50	85.30, 112.10
Min, Max	82.0, 143.2	82.0, 142.8	79.0, 140.8	76.7, 138.7	74.5, 138.1	75.0, 141.9
Placebo (N=24)						
n/nmiss	24/0	24/0	24/0	23/1	21/3	20/4
Mean (SD)	102.61 (16.96)	102.72 (17.26)	102.13 (17.30)	102.21 (17.75)	103.38 (18.56)	104.86 (17.38)

	Week -2-(-1)	Week 0 (Baseline)	Week 4	Week 8	Week 12	Week 24
Median	97.90	97.70	96.70	95.30	96.50	96.05
Q1, Q3	93.30, 111.95	93.50, 111.80	92.70, 112.55	91.30, 117.00	92.60, 117.20	94.05, 116.10
Min, Max	73.7, 144.9	73.6, 145.8	73.6, 145.0	74.0, 145.8	75.1, 149.7	83.3, 150.2
Total (N=49)						
n/nmiss	49/0	49/0	49/0	47/2	44/5	43/6
Mean (SD)	104.76 (16.28)	104.61 (16.35)	103.86 (16.46)	103.60 (16.57)	102.85 (17.09)	103.24 (17.23)
Median	99.80	99.60	99.70	98.90	98.40	97.50
Q1, Q3	92.90, 116.20	93.60, 115.00	92.70, 115.70	92.00, 116.10	92.55, 115.15	93.30, 114.80
Min, Max	73.7, 144.9	73.6, 145.8	73.6, 145.0	74.0, 145.8	74.5, 149.7	75.0, 150.2
Waist circumference (cm)						
Dapagliflozin/ Exenatide (N=25)						
n/nmiss	25/0	25/0	25/0	24/1	23/2	23/2
Mean (SD)	117.28 (10.85)	117.56 (11.34)	115.98 (10.22)	116.13 (10.87)	113.37 (11.13)	111.54 (12.02)
Median	117.50	117.00	115.00	115.00	113.00	112.00
Q1, Q3	111.50, 124.00	110.00, 125.00	109.50, 121.00	108.00, 122.50	105.00, 120.00	102.00, 120.00
Min, Max	94.5, 149.0	93.5, 148.5	96.0, 143.0	95.0, 147.5	91.5, 145.0	88.0, 143.0
Placebo (N=24)						
n/nmiss	24/0	24/0	24/0	23/1	21/3	20/4
Mean (SD)	114.23 (13.03)	114.35 (12.55)	112.96 (12.03)	114.65 (12.18)	112.60 (13.25)	113.00 (14.70)
Median	111.50	109.25	110.00	111.00	109.50	111.25
Q1, Q3	105.00, 119.75	107.00, 120.25	104.25, 117.00	105.00, 121.00	104.00, 116.50	101.25, 120.50
Min, Max	94.0, 143.0	94.0, 143.0	98.5, 141.5	101.0, 144.0	96.5, 144.0	94.0, 144.0
Total (N=49)						
n/nmiss	49/0	49/0	49/0	47/2	44/5	43/6
Mean (SD)	115.79 (11.94)	115.99 (11.93)	114.50 (11.13)	115.40 (11.42)	113.00 (12.05)	112.22 (13.19)
Median	114.50	114.00	112.50	113.00	111.50	111.50
Q1, Q3	107.00, 122.00	107.50, 122.00	108.00, 120.50	107.00, 122.00	104.50, 120.00	102.00, 120.00
Min, Max	94.0, 149.0	93.5, 148.5	96.0, 143.0	95.0, 147.5	91.5, 145.0	88.0, 144.0
Hip circumference (cm)						
Dapagliflozin/ Exenatide (N=25)						
n/nmiss	25/0	25/0	25/0	24/1	23/2	23/2
Mean (SD)	120.90 (9.12)	121.18 (7.54)	119.92 (7.96)	120.35 (7.67)	118.48 (7.92)	117.80 (9.22)
Median	119.00	120.00	118.00	118.50	115.00	114.00
Q1, Q3	114.00, 129.00	115.00, 124.50	115.00, 124.00	115.00, 124.00	113.50, 124.50	111.50, 124.00
Min, Max	105.0, 138.0	111.5, 138.0	107.5, 137.5	109.0, 136.0	106.0, 135.5	106.0, 139.0

	Week -2-(-1)	Week 0 (Baseline)	Week 4	Week 8	Week 12	Week 24
Placebo (N=24)						
n/nmiss	24/0	24/0	24/0	23/1	21/3	20/4
Mean (SD)	117.73 (5.75)	117.60 (6.50)	116.96 (5.30)	118.57 (6.49)	117.62 (6.63)	118.20 (6.49)
Median	118.75	118.00	117.75	119.00	117.00	117.25
Q1, Q3	113.50, 120.75	112.50, 121.25	112.75, 121.75	113.50, 121.50	112.50, 121.00	113.25, 120.75
Min, Max	106.5, 129.0	107.0, 133.0	108.0, 126.0	108.0, 132.0	107.0, 130.5	107.0, 133.0
Total (N=49)						
n/nmiss	49/0	49/0	49/0	47/2	44/5	43/6
Mean (SD)	119.35 (7.75)	119.43 (7.21)	118.47 (6.88)	119.48 (7.10)	118.07 (7.26)	117.99 (7.98)
Median	119.00	118.50	118.00	119.00	116.00	117.00
Q1, Q3	114.00, 122.00	114.50, 123.00	114.00, 122.50	114.00, 122.00	113.00, 121.75	112.00, 121.00
Min, Max	105.0, 138.0	107.0, 138.0	107.5, 137.5	108.0, 136.0	106.0, 135.5	106.0, 139.0
Body mass index (BMI) (kg/m2)						
Dapagliflozin/ Exenatide (N=25)						
n/nmiss	25/0	25/0	25/0	24/1	23/2	23/2
Mean (SD)	35.94 (2.92)	35.82 (2.88)	35.51 (3.05)	35.26 (3.15)	34.59 (3.50)	34.40 (4.01)
Median	36.13	36.13	35.79	35.76	35.22	35.05
Q1, Q3	33.83, 37.89	33.74, 37.55	32.99, 37.31	32.71, 37.03	31.29, 36.80	30.82, 36.60
Min, Max	30.9, 44.2	30.9, 44.1	29.8, 43.5	28.9, 42.8	27.6, 42.6	26.1, 43.8
Placebo (N=24)						
n/nmiss	24/0	24/0	24/0	23/1	21/3	20/4
Mean (SD)	34.95 (3.59)	34.98 (3.69)	34.77 (3.62)	34.86 (3.68)	35.06 (3.98)	35.31 (4.05)
Median	33.94	33.92	33.88	34.11	34.02	34.14
Q1, Q3	33.08, 35.87	32.98, 35.95	32.48, 35.36	32.43, 35.78	32.47, 35.78	32.47, 37.50
Min, Max	30.7, 44.7	30.6, 44.8	30.6, 44.6	30.6, 45.0	30.3, 45.2	31.2, 45.3
Total (N=49)						
n/nmiss	49/0	49/0	49/0	47/2	44/5	43/6
Mean (SD)	35.46 (3.27)	35.41 (3.29)	35.15 (3.33)	35.07 (3.39)	34.81 (3.70)	34.82 (4.01)
Median	34.71	34.52	34.50	34.47	34.40	34.24
Q1, Q3	33.41, 37.52	33.34, 37.36	32.87, 37.27	32.43, 36.86	32.45, 36.80	32.46, 36.70
Min, Max	30.7, 44.7	30.6, 44.8	29.8, 44.6	28.9, 45.0	27.6, 45.2	26.1, 45.3

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.

Table 66 Body weight and other anthropometric measures. Safety analysis set

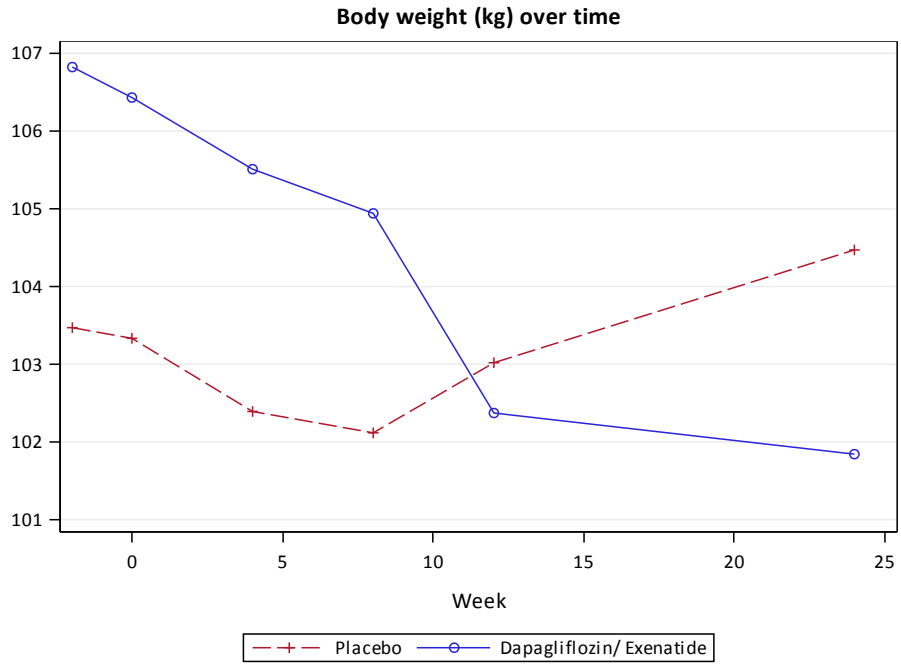
	Week -2-(-1)	Week 0 (Baseline)	Week 4	Week 8	Week 12	Week 24
Height (cm)						
Dapagliflozin/ Exenatide (N=25)						
n/nmiss	25/0					
Mean (SD)	171.98 (8.87)					
Median	171.00					
Q1, Q3	166.50, 179.00					
Min, Max	156.0, 191.5					
Placebo (N=25)						
n/nmiss	25/0					
Mean (SD)	171.32 (9.58)					
Median	172.00					
Q1, Q3	165.00, 179.50					
Min, Max	155.0, 190.0					
Total (N=50)						
n/nmiss	50/0					
Mean (SD)	171.65 (9.14)					
Median	171.75					
Q1, Q3	165.00, 179.00					
Min, Max	155.0, 191.5					
Body weight (kg)						
Dapagliflozin/ Exenatide (N=25)						
n/nmiss	25/0	25/0	25/0	24/1	23/2	23/2
Mean (SD)	106.82 (15.67)	106.43 (15.55)	105.51 (15.79)	104.93 (15.63)	102.37 (16.05)	101.84 (17.36)
Median	110.10	108.10	105.70	106.30	98.70	98.50
Q1, Q3	92.00, 116.30	93.60, 116.30	92.20, 116.10	92.25, 116.00	87.90, 113.50	85.30, 112.10
Min, Max	82.0, 143.2	82.0, 142.8	79.0, 140.8	76.7, 138.7	74.5, 138.1	75.0, 141.9
Placebo (N=25)						
n/nmiss	25/0	25/0	25/0	24/1	22/3	21/4
Mean (SD)	103.46 (17.14)	103.33 (17.17)	102.40 (16.99)	102.11 (17.36)	103.01 (18.19)	104.47 (17.03)
Median	98.20	98.00	96.80	95.90	96.00	96.50
Q1, Q3	93.70, 115.50	94.50, 115.00	92.70, 109.40	92.30, 113.45	92.60, 117.20	94.30, 114.80
Min, Max	73.7, 144.9	73.6, 145.8	73.6, 145.0	74.0, 145.8	75.1, 149.7	83.3, 150.2

	Week -2-(-1)	Week 0 (Baseline)	Week 4	Week 8	Week 12	Week 24
Total (N=50)						
n/nmiss	50/0	50/0	50/0	48/2	45/5	44/6
Mean (SD)	105.14 (16.34)	104.88 (16.29)	103.96 (16.31)	103.52 (16.41)	102.69 (16.94)	103.10 (17.05)
Median	100.85	100.10	100.30	99.00	98.20	97.15
Q1, Q3	92.90, 116.30	93.60, 116.30	92.70, 115.70	92.25, 116.00	92.60, 113.50	93.40, 113.45
Min, Max	73.7, 144.9	73.6, 145.8	73.6, 145.0	74.0, 145.8	74.5, 149.7	75.0, 150.2
Waist circumference (cm)						
Dapagliflozin/ Exenatide (N=25)						
n/nmiss	25/0	25/0	25/0	24/1	23/2	23/2
Mean (SD)	117.28 (10.85)	117.56 (11.34)	115.98 (10.22)	116.13 (10.87)	113.37 (11.13)	111.54 (12.02)
Median	117.50	117.00	115.00	115.00	113.00	112.00
Q1, Q3	111.50, 124.00	110.00, 125.00	109.50, 121.00	108.00, 122.50	105.00, 120.00	102.00, 120.00
Min, Max	94.5, 149.0	93.5, 148.5	96.0, 143.0	95.0, 147.5	91.5, 145.0	88.0, 143.0
Placebo (N=25)						
n/nmiss	25/0	25/0	25/0	24/1	22/3	21/4
Mean (SD)	114.94 (13.24)	114.94 (12.63)	113.32 (11.92)	114.58 (11.91)	112.52 (12.93)	112.86 (14.34)
Median	111.50	109.50	111.00	112.00	109.75	111.00
Q1, Q3	106.00, 120.00	107.00, 120.50	105.00, 119.50	106.00, 119.00	104.00, 116.50	102.50, 120.00
Min, Max	94.0, 143.0	94.0, 143.0	98.5, 141.5	101.0, 144.0	96.5, 144.0	94.0, 144.0
Total (N=50)						
n/nmiss	50/0	50/0	50/0	48/2	45/5	44/6
Mean (SD)	116.11 (12.04)	116.25 (11.95)	114.65 (11.07)	115.35 (11.31)	112.96 (11.91)	112.17 (13.04)
Median	115.00	114.25	112.50	113.00	111.00	111.25
Q1, Q3	107.00, 122.50	107.50, 122.00	108.00, 121.00	107.25, 121.75	104.50, 120.00	102.25, 120.00
Min, Max	94.0, 149.0	93.5, 148.5	96.0, 143.0	95.0, 147.5	91.5, 145.0	88.0, 144.0
Hip circumference (cm)						
Dapagliflozin/ Exenatide (N=25)						
n/nmiss	25/0	25/0	25/0	24/1	23/2	23/2
Mean (SD)	120.90 (9.12)	121.18 (7.54)	119.92 (7.96)	120.35 (7.67)	118.48 (7.92)	117.80 (9.22)
Median	119.00	120.00	118.00	118.50	115.00	114.00
Q1, Q3	114.00, 129.00	115.00, 124.50	115.00, 124.00	115.00, 124.00	113.50, 124.50	111.50, 124.00
Min, Max	105.0, 138.0	111.5, 138.0	107.5, 137.5	109.0, 136.0	106.0, 135.5	106.0, 139.0
Placebo (N=25)						
n/nmiss	25/0	25/0	25/0	24/1	22/3	21/4
Mean (SD)	117.88 (5.68)	117.86 (6.49)	116.56 (5.56)	118.21 (6.59)	117.27 (6.67)	117.76 (6.64)

	Week -2-(-1)	Week 0 (Baseline)	Week 4	Week 8	Week 12	Week 24
Median	119.50	118.00	117.50	118.50	116.00	117.00
Q1, Q3	115.00, 121.00	113.00, 121.50	112.50, 121.50	112.75, 121.25	112.00, 121.00	113.00, 120.50
Min, Max	106.5, 129.0	107.0, 133.0	107.0, 126.0	108.0, 132.0	107.0, 130.5	107.0, 133.0
Total (N=50)						
n/nmiss	50/0	50/0	50/0	48/2	45/5	44/6
Mean (SD)	119.39 (7.67)	119.52 (7.16)	118.24 (7.00)	119.28 (7.15)	117.89 (7.28)	117.78 (8.00)
Median	119.25	118.50	117.75	118.50	115.00	116.50
Q1, Q3	114.00, 122.00	114.50, 123.00	113.00, 122.50	114.00, 121.75	113.00, 121.00	112.00, 121.00
Min, Max	105.0, 138.0	107.0, 138.0	107.0, 137.5	108.0, 136.0	106.0, 135.5	106.0, 139.0
Body mass index (BMI) (kg/m2)						
Dapagliflozin/ Exenatide (N=25)						
n/nmiss	25/0	25/0	25/0	24/1	23/2	23/2
Mean (SD)	35.94 (2.92)	35.82 (2.88)	35.51 (3.05)	35.26 (3.15)	34.59 (3.50)	34.40 (4.01)
Median	36.13	36.13	35.79	35.76	35.22	35.05
Q1, Q3	33.83, 37.89	33.74, 37.55	32.99, 37.31	32.71, 37.03	31.29, 36.80	30.82, 36.60
Min, Max	30.9, 44.2	30.9, 44.1	29.8, 43.5	28.9, 42.8	27.6, 42.6	26.1, 43.8
Placebo (N=25)						
n/nmiss	25/0	25/0	25/0	24/1	22/3	21/4
Mean (SD)	35.08 (3.56)	35.03 (3.62)	34.72 (3.56)	34.68 (3.70)	34.80 (4.07)	35.04 (4.13)
Median	34.12	34.12	33.81	33.95	33.84	34.05
Q1, Q3	33.35, 36.18	33.23, 36.14	32.53, 34.83	32.42, 35.18	32.43, 35.78	32.46, 36.73
Min, Max	30.7, 44.7	30.6, 44.8	30.6, 44.6	30.6, 45.0	29.3, 45.2	29.7, 45.3
Total (N=50)						
n/nmiss	50/0	50/0	50/0	48/2	45/5	44/6
Mean (SD)	35.51 (3.25)	35.43 (3.26)	35.11 (3.31)	34.97 (3.41)	34.69 (3.75)	34.71 (4.04)
Median	34.88	34.55	34.47	34.46	34.38	34.24
Q1, Q3	33.41, 37.69	33.34, 37.36	32.87, 37.27	32.42, 36.77	32.43, 36.80	32.45, 36.65
Min, Max	30.7, 44.7	30.6, 44.8	29.8, 44.6	28.9, 45.0	27.6, 45.2	26.1, 45.3

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.

Figure 14 Body weight (kg) series plot by week. Safety analysis set



14.1.4.2 Waist-hip Ratio

Table 67 Waist-hip ratio. Full analysis set.

Waist-hip ratio	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Week -2-(-1)		
n/nmiss	25/0	24/0
Mean (SD)	0.97 (0.10)	0.97 (0.11)
Median	0.96	0.98
Q1, Q3	0.91, 1.04	0.87, 1.05
Min, Max	0.8, 1.2	0.8, 1.2
Week 0 (Baseline)		
n/nmiss	25/0	24/0
Mean (SD)	0.97 (0.10)	0.97 (0.09)
Median	0.97	0.99
Q1, Q3	0.89, 1.03	0.90, 1.03
Min, Max	0.8, 1.1	0.8, 1.2
Week 4		
n/nmiss	25/0	24/0
Mean (SD)	0.97 (0.10)	0.97 (0.10)
Median	0.96	0.98
Q1, Q3	0.90, 1.03	0.89, 1.02
Min, Max	0.8, 1.1	0.8, 1.2
Week 8		
n/nmiss	24/1	23/1
Mean (SD)	0.97 (0.09)	0.97 (0.09)
Median	0.96	0.98
Q1, Q3	0.93, 1.05	0.91, 1.03
Min, Max	0.8, 1.1	0.8, 1.1
Week 12		
n/nmiss	23/2	21/3
Mean (SD)	0.96 (0.08)	0.96 (0.10)
Median	0.95	0.95
Q1, Q3	0.90, 1.00	0.88, 1.04
Min, Max	0.8, 1.1	0.8, 1.1
Week 24		
n/nmiss	23/2	20/4
Mean (SD)	0.95 (0.11)	0.96 (0.12)
Median	0.96	1.00
Q1, Q3	0.86, 1.02	0.83, 1.05
Min, Max	0.8, 1.2	0.8, 1.1

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.

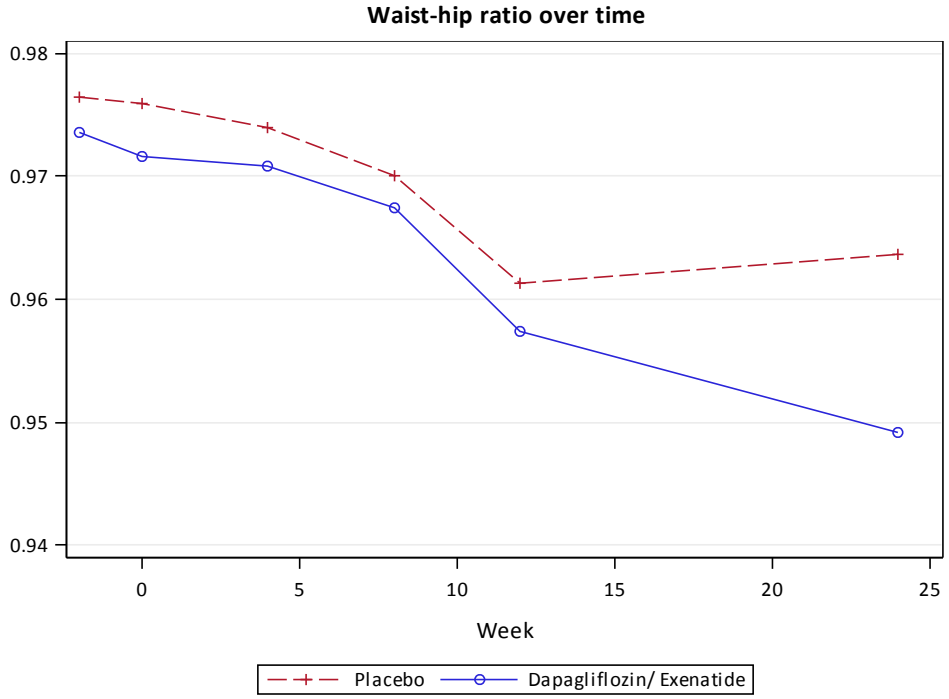
Source: G:\StudData\Uppsala University\Dapalost\BIS\SASprog\DDP\BIS\Tables\Waist-hip ratio.sas

Table 68 Waist-hip ratio. Safety analysis set

Waist-hip ratio	Dapagliflozin/ Exenatide (N=25)	Placebo (N=25)
Week -2-(-1)		
n/nmiss	25/0	25/0
Mean (SD)	0.97 (0.10)	0.98 (0.11)
Median	0.96	0.98
Q1, Q3	0.91, 1.04	0.87, 1.06
Min, Max	0.8, 1.2	0.8, 1.2
Week 0 (Baseline)		
n/nmiss	25/0	25/0
Mean (SD)	0.97 (0.10)	0.98 (0.09)
Median	0.97	0.99
Q1, Q3	0.89, 1.03	0.91, 1.03
Min, Max	0.8, 1.1	0.8, 1.2
Week 4		
n/nmiss	25/0	25/0
Mean (SD)	0.97 (0.10)	0.97 (0.10)
Median	0.96	0.98
Q1, Q3	0.90, 1.03	0.89, 1.02
Min, Max	0.8, 1.1	0.8, 1.2
Week 8		
n/nmiss	24/1	24/1
Mean (SD)	0.97 (0.09)	0.97 (0.09)
Median	0.96	0.98
Q1, Q3	0.93, 1.05	0.92, 1.03
Min, Max	0.8, 1.1	0.8, 1.1
Week 12		
n/nmiss	23/2	22/3
Mean (SD)	0.96 (0.08)	0.96 (0.10)
Median	0.95	0.97
Q1, Q3	0.90, 1.00	0.88, 1.04
Min, Max	0.8, 1.1	0.8, 1.1
Week 24		
n/nmiss	23/2	21/4
Mean (SD)	0.95 (0.11)	0.96 (0.11)
Median	0.96	1.00
Q1, Q3	0.86, 1.02	0.85, 1.04
Min, Max	0.8, 1.2	0.8, 1.1

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.

Figure 15 Waist-hip ratio series plot by week. Safety analysis set



14.1.5 Obesity History

Table 69 Obesity history. Safety analysis set

	Dapagliflozin/ Exenatide (N=25)	Placebo (N=25)
Time since obesity started (years)		
n/nmiss	25/0	25/0
Mean (SD)	27.32 (17.29)	19.24 (13.37)
Median	23.00	16.00
Q1, Q3	15.00, 35.00	9.00, 28.00
Min, Max	5.0, 69.0	0.0, 50.0
Max weight (kg)		
n/nmiss	25/0	25/0
Mean (SD)	111.05 (18.15)	108.46 (19.79)
Median	111.00	103.00
Q1, Q3	98.00, 120.80	95.00, 120.00
Min, Max	83.0, 157.0	74.0, 152.0
Weight (kg) 12 months before baseline		
n/nmiss	25/0	25/0
Mean (SD)	104.32 (16.70)	101.24 (16.47)
Median	103.00	96.00
Q1, Q3	93.00, 117.00	90.00, 108.00
Min, Max	79.0, 148.0	74.0, 146.0
Weight (kg) 3 months before baseline		
n/nmiss	25/0	25/0
Mean (SD)	105.53 (15.65)	102.28 (17.20)
Median	105.00	96.00
Q1, Q3	93.00, 115.00	92.00, 113.00
Min, Max	79.0, 144.0	74.0, 146.0

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.

14.1.6 Medical History

Table 70 Medical history. Safety analysis set

System organ class/Preferred term	Dapagliflozin/ Exenatide (N=25)	Placebo (N=25)
Infections and infestations	1 (4.0%)	2 (8.0%)
Cytomegalovirus infection	0	1 (4.0%)
Neuroborreliosis	0	1 (4.0%)
Orchitis	1 (4.0%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (8.0%)	1 (4.0%)
Choriocarcinoma	1 (4.0%)	0
Malignant melanoma	0	1 (4.0%)
Seborrhoeic keratosis	1 (4.0%)	0
Metabolism and nutrition disorders	0	1 (4.0%)
Vitamin B12 deficiency	0	1 (4.0%)
Psychiatric disorders	0	2 (8.0%)
Depression	0	1 (4.0%)
Postpartum depression	0	1 (4.0%)
Nervous system disorders	1 (4.0%)	0
Cerebral haemorrhage	1 (4.0%)	0
Muscle spasticity	1 (4.0%)	0
Ear and labyrinth disorders	1 (4.0%)	0
Vertigo positional	1 (4.0%)	0
Cardiac disorders	0	1 (4.0%)
Myocardial infarction	0	1 (4.0%)
Gastrointestinal disorders	0	1 (4.0%)
Inguinal hernia	0	1 (4.0%)
Musculoskeletal and connective tissue disorders	1 (4.0%)	2 (8.0%)
Intervertebral disc protrusion	0	2 (8.0%)
Osteoarthritis	1 (4.0%)	0
Renal and urinary disorders	0	1 (4.0%)
Nephrolithiasis	0	1 (4.0%)
General disorders and administration site conditions	1 (4.0%)	0
Inflammation	1 (4.0%)	0
Investigations	1 (4.0%)	0
Biopsy breast normal	1 (4.0%)	0
Injury, poisoning and procedural complications	3 (12.0%)	1 (4.0%)
Ankle fracture	1 (4.0%)	0
Concussion	1 (4.0%)	0
Ligament rupture	0	1 (4.0%)
Tendon rupture	1 (4.0%)	0
Wrist fracture	1 (4.0%)	0
Social circumstances	1 (4.0%)	2 (8.0%)
Clinical trial participant	1 (4.0%)	1 (4.0%)
Joint prosthesis user	0	1 (4.0%)

Medical history is coded according to MedDRA version 18.0E.
Percentages are based on the number of subjects in the applicable analysis set

Table 71 Medical History. Full analysis set

System organ class/Preferred term	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Infections and infestations	1 (4.0%)	2 (8.3%)
Cytomegalovirus infection	0	1 (4.2%)
Neuroborreliosis	0	1 (4.2%)
Orchitis	1 (4.0%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (8.0%)	1 (4.2%)
Choriocarcinoma	1 (4.0%)	0
Malignant melanoma	0	1 (4.2%)
Seborrhoeic keratosis	1 (4.0%)	0
Metabolism and nutrition disorders	0	1 (4.2%)
Vitamin B12 deficiency	0	1 (4.2%)
Psychiatric disorders	0	2 (8.3%)
Depression	0	1 (4.2%)
Postpartum depression	0	1 (4.2%)
Nervous system disorders	1 (4.0%)	0
Cerebral haemorrhage	1 (4.0%)	0
Muscle spasticity	1 (4.0%)	0
Ear and labyrinth disorders	1 (4.0%)	0
Vertigo positional	1 (4.0%)	0
Cardiac disorders	0	1 (4.2%)
Myocardial infarction	0	1 (4.2%)
Gastrointestinal disorders	0	1 (4.2%)
Inguinal hernia	0	1 (4.2%)
Musculoskeletal and connective tissue disorders	1 (4.0%)	2 (8.3%)
Intervertebral disc protrusion	0	2 (8.3%)
Osteoarthritis	1 (4.0%)	0
Renal and urinary disorders	0	1 (4.2%)
Nephrolithiasis	0	1 (4.2%)
General disorders and administration site conditions	1 (4.0%)	0
Inflammation	1 (4.0%)	0
Investigations	1 (4.0%)	0
Biopsy breast normal	1 (4.0%)	0
Injury, poisoning and procedural complications	3 (12.0%)	1 (4.2%)
Ankle fracture	1 (4.0%)	0
Concussion	1 (4.0%)	0
Ligament rupture	0	1 (4.2%)
Tendon rupture	1 (4.0%)	0
Wrist fracture	1 (4.0%)	0
Social circumstances	1 (4.0%)	2 (8.3%)
Clinical trial participant	1 (4.0%)	1 (4.2%)
Joint prosthesis user	0	1 (4.2%)

Medical history is coded according to MedDRA version 18.0E.
Percentages are based on the number of subjects in the applicable analysis set

14.1.7 Concurrent Diseases

Table 72 Concurrent diseases. Safety analysis set

System organ class/Preferred term	Dapagliflozin/ Exenatide (N=25)	Placebo (N=25)
Infections and infestations	2 (8.0%)	1 (4.0%)
Chronic sinusitis	1 (4.0%)	0
Herpes simplex	0	1 (4.0%)
Herpes virus infection	1 (4.0%)	0
Blood and lymphatic system disorders	1 (4.0%)	1 (4.0%)
Anaemia folate deficiency	0	1 (4.0%)
Anaemia macrocytic	1 (4.0%)	0
Immune system disorders	1 (4.0%)	3 (12.0%)
Seasonal allergy	1 (4.0%)	3 (12.0%)
Endocrine disorders	3 (12.0%)	3 (12.0%)
Goitre	0	1 (4.0%)
Hypopituitarism	0	1 (4.0%)
Hypothyroidism	3 (12.0%)	1 (4.0%)
Metabolism and nutrition disorders	2 (8.0%)	1 (4.0%)
Hyperlipidaemia	1 (4.0%)	0
Vitamin B12 deficiency	1 (4.0%)	0
Vitamin D deficiency	0	1 (4.0%)
Psychiatric disorders	3 (12.0%)	1 (4.0%)
Depression	2 (8.0%)	1 (4.0%)
Sleep disorder	1 (4.0%)	0
Nervous system disorders	3 (12.0%)	2 (8.0%)
Hemianopia homonymous	1 (4.0%)	0
Hemiparesis	1 (4.0%)	0
Migraine	1 (4.0%)	0
Restless legs syndrome	1 (4.0%)	0
Sciatica	0	1 (4.0%)
Tension headache	0	1 (4.0%)
Eye disorders	0	1 (4.0%)
Ocular hypertension	0	1 (4.0%)
Cardiac disorders	0	1 (4.0%)
Palpitations	0	1 (4.0%)
Vascular disorders	6 (24.0%)	4 (16.0%)
Hypertension	6 (24.0%)	4 (16.0%)
Respiratory, thoracic and mediastinal disorders	4 (16.0%)	6 (24.0%)
Asthma	2 (8.0%)	5 (20.0%)
Nasal polyps	0	1 (4.0%)
Sleep apnoea syndrome	2 (8.0%)	1 (4.0%)
Gastrointestinal disorders	7 (28.0%)	3 (12.0%)
Constipation	1 (4.0%)	0
Duodenal ulcer	0	1 (4.0%)
Flatulence	0	1 (4.0%)
Gastrointestinal disorder	1 (4.0%)	0
Gastrooesophageal reflux disease	1 (4.0%)	0
Haemorrhoids	1 (4.0%)	1 (4.0%)
Hiatus hernia	2 (8.0%)	0
Irritable bowel syndrome	1 (4.0%)	0

System organ class/Preferred term	Dapagliflozin/ Exenatide (N=25)	Placebo (N=25)
Hepatobiliary disorders	1 (4.0%)	0
Hepatic steatosis	1 (4.0%)	0
Skin and subcutaneous tissue disorders	2 (8.0%)	3 (12.0%)
Cutaneous vasculitis	0	1 (4.0%)
Eczema	0	1 (4.0%)
Psoriasis	1 (4.0%)	1 (4.0%)
Rash	1 (4.0%)	0
Musculoskeletal and connective tissue disorders	4 (16.0%)	6 (24.0%)
Arthralgia	1 (4.0%)	2 (8.0%)
Osteoarthritis	2 (8.0%)	1 (4.0%)
Pain in extremity	1 (4.0%)	0
Psoriatic arthropathy	0	1 (4.0%)
Rheumatic disorder	0	1 (4.0%)
Spondyloarthropathy	0	1 (4.0%)
Synovial cyst	0	1 (4.0%)
Reproductive system and breast disorders	2 (8.0%)	0
Benign prostatic hyperplasia	1 (4.0%)	0
Menorrhagia	1 (4.0%)	0
Congenital, familial and genetic disorders	1 (4.0%)	0
Thalassaemia beta	1 (4.0%)	0
General disorders and administration site conditions	0	2 (8.0%)
Fatigue	0	1 (4.0%)
Peripheral swelling	0	1 (4.0%)
Injury, poisoning and procedural complications	0	2 (8.0%)
Injury	0	1 (4.0%)
Meniscus injury	0	1 (4.0%)

Concurrent diseases are coded according to MedDRA version 18.0E.
Percentages are based on the number of subjects in the applicable analysis set.

Table 73 Concurrent Diseases. Full analysis set

System organ class/Preferred term	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Infections and infestations	2 (8.0%)	1 (4.2%)
Chronic sinusitis	1 (4.0%)	0
Herpes simplex	0	1 (4.2%)
Herpes virus infection	1 (4.0%)	0
Blood and lymphatic system disorders	1 (4.0%)	1 (4.2%)
Anaemia folate deficiency	0	1 (4.2%)
Anaemia macrocytic	1 (4.0%)	0
Immune system disorders	1 (4.0%)	3 (12.5%)
Seasonal allergy	1 (4.0%)	3 (12.5%)
Endocrine disorders	3 (12.0%)	3 (12.5%)
Goitre	0	1 (4.2%)
Hypopituitarism	0	1 (4.2%)
Hypothyroidism	3 (12.0%)	1 (4.2%)
Metabolism and nutrition disorders	2 (8.0%)	1 (4.2%)
Hyperlipidaemia	1 (4.0%)	0
Vitamin B12 deficiency	1 (4.0%)	0
Vitamin D deficiency	0	1 (4.2%)
Psychiatric disorders	3 (12.0%)	1 (4.2%)
Depression	2 (8.0%)	1 (4.2%)
Sleep disorder	1 (4.0%)	0
Nervous system disorders	3 (12.0%)	2 (8.3%)
Hemianopia homonymous	1 (4.0%)	0
Hemiparesis	1 (4.0%)	0
Migraine	1 (4.0%)	0
Restless legs syndrome	1 (4.0%)	0
Sciatica	0	1 (4.2%)
Tension headache	0	1 (4.2%)
Eye disorders	0	1 (4.2%)
Ocular hypertension	0	1 (4.2%)
Cardiac disorders	0	1 (4.2%)
Palpitations	0	1 (4.2%)
Vascular disorders	6 (24.0%)	4 (16.7%)
Hypertension	6 (24.0%)	4 (16.7%)
Respiratory, thoracic and mediastinal disorders	4 (16.0%)	6 (25.0%)
Asthma	2 (8.0%)	5 (20.8%)
Nasal polyps	0	1 (4.2%)
Sleep apnoea syndrome	2 (8.0%)	1 (4.2%)
Gastrointestinal disorders	7 (28.0%)	3 (12.5%)
Constipation	1 (4.0%)	0
Duodenal ulcer	0	1 (4.2%)
Flatulence	0	1 (4.2%)
Gastrointestinal disorder	1 (4.0%)	0
Gastrooesophageal reflux disease	1 (4.0%)	0
Haemorrhoids	1 (4.0%)	1 (4.2%)

System organ class/Preferred term	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Hiatus hernia	2 (8.0%)	0
Irritable bowel syndrome	1 (4.0%)	0
Hepatobiliary disorders	1 (4.0%)	0
Hepatic steatosis	1 (4.0%)	0
Skin and subcutaneous tissue disorders	2 (8.0%)	3 (12.5%)
Cutaneous vasculitis	0	1 (4.2%)
Eczema	0	1 (4.2%)
Psoriasis	1 (4.0%)	1 (4.2%)
Rash	1 (4.0%)	0
Musculoskeletal and connective tissue disorders	4 (16.0%)	6 (25.0%)
Arthralgia	1 (4.0%)	2 (8.3%)
Osteoarthritis	2 (8.0%)	1 (4.2%)
Pain in extremity	1 (4.0%)	0
Psoriatic arthropathy	0	1 (4.2%)
Rheumatic disorder	0	1 (4.2%)
Spondyloarthropathy	0	1 (4.2%)
Synovial cyst	0	1 (4.2%)
Reproductive system and breast disorders	2 (8.0%)	0
Benign prostatic hyperplasia	1 (4.0%)	0
Menorrhagia	1 (4.0%)	0
Congenital, familial and genetic disorders	1 (4.0%)	0
Thalassaemia beta	1 (4.0%)	0
General disorders and administration site conditions	0	2 (8.3%)
Fatigue	0	1 (4.2%)
Peripheral swelling	0	1 (4.2%)
Injury, poisoning and procedural complications	0	2 (8.3%)
Injury	0	1 (4.2%)
Meniscus injury	0	1 (4.2%)

Concurrent diseases are coded according to MedDRA version 18.0E.
Percentages are based on the number of subjects in the applicable analysis set.

14.1.8 Prior Procedures

Table 74 Prior procedures. Safety analysis set

System organ class/Preferred term	Dapagliflozin/ Exenatide (N=25)	Placebo (N=25)
Surgical and medical procedures	15 (60.0%)	10 (40.0%)
Appendicectomy	6 (24.0%)	2 (8.0%)
Chemotherapy	0	1 (4.0%)
Cholecystectomy	1 (4.0%)	3 (12.0%)
Hip arthroplasty	0	1 (4.0%)
Hysterectomy	1 (4.0%)	0
Inguinal hernia repair	1 (4.0%)	0
Knee arthroplasty	2 (8.0%)	1 (4.0%)
Knee operation	1 (4.0%)	2 (8.0%)
Lymphoma operation	0	1 (4.0%)
Neck surgery	0	1 (4.0%)
Oesophagogastric fundoplasty	1 (4.0%)	0
Renal stone removal	0	1 (4.0%)
Shoulder operation	2 (8.0%)	0
Surgery	1 (4.0%)	1 (4.0%)
Tendon operation	2 (8.0%)	0
Testicular operation	1 (4.0%)	0
Thrombosis prophylaxis	1 (4.0%)	0
Thyroidectomy	2 (8.0%)	0
Tonsillectomy	1 (4.0%)	1 (4.0%)
Uterine prolapse repair	0	1 (4.0%)
Varicose vein operation	1 (4.0%)	0

Surgical history is coded according to MedDRA version 18.0E.
Percentages are based on the number of subjects in the applicable analysis set.

Table 75 Prior procedures. Full analysis set

System organ class/Preferred term	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Surgical and medical procedures	15 (60.0%)	10 (41.7%)
Appendicectomy	6 (24.0%)	2 (8.3%)
Chemotherapy	0	1 (4.2%)
Cholecystectomy	1 (4.0%)	3 (12.5%)
Hip arthroplasty	0	1 (4.2%)
Hysterectomy	1 (4.0%)	0
Inguinal hernia repair	1 (4.0%)	0
Knee arthroplasty	2 (8.0%)	1 (4.2%)
Knee operation	1 (4.0%)	2 (8.3%)
Lymphoma operation	0	1 (4.2%)
Neck surgery	0	1 (4.2%)
Oesophagogastric fundoplasty	1 (4.0%)	0
Renal stone removal	0	1 (4.2%)
Shoulder operation	2 (8.0%)	0
Surgery	1 (4.0%)	1 (4.2%)
Tendon operation	2 (8.0%)	0
Testicular operation	1 (4.0%)	0
Thrombosis prophylaxis	1 (4.0%)	0
Thyroidectomy	2 (8.0%)	0
Tonsillectomy	1 (4.0%)	1 (4.2%)
Uterine prolapse repair	0	1 (4.2%)
Varicose vein operation	1 (4.0%)	0

Surgical history is coded according to MedDRA version 18.0E.
Percentages are based on the number of subjects in the applicable analysis set.

14.1.9 Concomitant Procedures

Table 76 Concomitant procedures. Safety analysis set

System organ class/Preferred term	Dapagliflozin/ Exenatide (N=25)	Placebo (N=25)
Surgical and medical procedures	3 (12.0%)	6 (24.0%)
Continuous positive airway pressure	1 (4.0%)	0
Contraception	0	1 (4.0%)
Contraceptive implant	0	1 (4.0%)
Hormone replacement therapy	1 (4.0%)	0
Hysterectomy	0	1 (4.0%)
Knee arthroplasty	1 (4.0%)	0
Nasal polypectomy	0	1 (4.0%)
Oral contraception	0	1 (4.0%)
Rotator cuff repair	0	1 (4.0%)

Concurrent surgical procedures are coded according to MedDRA version 18.0E.
Percentages are based on the number of subjects in the applicable analysis set.

Table 77 Concomitant procedures. Full analysis set

System organ class/Preferred term	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Surgical and medical procedures	3 (12.0%)	6 (25.0%)
Continuous positive airway pressure	1 (4.0%)	0
Contraception	0	1 (4.2%)
Contraceptive implant	0	1 (4.2%)
Hormone replacement therapy	1 (4.0%)	0
Hysterectomy	0	1 (4.2%)
Knee arthroplasty	1 (4.0%)	0
Nasal polypectomy	0	1 (4.2%)
Oral contraception	0	1 (4.2%)
Rotator cuff repair	0	1 (4.2%)

Concurrent surgical procedures are coded according to MedDRA version 18.0E.
Percentages are based on the number of subjects in the applicable analysis set.

14.1.10 Prior Medication

Table 78 Prior medication. Safety analysis set

Therapeutic main group/Preferred term	Dapagliflozin/ Exenatide (N=25)	Placebo (N=25)
ANALGESICS	1 (4.0%)	1 (4.0%)
PARACETAMOL	1 (4.0%)	1 (4.0%)
TRAMADOL	0	1 (4.0%)
ANTHELMINTICS	0	1 (4.0%)
MEBENDAZOLE	0	1 (4.0%)
ANTIANEMIC PREPARATIONS	1 (4.0%)	0
CALCIUM PHOSPHATE+FOLIC ACID	1 (4.0%)	0
ANTIBACTERIALS FOR SYSTEMIC USE	1 (4.0%)	0
DOXYCYCLINE	1 (4.0%)	0
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	1 (4.0%)	1 (4.0%)
DICLOFENAC	0	1 (4.0%)
IBUPROFEN	1 (4.0%)	1 (4.0%)
ANTINEOPLASTIC AGENTS	1 (4.0%)	0
* ANTINEOPLASTIC AGENTS	1 (4.0%)	0
ANTIOBESITY PREPARATIONS, EXCL. DIET PRODUCTS	6 (24.0%)	1 (4.0%)
ORLISTAT	4 (16.0%)	1 (4.0%)
SIBUTRAMINE HYDROCHLORIDE	3 (12.0%)	0
ANTITHROMBOTIC AGENTS	1 (4.0%)	0
ACETYLSALICYLIC ACID	1 (4.0%)	0
ANTIVIRALS FOR SYSTEMIC USE	1 (4.0%)	0
VALACICLOVIR HYDROCHLORIDE	1 (4.0%)	0
NO MATCH	1 (4.0%)	0
RIMONABANT	1 (4.0%)	0
PSYCHOANALEPTICS	1 (4.0%)	0
CITALOPRAM	1 (4.0%)	0
PSYCHOLEPTICS	0	1 (4.0%)
PREGABALIN	0	1 (4.0%)

Prior medication is coded according to AZ Drug Dictionary version 14.2.
Percentages are based on the number of subjects in the applicable analysis set..
Source: G:\StudData\Uppsala University\Dapalost\BIS\SASprog\DDP\BIS\Tables\Prior medication.sas

Table 79 Prior medication. Full analysis set

Therapeutic main group/Preferred term	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
ANALGESICS	1 (4.0%)	1 (4.2%)
PARACETAMOL	1 (4.0%)	1 (4.2%)
TRAMADOL	0	1 (4.2%)
ANTHELMINTICS	0	1 (4.2%)
MEBENDAZOLE	0	1 (4.2%)
ANTIANEMIC PREPARATIONS	1 (4.0%)	0
CALCIUM PHOSPHATE+FOLIC ACID	1 (4.0%)	0
ANTIBACTERIALS FOR SYSTEMIC USE	1 (4.0%)	0
DOXYCYCLINE	1 (4.0%)	0
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	1 (4.0%)	1 (4.2%)
DICLOFENAC	0	1 (4.2%)
IBUPROFEN	1 (4.0%)	1 (4.2%)
ANTINEOPLASTIC AGENTS	1 (4.0%)	0
* ANTINEOPLASTIC AGENTS	1 (4.0%)	0
ANTIOBESITY PREPARATIONS, EXCL. DIET PRODUCTS	6 (24.0%)	1 (4.2%)
ORLISTAT	4 (16.0%)	1 (4.2%)
SIBUTRAMINE HYDROCHLORIDE	3 (12.0%)	0
ANTITHROMBOTIC AGENTS	1 (4.0%)	0
ACETYLSALICYLIC ACID	1 (4.0%)	0
ANTIVIRALS FOR SYSTEMIC USE	1 (4.0%)	0
VALACICLOVIR HYDROCHLORIDE	1 (4.0%)	0
NO MATCH	1 (4.0%)	0
RIMONABANT	1 (4.0%)	0
PSYCHOANALEPTICS	1 (4.0%)	0
CITALOPRAM	1 (4.0%)	0
PSYCHOLEPTICS	0	1 (4.2%)
PREGABALIN	0	1 (4.2%)

Prior medication is coded according to AZ Drug Dictionary version 14.2.
Percentages are based on the number of subjects in the applicable analysis set..
Source: G:\StudData\Uppsala University\Dapalost\BIS\SASprog\DDP\BIS\Tables\Prior medication.sas

14.1.11 Concomitant Medication

Table 80 Concomitant medication. Safety analysis set

Therapeutic main group/Preferred term	Dapagliflozin/ Exenatide (N=25)	Placebo (N=25)
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	4 (16.0%)	6 (24.0%)
CANDESARTAN	0	1 (4.0%)
CANDESARTAN CILEXETIL	1 (4.0%)	0
ENALAPRIL	0	2 (8.0%)
LOSARTAN	2 (8.0%)	3 (12.0%)
RAMIPRIL	1 (4.0%)	0
ANALGESICS	12 (48.0%)	9 (36.0%)
ACETYLSALICYLIC ACID	3 (12.0%)	0
BUPRENORPHINE	0	1 (4.0%)
MORPHINE	0	2 (8.0%)
MORPHINE SULFATE	0	1 (4.0%)
OXYCODONE HYDROCHLORIDE	0	1 (4.0%)
PARACETAMOL	11 (44.0%)	9 (36.0%)
PARACETAMOL+PHENYLEPHRINE	1 (4.0%)	0
SUMATRIPTAN	0	1 (4.0%)
TRAMADOL	0	1 (4.0%)
TRAMADOL HYDROCHLORIDE	0	1 (4.0%)
ANESTHETICS	1 (4.0%)	0
LIDOCAINE	1 (4.0%)	0
ANTI-PARKINSON DRUGS	1 (4.0%)	0
BENSERAZIDE+LEVODOPA	1 (4.0%)	0
ANTIANEMIC PREPARATIONS	5 (20.0%)	1 (4.0%)
CALCIUM PHOSPHATE+FOLIC ACID	1 (4.0%)	1 (4.0%)
CYANOCOBALAMIN	5 (20.0%)	0
FERROUS SULFATE	1 (4.0%)	0
ANTIBACTERIALS FOR SYSTEMIC USE	4 (16.0%)	4 (16.0%)
* ANTIBACTERIALS FOR SYSTEMIC USE	1 (4.0%)	0
AMOXICILLIN	1 (4.0%)	0
AMOXICILLIN+CLAVULANIC ACID	0	1 (4.0%)
BENZYLPENICILLIN	0	1 (4.0%)
CEFIXIME	0	1 (4.0%)
DOXYCYCLINE MONOHYDRATE	0	1 (4.0%)
FLUCLOXACILLIN SODIUM	2 (8.0%)	1 (4.0%)
GENTAMICIN SULFATE	0	1 (4.0%)
PHENOXYMETHYLPENICILLIN POTASSIUM	2 (8.0%)	1 (4.0%)
ANTIFUNGALS FOR DERMATOLOGICAL USE	3 (12.0%)	0
ECONAZOLE NITRATE	1 (4.0%)	0
HYDROCORTISONE+MICONAZOLE	2 (8.0%)	0

Therapeutic main group/Preferred term	Dapagliflozin/ Exenatide (N=25)	Placebo (N=25)
ANTIHISTAMINES FOR SYSTEMIC USE	4 (16.0%)	3 (12.0%)
CETIRIZINE	0	1 (4.0%)
CETIRIZINE HYDROCHLORIDE	0	1 (4.0%)
CLEMASTINE	1 (4.0%)	0
EBASTINE	1 (4.0%)	1 (4.0%)
LORATADINE	2 (8.0%)	0
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	9 (36.0%)	9 (36.0%)
CELECOXIB	0	1 (4.0%)
DICLOFENAC	2 (8.0%)	1 (4.0%)
DICLOFENAC POTASSIUM	1 (4.0%)	0
IBUPROFEN	6 (24.0%)	4 (16.0%)
KETOPROFEN	0	2 (8.0%)
NAPROXEN	2 (8.0%)	1 (4.0%)
ANTINEOPLASTIC AGENTS	0	1 (4.0%)
METHOTREXATE	0	1 (4.0%)
ANTITHROMBOTIC AGENTS	0	3 (12.0%)
ACETYLSALICYLIC ACID	0	2 (8.0%)
* ANTITHROMBOTIC AGENTS	0	1 (4.0%)
ANTIVIRALS FOR SYSTEMIC USE	0	1 (4.0%)
VALACICLOVIR	0	1 (4.0%)
BETA BLOCKING AGENTS	0	1 (4.0%)
METOPROLOL TARTRATE	0	1 (4.0%)
CALCIUM CHANNEL BLOCKERS	0	3 (12.0%)
AMLODIPINE	0	1 (4.0%)
FELODIPINE	0	2 (8.0%)
CORTICOSTEROIDS FOR SYSTEMIC USE	0	3 (12.0%)
BETAMETHASONE	0	1 (4.0%)
BUDESONIDE	0	1 (4.0%)
CORTISONE	0	1 (4.0%)
CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS	3 (12.0%)	2 (8.0%)
BETAMETHASONE	0	1 (4.0%)
* CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS	1 (4.0%)	0
CLOBETASOL PROPIONATE	1 (4.0%)	0
HYDROCORTISONE	1 (4.0%)	1 (4.0%)
COUGH AND COLD PREPARATIONS	0	1 (4.0%)
BROMHEXINE HYDROCHLORIDE	0	1 (4.0%)
DIURETICS	4 (16.0%)	1 (4.0%)

Therapeutic main group/Preferred term	Dapagliflozin/ Exenatide (N=25)	Placebo (N=25)
AMILORIDE	1 (4.0%)	0
AMILORIDE+HYDROCHLOROTHIAZIDE	2 (8.0%)	0
BENDROFLUMETHIAZIDE	1 (4.0%)	0
FUROSEMIDE	0	1 (4.0%)
HYDROCHLOROTHIAZIDE	1 (4.0%)	0
DRUGS FOR ACID RELATED DISORDERS	8 (32.0%)	3 (12.0%)
CALCIUM CARBONATE+MAGNESIUM HYDROXIDE	2 (8.0%)	0
FAMOTIDINE	1 (4.0%)	0
GAVISCON /OLD FORM/	1 (4.0%)	0
OMEPRAZOLE	5 (20.0%)	3 (12.0%)
PANTOPRAZOLE	1 (4.0%)	0
DRUGS FOR CONSTIPATION	1 (4.0%)	0
PLANTAGO AFRA SEED+SODIUM CHLORIDE+THIAMINE	1 (4.0%)	0
DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS	0	2 (8.0%)
DIMETICONE	0	1 (4.0%)
HYOSCINE BUTYLBROMIDE	0	1 (4.0%)
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	2 (8.0%)	5 (20.0%)
BUDESONIDE+FORMOTEROL	1 (4.0%)	1 (4.0%)
MONTELUKAST	1 (4.0%)	2 (8.0%)
TERBUTALINE	1 (4.0%)	0
TERBUTALINE SULFATE	0	4 (16.0%)
GENERAL NUTRIENTS	0	1 (4.0%)
GLUCOSE	0	1 (4.0%)
GYNECOLOGICAL ANTIINFECTIVES AND ANTISEPTICS	3 (12.0%)	0
CIPROFLOXACIN	1 (4.0%)	0
CLINDAMYCIN HYDROCHLORIDE	1 (4.0%)	0
FLUCONAZOLE	1 (4.0%)	0
IMMUNOSTIMULANTS	1 (4.0%)	0
ECHINACEA PURPUREA	1 (4.0%)	0
IMMUNOSUPPRESSANTS	1 (4.0%)	0
ETANERCEPT	1 (4.0%)	0
LIPID MODIFYING AGENTS	1 (4.0%)	2 (8.0%)
ATORVASTATIN	0	1 (4.0%)
EZETIMIBE	0	1 (4.0%)
SIMVASTATIN	1 (4.0%)	1 (4.0%)
MINERAL SUPPLEMENTS	1 (4.0%)	1 (4.0%)
CALCIUM CARBONATE+COLECALCIFEROL	0	1 (4.0%)
POTASSIUM CHLORIDE	1 (4.0%)	0

Therapeutic main group/Preferred term	Dapagliflozin/ Exenatide (N=25)	Placebo (N=25)
NASAL PREPARATIONS	1 (4.0%)	2 (8.0%)
MOMETASONE FUROATE	1 (4.0%)	1 (4.0%)
PHENYLPROPANOLAMINE HYDROCHLORIDE	0	1 (4.0%)
NO MATCH	2 (8.0%)	3 (12.0%)
AL DIACETATE+HYDROCORTISONE+LIDOCAINE+ZN OXID	1 (4.0%)	0
AZELASTINE+FLUTICASONE	0	1 (4.0%)
BETAMETHASONE+CALCIPOTRIOL	0	1 (4.0%)
CICLESONIDE	0	1 (4.0%)
MACROGOL+K CHLORIDE+NA BICARBONATE+NA CHLORID	1 (4.0%)	0
PSYCHOANALEPTICS	2 (8.0%)	3 (12.0%)
CITALOPRAM	0	2 (8.0%)
FLUOXETINE	1 (4.0%)	0
MIANSERIN	1 (4.0%)	0
SERTRALINE	0	1 (4.0%)
PSYCHOLEPTICS	1 (4.0%)	1 (4.0%)
ZOLPIDEM TARTRATE	0	1 (4.0%)
ZOPICLONE	1 (4.0%)	0
SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM	2 (8.0%)	6 (24.0%)
DESOGESTREL	1 (4.0%)	1 (4.0%)
ESTRADIOL+MEDROXYPROGESTERONE	1 (4.0%)	0
ESTRIOL	0	1 (4.0%)
ETONOGESTREL	0	1 (4.0%)
NORETHISTERONE	0	1 (4.0%)
PROGESTERONE	0	1 (4.0%)
TESTOSTERONE UNDECANOATE	0	1 (4.0%)
THROAT PREPARATIONS	1 (4.0%)	0
BAFUCIN	1 (4.0%)	0
THYROID THERAPY	5 (20.0%)	2 (8.0%)
LEVOTHYROXINE SODIUM	5 (20.0%)	2 (8.0%)
LIOTHYRONINE	1 (4.0%)	0
TOPICAL PRODUCTS FOR JOINT AND MUSCULAR PAIN	2 (8.0%)	0
ACETYLSALICYLIC ACID	1 (4.0%)	0
DICLOFENAC	1 (4.0%)	0
UROLOGICALS	1 (4.0%)	0
ALFUZOSIN	1 (4.0%)	0
FINASTERIDE	1 (4.0%)	0
VITAMINS	0	2 (8.0%)
* VITAMIN D AND ANALOGUES	0	1 (4.0%)

Therapeutic main group/Preferred term	Dapagliflozin/ Exenatide (N=25)	Placebo (N=25)
COLECALCIFEROL	0	1 (4.0%)

Concomitant medication is coded according to AZ Drug Dictionary version 14.2.
Percentages are based on the number of subjects in the applicable analysis set.
Source: G:\StudData\Uppsala University\Dapalost\BIS\SASprog\DDP\BIS\Tables\Concomitant medication.sas

Table 81 Concomitant medication. Full analysis set

Therapeutic main group/Preferred term	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	4 (16.0%)	6 (25.0%)
CANDESARTAN	0	1 (4.2%)
CANDESARTAN CILEXETIL	1 (4.0%)	0
ENALAPRIL	0	2 (8.3%)
LOSARTAN	2 (8.0%)	3 (12.5%)
RAMIPRIL	1 (4.0%)	0
ANALGESICS	12 (48.0%)	8 (33.3%)
ACETYLSALICYLIC ACID	3 (12.0%)	0
BUPRENORPHINE	0	1 (4.2%)
MORPHINE	0	2 (8.3%)
MORPHINE SULFATE	0	1 (4.2%)
OXYCODONE HYDROCHLORIDE	0	1 (4.2%)
PARACETAMOL	11 (44.0%)	8 (33.3%)
PARACETAMOL+PHENYLEPHRINE	1 (4.0%)	0
SUMATRIPTAN	0	1 (4.2%)
TRAMADOL	0	1 (4.2%)
TRAMADOL HYDROCHLORIDE	0	1 (4.2%)
ANESTHETICS	1 (4.0%)	0
LIDOCAINE	1 (4.0%)	0
ANTI-PARKINSON DRUGS	1 (4.0%)	0
BENSERAZIDE+LEVODOPA	1 (4.0%)	0
ANTIANEMIC PREPARATIONS	5 (20.0%)	1 (4.2%)
CALCIUM PHOSPHATE+FOLIC ACID	1 (4.0%)	1 (4.2%)
CYANOCOBALAMIN	5 (20.0%)	0
FERROUS SULFATE	1 (4.0%)	0
ANTIBACTERIALS FOR SYSTEMIC USE	4 (16.0%)	4 (16.7%)
* ANTIBACTERIALS FOR SYSTEMIC USE	1 (4.0%)	0
AMOXICILLIN	1 (4.0%)	0
AMOXICILLIN+CLAVULANIC ACID	0	1 (4.2%)
BENZYLPENICILLIN	0	1 (4.2%)
CEFIXIME	0	1 (4.2%)
DOXYCYCLINE MONOHYDRATE	0	1 (4.2%)
FLUCLOXACILLIN SODIUM	2 (8.0%)	1 (4.2%)
GENTAMICIN SULFATE	0	1 (4.2%)
PHENOXYMETHYLPENICILLIN POTASSIUM	2 (8.0%)	1 (4.2%)
ANTIFUNGALS FOR DERMATOLOGICAL USE	3 (12.0%)	0
ECONAZOLE NITRATE	1 (4.0%)	0
HYDROCORTISONE+MICONAZOLE	2 (8.0%)	0
ANTIHISTAMINES FOR SYSTEMIC USE	4 (16.0%)	3 (12.5%)

Therapeutic main group/Preferred term	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
CETIRIZINE	0	1 (4.2%)
CETIRIZINE HYDROCHLORIDE	0	1 (4.2%)
CLEMASTINE	1 (4.0%)	0
EBASTINE	1 (4.0%)	1 (4.2%)
LORATADINE	2 (8.0%)	0
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	9 (36.0%)	9 (37.5%)
CELECOXIB	0	1 (4.2%)
DICLOFENAC	2 (8.0%)	1 (4.2%)
DICLOFENAC POTASSIUM	1 (4.0%)	0
IBUPROFEN	6 (24.0%)	4 (16.7%)
KETOPROFEN	0	2 (8.3%)
NAPROXEN	2 (8.0%)	1 (4.2%)
ANTINEOPLASTIC AGENTS	0	1 (4.2%)
METHOTREXATE	0	1 (4.2%)
ANTITHROMBOTIC AGENTS	0	3 (12.5%)
ACETYLSALICYLIC ACID	0	2 (8.3%)
* ANTITHROMBOTIC AGENTS	0	1 (4.2%)
ANTIVIRALS FOR SYSTEMIC USE	0	1 (4.2%)
VALACICLOVIR	0	1 (4.2%)
BETA BLOCKING AGENTS	0	1 (4.2%)
METOPROLOL TARTRATE	0	1 (4.2%)
CALCIUM CHANNEL BLOCKERS	0	3 (12.5%)
AMLODIPINE	0	1 (4.2%)
FELODIPINE	0	2 (8.3%)
CORTICOSTEROIDS FOR SYSTEMIC USE	0	3 (12.5%)
BETAMETHASONE	0	1 (4.2%)
BUDESONIDE	0	1 (4.2%)
CORTISONE	0	1 (4.2%)
CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS	3 (12.0%)	2 (8.3%)
BETAMETHASONE	0	1 (4.2%)
* CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS	1 (4.0%)	0
CLOBETASOL PROPIONATE	1 (4.0%)	0
HYDROCORTISONE	1 (4.0%)	1 (4.2%)
COUGH AND COLD PREPARATIONS	0	1 (4.2%)
BROMHEXINE HYDROCHLORIDE	0	1 (4.2%)
DIURETICS	4 (16.0%)	1 (4.2%)
AMILORIDE	1 (4.0%)	0
AMILORIDE+HYDROCHLOROTHIAZIDE	2 (8.0%)	0

Therapeutic main group/Preferred term	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
BENDROFLUMETHIAZIDE	1 (4.0%)	0
FUROSEMIDE	0	1 (4.2%)
HYDROCHLOROTHIAZIDE	1 (4.0%)	0
DRUGS FOR ACID RELATED DISORDERS	8 (32.0%)	3 (12.5%)
CALCIUM CARBONATE+MAGNESIUM HYDROXIDE	2 (8.0%)	0
FAMOTIDINE	1 (4.0%)	0
GAVISCON /OLD FORM/	1 (4.0%)	0
OMEPRAZOLE	5 (20.0%)	3 (12.5%)
PANTOPRAZOLE	1 (4.0%)	0
DRUGS FOR CONSTIPATION	1 (4.0%)	0
PLANTAGO AFRA SEED+SODIUM CHLORIDE+THIAMINE	1 (4.0%)	0
DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS	0	2 (8.3%)
DIMETICONE	0	1 (4.2%)
HYOSCINE BUTYLBROMIDE	0	1 (4.2%)
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	2 (8.0%)	5 (20.8%)
BUDESONIDE+FORMOTEROL	1 (4.0%)	1 (4.2%)
MONTELUKAST	1 (4.0%)	2 (8.3%)
TERBUTALINE	1 (4.0%)	0
TERBUTALINE SULFATE	0	4 (16.7%)
GENERAL NUTRIENTS	0	1 (4.2%)
GLUCOSE	0	1 (4.2%)
GYNECOLOGICAL ANTIINFECTIVES AND ANTISEPTICS	3 (12.0%)	0
CIPROFLOXACIN	1 (4.0%)	0
CLINDAMYCIN HYDROCHLORIDE	1 (4.0%)	0
FLUCONAZOLE	1 (4.0%)	0
IMMUNOSTIMULANTS	1 (4.0%)	0
ECHINACEA PURPUREA	1 (4.0%)	0
IMMUNOSUPPRESSANTS	1 (4.0%)	0
ETANERCEPT	1 (4.0%)	0
LIPID MODIFYING AGENTS	1 (4.0%)	2 (8.3%)
ATORVASTATIN	0	1 (4.2%)
EZETIMIBE	0	1 (4.2%)
SIMVASTATIN	1 (4.0%)	1 (4.2%)
MINERAL SUPPLEMENTS	1 (4.0%)	1 (4.2%)
CALCIUM CARBONATE+COLECALCIFEROL	0	1 (4.2%)
POTASSIUM CHLORIDE	1 (4.0%)	0
NASAL PREPARATIONS	1 (4.0%)	2 (8.3%)

Therapeutic main group/Preferred term	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
MOMETASONE FUROATE	1 (4.0%)	1 (4.2%)
PHENYLPROPANOLAMINE HYDROCHLORIDE	0	1 (4.2%)
NO MATCH	2 (8.0%)	3 (12.5%)
AL DIACETATE+HYDROCORTISONE+LIDOCAINE+ZN OXID	1 (4.0%)	0
AZELASTINE+FLUTICASONE	0	1 (4.2%)
BETAMETHASONE+CALCIPOTRIOL	0	1 (4.2%)
CICLESONIDE	0	1 (4.2%)
MACROGOL+K CHLORIDE+NA BICARBONATE+NA CHLORID	1 (4.0%)	0
PSYCHOANALEPTICS	2 (8.0%)	3 (12.5%)
CITALOPRAM	0	2 (8.3%)
FLUOXETINE	1 (4.0%)	0
MIANSERIN	1 (4.0%)	0
SERTRALINE	0	1 (4.2%)
PSYCHOLEPTICS	1 (4.0%)	1 (4.2%)
ZOLPIDEM TARTRATE	0	1 (4.2%)
ZOPICLONE	1 (4.0%)	0
SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM	2 (8.0%)	6 (25.0%)
DESOGESTREL	1 (4.0%)	1 (4.2%)
ESTRADIOL+MEDROXYPROGESTERONE	1 (4.0%)	0
ESTRIOL	0	1 (4.2%)
ETONOGESTREL	0	1 (4.2%)
NORETHISTERONE	0	1 (4.2%)
PROGESTERONE	0	1 (4.2%)
TESTOSTERONE UNDECANOATE	0	1 (4.2%)
THROAT PREPARATIONS	1 (4.0%)	0
BAFUCIN	1 (4.0%)	0
THYROID THERAPY	5 (20.0%)	2 (8.3%)
LEVOTHYROXINE SODIUM	5 (20.0%)	2 (8.3%)
LIOTHYRONINE	1 (4.0%)	0
TOPICAL PRODUCTS FOR JOINT AND MUSCULAR PAIN	2 (8.0%)	0
ACETYLSALICYLIC ACID	1 (4.0%)	0
DICLOFENAC	1 (4.0%)	0
UROLOGICALS	1 (4.0%)	0
ALFUZOSIN	1 (4.0%)	0
FINASTERIDE	1 (4.0%)	0
VITAMINS	0	2 (8.3%)
* VITAMIN D AND ANALOGUES	0	1 (4.2%)

Therapeutic main group/Preferred term	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
COLECALCIFEROL	0	1 (4.2%)

Concomitant medication is coded according to AZ Drug Dictionary version 14.2.
Percentages are based on the number of subjects in the applicable analysis set.
Source: G:\StudData\Uppsala University\Dapalost\BIS\SASprog\DDP\BIS\Tables\Concomitant medication.sas

14.1.12 Treatment Compliance

Table 82 Compliance. Safety analysis set

	Dapagliflozin/ Exenatide (N=25)	Placebo (N=25)
Number of injections (received/planned)		
n/nmiss	25/0	25/0
Mean (SD)	97.46 (12.03)	99.04 (3.86)
Median	101.80	100.00
Q1, Q3	100.00, 102.90	98.20, 100.60
Min, Max	48.3, 104.8	86.0, 104.2
Number of tablets (received/planned)		
n/nmiss	25/0	24/1
Mean (SD)	96.02 (12.70)	98.91 (5.39)
Median	100.00	98.80
Q1, Q3	91.40, 101.20	97.60, 100.60
Min, Max	51.7, 115.6	88.9, 111.9

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.

14.2 EFFICACY DATA

14.2.1 Primary Efficacy Variable

Table 83 Mixed model for repeated measures of change from baseline in Body weight (kg) at week 24. Per-protocol analysis set

Body weight (kg)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Number of subjects included in analysis	22 (100.0%)	20 (100.0%)
Adjusted mean change (95% CI)	-4.36 (-6.04, -2.67)	-0.64 (-2.40, 1.12)
Difference (95% CI)	-3.72 (-6.14, -1.29)	
p-value	0.0036	

A mixed model for repeated measures (MMRM) adjusted for treatment, week, treatment*week, gender and baseline body weight was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Baseline = randomization (week 0)

Table 84 Mixed model for repeated measures of change from baseline in Body weight (kg). Full analysis set

Body weight (kg)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Week -2(-1)		
n/nmiss	25/0	24/0
Mean (SD)	106.82 (15.67)	102.61 (16.96)
Median	110.10	97.90
Q1, Q3	92.00, 116.30	93.30, 111.95
Min, Max	82.0, 143.2	73.7, 144.9
Week 0 (Baseline)		
n/nmiss	25/0	24/0
Mean (SD)	106.43 (15.55)	102.72 (17.26)
Median	108.10	97.70
Q1, Q3	93.60, 116.30	93.50, 111.80
Min, Max	82.0, 142.8	73.6, 145.8
Week 4		
n/nmiss	25/0	24/0
Mean (SD)	105.51 (15.79)	102.13 (17.30)
Median	105.70	96.70
Q1, Q3	92.20, 116.10	92.70, 112.55
Min, Max	79.0, 140.8	73.6, 145.0
Adjusted mean change (95% CI)	-0.97 (-1.64, -0.29)	-0.60 (-1.28, 0.08)
Difference (95% CI)	-0.37 (-1.31, 0.58)	
p-value	0.4384	
Week 8		
n/nmiss	24/1	23/1
Mean (SD)	104.93 (15.63)	102.21 (17.75)
Median	106.30	95.30
Q1, Q3	92.25, 116.00	91.30, 117.00
Min, Max	76.7, 138.7	74.0, 145.8

Body weight (kg)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Adjusted mean change (95% CI)	-2.15 (-3.09, -1.22)	-0.47 (-1.41, 0.47)
Difference (95% CI)	-1.68 (-3.00, -0.36)	
p-value	0.0136	
Week 12		
n/nmiss	23/2	21/3
Mean (SD)	102.37 (16.05)	103.38 (18.56)
Median	98.70	96.50
Q1, Q3	87.90, 113.50	92.60, 117.20
Min, Max	74.5, 138.1	75.1, 149.7
Adjusted mean change (95% CI)	-3.95 (-5.16, -2.75)	-0.44 (-1.66, 0.79)
Difference (95% CI)	-3.51 (-5.23, -1.80)	
p-value	0.0002	
Week 24		
n/nmiss	23/2	20/4
Mean (SD)	101.84 (17.36)	104.86 (17.38)
Median	98.50	96.05
Q1, Q3	85.30, 112.10	94.05, 116.10
Min, Max	75.0, 141.9	83.3, 150.2
Adjusted mean change (95% CI)	-4.48 (-6.08, -2.87)	-0.35 (-2.02, 1.32)
Difference (95% CI)	-4.13 (-6.44, -1.81)	
p-value	0.0008	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
A mixed model for repeated measures (MMRM) adjusted for treatment, week, treatment*week, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.

Table 85 Mixed model for repeated measures of change from baseline in Body weight (kg). Per-protocol analysis set

Body weight (kg)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Week -2(-1)		
n/nmiss	22/0	20/0
Mean (SD)	106.25 (15.82)	105.28 (16.69)
Median	106.65	98.95
Q1, Q3	91.70, 116.20	93.75, 116.55
Min, Max	82.0, 143.2	82.9, 144.9
Week 0 (Baseline)		
n/nmiss	22/0	20/0
Mean (SD)	105.72 (15.71)	105.46 (16.99)
Median	105.65	98.80
Q1, Q3	90.80, 115.00	94.70, 117.00
Min, Max	82.0, 142.8	82.3, 145.8
Week 4		
n/nmiss	22/0	20/0
Mean (SD)	104.98 (15.97)	104.68 (17.21)
Median	103.30	97.85

Body weight (kg)	**Dapagliflozin/ Exenatide (N=22)**	**Placebo (N=20)**
Q1, Q3	92.20, 116.10	92.85, 117.50
Min, Max	79.0, 140.8	81.9, 145.0
Adjusted mean change (95% CI)	-0.80 (-1.52, -0.08)	-0.82 (-1.56, -0.08)
Difference (95% CI)	0.02 (-0.99, 1.02)	
p-value	0.9711	
Week 8		
n/nmiss	22/0	20/0
Mean (SD)	103.86 (15.80)	104.81 (17.31)
Median	100.70	97.55
Q1, Q3	92.00, 115.90	93.35, 117.75
Min, Max	76.7, 138.7	81.9, 145.8
Adjusted mean change (95% CI)	-1.91 (-2.91, -0.92)	-0.68 (-1.72, 0.35)
Difference (95% CI)	-1.23 (-2.65, 0.18)	
p-value	0.0865	
Week 12		
n/nmiss	22/0	20/0
Mean (SD)	102.11 (16.38)	104.79 (17.84)
Median	98.45	97.55
Q1, Q3	87.90, 113.50	92.75, 118.05
Min, Max	74.5, 138.1	81.1, 149.7
Adjusted mean change (95% CI)	-3.66 (-4.92, -2.41)	-0.70 (-2.01, 0.60)
Difference (95% CI)	-2.96 (-4.76, -1.16)	
p-value	0.0019	
Week 24		
n/nmiss	22/0	20/0
Mean (SD)	101.42 (17.65)	104.86 (17.38)
Median	98.00	96.05
Q1, Q3	85.30, 112.10	94.05, 116.10
Min, Max	75.0, 141.9	83.3, 150.2
Adjusted mean change (95% CI)	-4.36 (-6.04, -2.67)	-0.64 (-2.40, 1.12)
Difference (95% CI)	-3.72 (-6.14, -1.29)	
p-value	0.0036	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
A mixed model for repeated measures (MMRM) adjusted for treatment, week, treatment*week, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Source: G:\StudData\Uppsala University\Dapalost\BIS\SASprog\DDP\BIS\Tables\Exploratory - Extended MMRM.sas

14.2.2 Alternative Primary Efficacy Model (Post-hoc Analysis)

Table 86 Mixed model for repeated measures of change from baseline in body weight (kg) at week 24. Alternative model. Per-protocol analysis set

Body weight (kg)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Number of subjects included in analysis	22	20
Adjusted mean change (95% CI)	-4.36 (-6.05, -2.67)	-0.63 (-2.40, 1.13)
Difference (95% CI)	-3.73 (-6.16, -1.30)	
p-value	0.0036	

A mixed model for repeated measures (MMRM) adjusted for treatment, week, the interaction between treatment and week, gender, baseline body weight and the interaction between baseline body weight and week was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.

14.2.1 Secondary Efficacy Variable

Table 87 Mixed model for repeated measures of percentage change from baseline in Body weight to week 24. Per-protocol analysis set

Body weight (%)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Number of subjects included in analysis	22 (100.0%)	20 (100.0%)
Adjusted mean change (95% CI)	-4.38 (-6.02, -2.75)	-0.64 (-2.35, 1.07)
Difference (95% CI)	-3.74 (-6.10, -1.39)	
p-value	0.0026	

A mixed model for repeated measures (MMRM) adjusted for treatment, week, treatment*week, gender and baseline body weight was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Baseline = randomization (week 0)

14.2.2 Exploratory Variables

14.2.2.1 At Least 5% and 10% Weight Reduction at Week 24

Table 88 At least 5% and 10% weight reduction at week 24. Per-protocol analysis set

	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
At least 5%	9 (40.9%)	0
At least 10%	3 (13.6%)	0

The percentage was based on N for the PPAS.
Baseline = randomization (week 0)
At least 5% = more than or equal to 5%
At least 10% = more than or equal to 10%

14.2.2.2 Absolute Change in Body Weight (kg) Between Screening and Week 24

Table 89 Mixed model for repeated measures of change from screening in body weight (kg) at week 24. Full analysis set

Body weight (kg)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Week -2-(-1) (Baseline)		
n/nmiss	25/0	24/0
Mean (SD)	106.82 (15.67)	102.61 (16.96)
Median	110.10	97.90
Q1, Q3	92.00, 116.30	93.30, 111.95
Min, Max	82.0, 143.2	73.7, 144.9
Week 0		
n/nmiss	25/0	24/0
Mean (SD)	106.43 (15.55)	102.72 (17.26)
Median	108.10	97.70
Q1, Q3	93.60, 116.30	93.50, 111.80
Min, Max	82.0, 142.8	73.6, 145.8
Week 4		
n/nmiss	25/0	24/0
Mean (SD)	105.51 (15.79)	102.13 (17.30)
Median	105.70	96.70
Q1, Q3	92.20, 116.10	92.70, 112.55
Min, Max	79.0, 140.8	73.6, 145.0
Week 8		
n/nmiss	24/1	23/1
Mean (SD)	104.93 (15.63)	102.21 (17.75)
Median	106.30	95.30
Q1, Q3	92.25, 116.00	91.30, 117.00
Min, Max	76.7, 138.7	74.0, 145.8
Week 12		
n/nmiss	23/2	21/3
Mean (SD)	102.37 (16.05)	103.38 (18.56)
Median	98.70	96.50
Q1, Q3	87.90, 113.50	92.60, 117.20
Min, Max	74.5, 138.1	75.1, 149.7
Week 24		
n/nmiss	23/2	20/4
Mean (SD)	101.84 (17.36)	104.86 (17.38)
Median	98.50	96.05
Q1, Q3	85.30, 112.10	94.05, 116.10
Min, Max	75.0, 141.9	83.3, 150.2
Number of subjects included in analysis	25	24
Adjusted mean change (95% CI)	-4.75 (-6.36, -3.15)	-0.23 (-1.91, 1.46)
Difference (95% CI)	-4.53 (-6.85, -2.21)	
p-value	0.0003	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
A mixed model for repeated measures (MMRM) adjusted for treatment, week, treatment*week, gender and screening body weight was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.

Table 90 Mixed model for repeated measures of change from screening in body weight (kg) at week 24. Per-protocol analysis set

Body weight (kg)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Week -2-(-1) (Baseline)		
n/nmiss	22/0	20/0
Mean (SD)	106.25 (15.82)	105.28 (16.69)
Median	106.65	98.95
Q1, Q3	91.70, 116.20	93.75, 116.55
Min, Max	82.0, 143.2	82.9, 144.9
Week 0		
n/nmiss	22/0	20/0
Mean (SD)	105.72 (15.71)	105.46 (16.99)
Median	105.65	98.80
Q1, Q3	90.80, 115.00	94.70, 117.00
Min, Max	82.0, 142.8	82.3, 145.8
Week 4		
n/nmiss	22/0	20/0
Mean (SD)	104.98 (15.97)	104.68 (17.21)
Median	103.30	97.85
Q1, Q3	92.20, 116.10	92.85, 117.50
Min, Max	79.0, 140.8	81.9, 145.0
Week 8		
n/nmiss	22/0	20/0
Mean (SD)	103.86 (15.80)	104.81 (17.31)
Median	100.70	97.55
Q1, Q3	92.00, 115.90	93.35, 117.75
Min, Max	76.7, 138.7	81.9, 145.8
Week 12		
n/nmiss	22/0	20/0
Mean (SD)	102.11 (16.38)	104.79 (17.84)
Median	98.45	97.55
Q1, Q3	87.90, 113.50	92.75, 118.05
Min, Max	74.5, 138.1	81.1, 149.7
Week 24		
n/nmiss	22/0	20/0
Mean (SD)	101.42 (17.65)	104.86 (17.38)
Median	98.00	96.05
Q1, Q3	85.30, 112.10	94.05, 116.10
Min, Max	75.0, 141.9	83.3, 150.2
Number of subjects included in analysis	22	20
Adjusted mean change (95% CI)	-4.79 (-6.52, -3.06)	-0.40 (-2.21, 1.41)
Difference (95% CI)	-4.39 (-6.89, -1.89)	
p-value	0.0010	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
A mixed model for repeated measures (MMRM) adjusted for treatment, week, treatment*week, gender and screening body weight was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.

14.2.2.3 Absolute Percentage Change in Body Weight (%) Between Screening and Week 24

Table 91 Mixed model for repeated measures of percentage change from screening in body weight (kg) at week 24. Full analysis set

Body weight (kg)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Week -2-(-1)		
n/nmiss	25/0	24/0
Mean (SD)	106.82 (15.67)	102.61 (16.96)
Median	110.10	97.90
Q1, Q3	92.00, 116.30	93.30, 111.95
Min, Max	82.0, 143.2	73.7, 144.9
Week 0 (Baseline)		
n/nmiss	25/0	24/0
Mean (SD)	106.43 (15.55)	102.72 (17.26)
Median	108.10	97.70
Q1, Q3	93.60, 116.30	93.50, 111.80
Min, Max	82.0, 142.8	73.6, 145.8
Week 4		
n/nmiss	25/0	24/0
Mean (SD)	105.51 (15.79)	102.13 (17.30)
Median	105.70	96.70
Q1, Q3	92.20, 116.10	92.70, 112.55
Min, Max	79.0, 140.8	73.6, 145.0
Week 8		
n/nmiss	24/1	23/1
Mean (SD)	104.93 (15.63)	102.21 (17.75)
Median	106.30	95.30
Q1, Q3	92.25, 116.00	91.30, 117.00
Min, Max	76.7, 138.7	74.0, 145.8
Week 12		
n/nmiss	23/2	21/3
Mean (SD)	102.37 (16.05)	103.38 (18.56)
Median	98.70	96.50
Q1, Q3	87.90, 113.50	92.60, 117.20
Min, Max	74.5, 138.1	75.1, 149.7
Week 24		
n/nmiss	23/2	20/4
Mean (SD)	101.84 (17.36)	104.86 (17.38)
Median	98.50	96.05
Q1, Q3	85.30, 112.10	94.05, 116.10
Min, Max	75.0, 141.9	83.3, 150.2
Number of subjects included in analysis	25	24
Adjusted mean change (95% CI)	-4.68 (-6.24, -3.11)	-0.19 (-1.83, 1.44)
Difference (95% CI)	-4.48 (-6.75, -2.22)	
p-value	0.0002	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
A mixed model for repeated measures (MMRM) adjusted for treatment, week, treatment*week, gender and screening body weight was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.

Table 92 Mixed model for repeated measures of percentage change from screening in body weight (kg) at week 24. Per-protocol analysis set

Body weight (kg)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Week -2-(-1)		
n/nmiss	22/0	20/0
Mean (SD)	106.25 (15.82)	105.28 (16.69)
Median	106.65	98.95
Q1, Q3	91.70, 116.20	93.75, 116.55
Min, Max	82.0, 143.2	82.9, 144.9
Week 0 (Baseline)		
n/nmiss	22/0	20/0
Mean (SD)	105.72 (15.71)	105.46 (16.99)
Median	105.65	98.80
Q1, Q3	90.80, 115.00	94.70, 117.00
Min, Max	82.0, 142.8	82.3, 145.8
Week 4		
n/nmiss	22/0	20/0
Mean (SD)	104.98 (15.97)	104.68 (17.21)
Median	103.30	97.85
Q1, Q3	92.20, 116.10	92.85, 117.50
Min, Max	79.0, 140.8	81.9, 145.0
Week 8		
n/nmiss	22/0	20/0
Mean (SD)	103.86 (15.80)	104.81 (17.31)
Median	100.70	97.55
Q1, Q3	92.00, 115.90	93.35, 117.75
Min, Max	76.7, 138.7	81.9, 145.8
Week 12		
n/nmiss	22/0	20/0
Mean (SD)	102.11 (16.38)	104.79 (17.84)
Median	98.45	97.55
Q1, Q3	87.90, 113.50	92.75, 118.05
Min, Max	74.5, 138.1	81.1, 149.7
Week 24		
n/nmiss	22/0	20/0
Mean (SD)	101.42 (17.65)	104.86 (17.38)
Median	98.00	96.05
Q1, Q3	85.30, 112.10	94.05, 116.10
Min, Max	75.0, 141.9	83.3, 150.2
Number of subjects included in analysis	22	20
Adjusted mean change (95% CI)	-4.75 (-6.42, -3.07)	-0.43 (-2.18, 1.33)
Difference (95% CI)	-4.32 (-6.74, -1.89)	
p-value	0.0009	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
A mixed model for repeated measures (MMRM) adjusted for treatment, week, treatment*week, gender and screening body weight was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.

14.2.2.4 Individual Body Weight Curves (Spaghetti plots)

Figure 16 **Body weight (kg) Subject level plot by week. Dapagliflozin/Exenatide. Full analysis set**

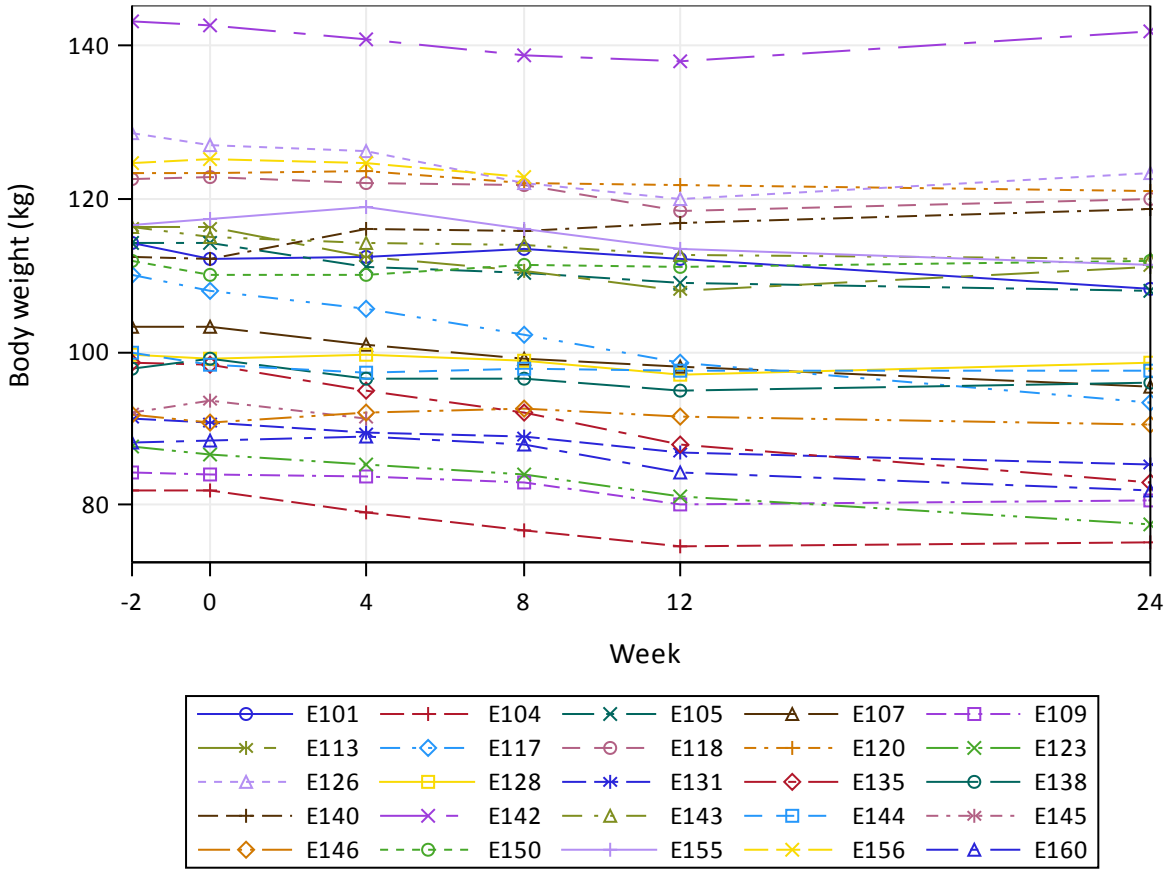


Figure 17 **Body weight (kg) Subject level plot by week. Placebo. Full analysis set**

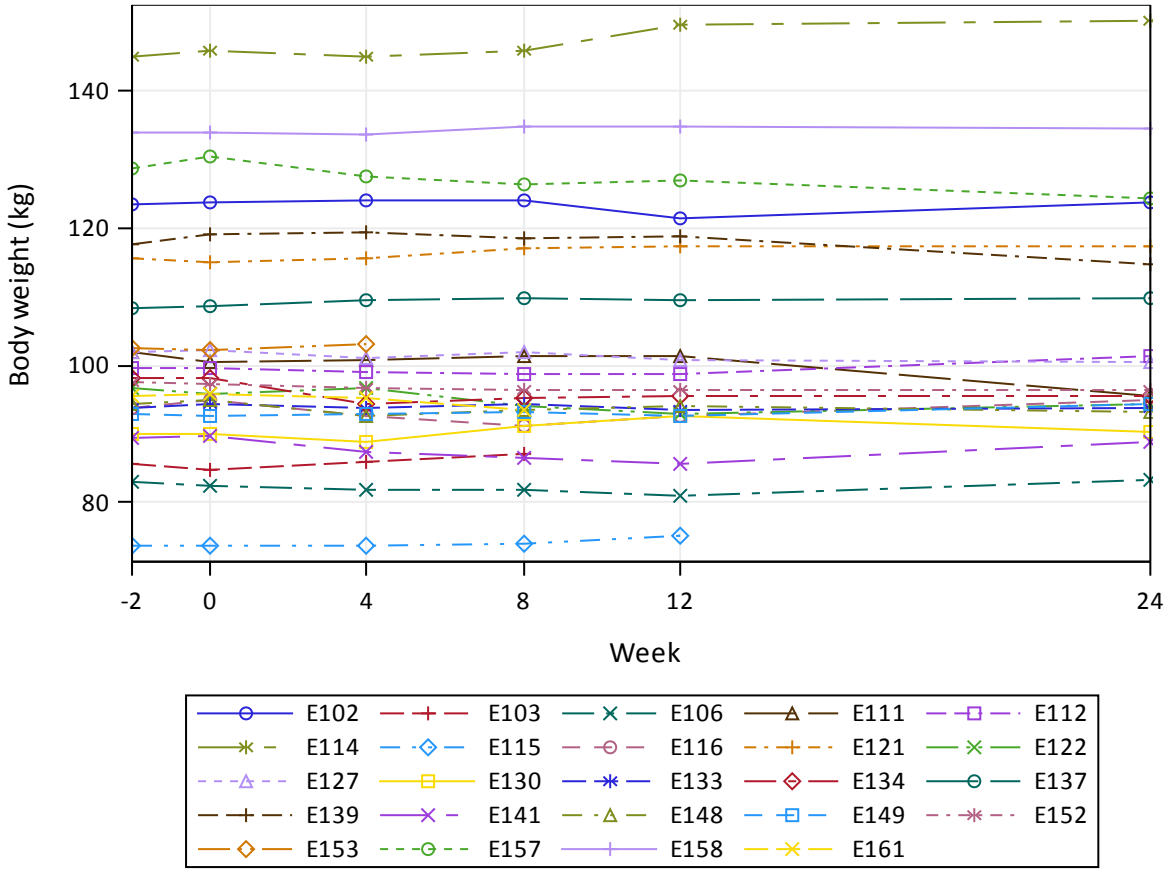


Figure 18 **Body weight (kg) Subject level plot by week. Dapagliflozin/Exenatide. Per-protocol analysis set**

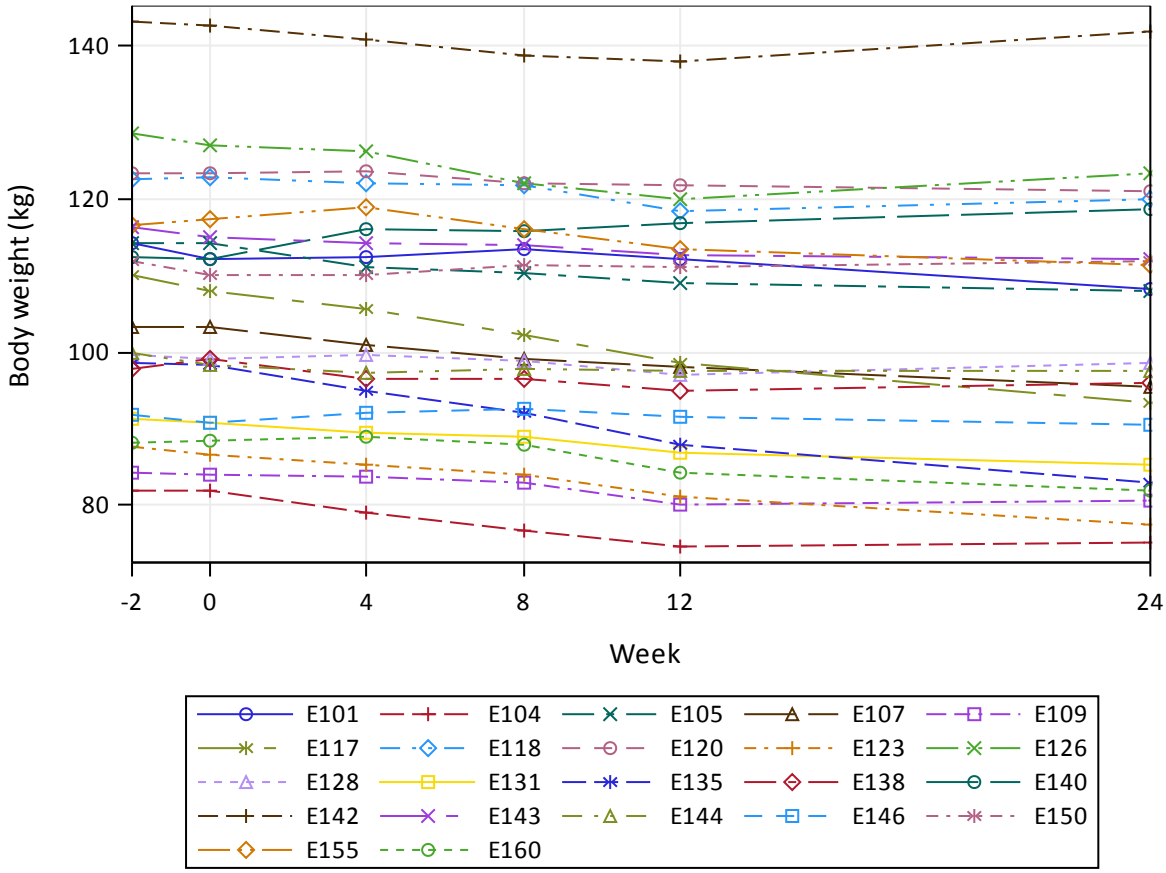
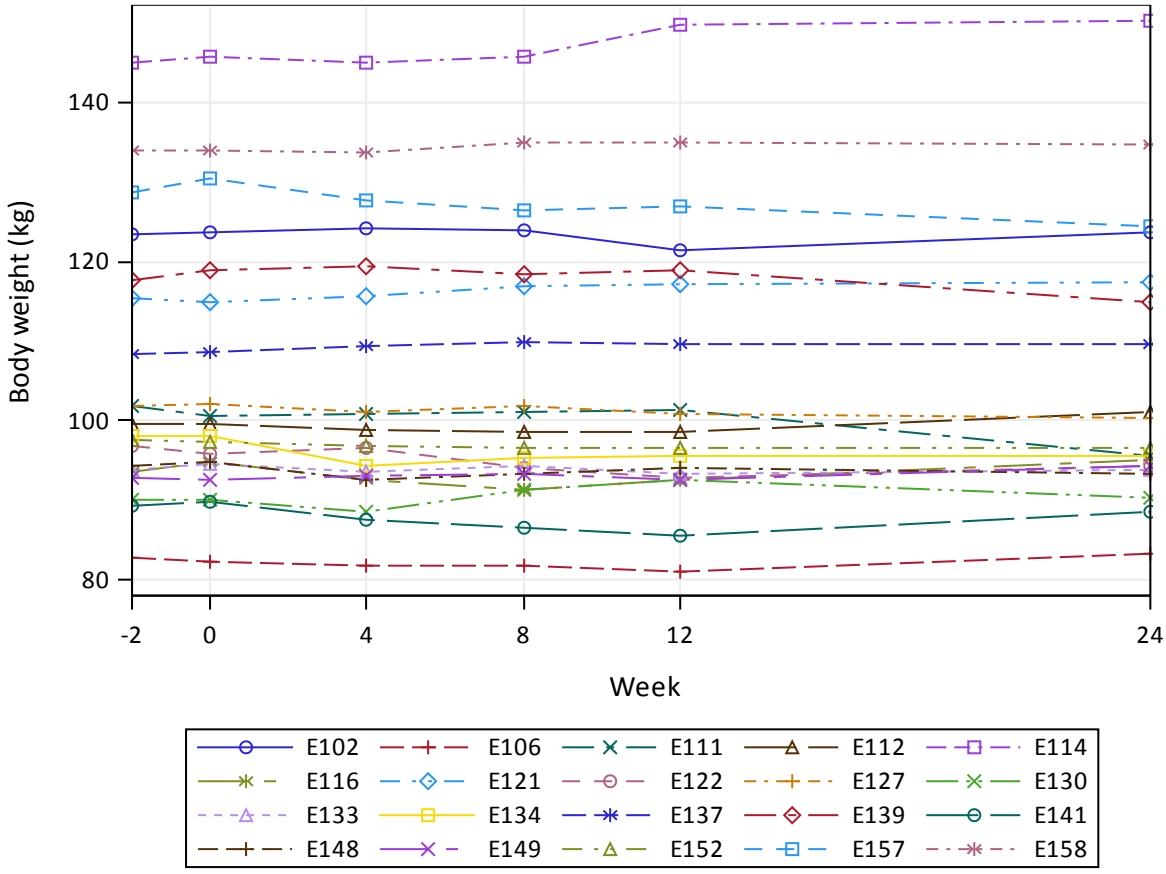


Figure 19 **Body weight (kg) Subject level plot by week. Placebo. Per-protocol analysis set**



14.2.2.5 Body Fat Composition

14.2.2.5.1 Total, visceral and subcutaneous adipose tissue and total lean tissue

Table 93 Analysis of covariance of change from baseline to week 24 in Total adipose tissue (L). Per-protocol analysis set

Total adipose tissue (L)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Week 0		
n/nmiss	21/1	19/1
Mean (SD)	56.64 (10.28)	54.00 (7.07)
Median	55.39	54.64
Q1, Q3	48.60, 65.95	48.65, 56.96
Min, Max	42.3, 76.1	41.3, 70.6
Week 24		
n/nmiss	22/0	19/1
Mean (SD)	52.67 (12.66)	53.75 (7.27)
Median	50.61	52.92
Q1, Q3	42.64, 62.19	49.86, 57.62
Min, Max	33.1, 76.0	39.0, 71.4
Number of subjects included in analysis	21	19
Adjusted mean change (95% CI)	-4.214 (-5.746, -2.681)	-0.142 (-1.753, 1.469)
Difference (95% CI)	-4.072 (-6.272, -1.872)	
p-value	0.0006	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Week 0 = Randomization

Table 94 Analysis of covariance of change from baseline to week 24 in Visceral adipose tissue (L). Per-protocol analysis set

Visceral adipose tissue (L)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Week 0		
n/nmiss	21/1	20/0
Mean (SD)	6.23 (3.17)	5.85 (2.56)
Median	5.58	4.89
Q1, Q3	3.69, 8.54	3.98, 7.49
Min, Max	2.0, 12.5	2.7, 11.0
Week 24		
n/nmiss	22/0	20/0
Mean (SD)	5.79 (3.05)	6.07 (2.58)
Median	4.72	5.29
Q1, Q3	3.54, 7.72	4.30, 7.68
Min, Max	1.8, 11.9	2.9, 11.7
Number of subjects included in analysis	21	20
Adjusted mean change (95% CI)	-0.378 (-0.622, -0.135)	0.228 (-0.013, 0.470)
Difference (95% CI)	-0.607 (-0.942, -0.271)	
p-value	0.0008	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Week 0 = Randomization

Table 95 Analysis of covariance of change from baseline to week 24 in Subcutaneous adipose tissue (L). Per-protocol analysis set

Subcutaneous adipose tissue (L)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Week 0		
n/nmiss	21/1	19/1
Mean (SD)	14.01 (3.91)	14.00 (2.64)
Median	13.06	13.35
Q1, Q3	11.68, 16.35	12.96, 14.54
Min, Max	8.2, 25.7	9.4, 19.6
Week 24		
n/nmiss	22/0	19/1
Mean (SD)	12.73 (4.59)	14.18 (2.63)
Median	11.98	13.32
Q1, Q3	9.03, 16.60	12.53, 15.24
Min, Max	7.2, 25.0	9.2, 19.5
Number of subjects included in analysis	21	19
Adjusted mean change (95% CI)	-1.323 (-1.841, -0.805)	0.127 (-0.418, 0.672)
Difference (95% CI)	-1.450 (-2.189, -0.710)	
p-value	0.0003	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Week 0 = Randomization

Table 96 Analysis of covariance of change from baseline to week 24 in Total lean tissue (L). Full analysis set

Total lean tissue (L)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Week 0		
n/nmiss	24/1	22/2
Mean (SD)	42.58 (9.58)	40.43 (9.06)
Median	41.24	36.78
Q1, Q3	34.31, 51.92	33.73, 50.34
Min, Max	29.5, 61.3	25.4, 56.4
Week 24		
n/nmiss	23/2	19/5
Mean (SD)	41.72 (9.31)	41.46 (8.19)
Median	38.70	37.99
Q1, Q3	35.35, 50.10	34.67, 49.30
Min, Max	28.1, 60.7	31.7, 56.2
Number of subjects included in analysis	22	19
Adjusted mean change (95% CI)	-0.910 (-1.446, -0.373)	-0.721 (-1.300, -0.142)
Difference (95% CI)	-0.188 (-0.939, 0.562)	
p-value	0.6137	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.

Table 97 Analysis of covariance of change from baseline to week 24 in Total lean tissue (L). Per-protocol analysis set

Total lean tissue (L)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Week 0		
n/nmiss	21/1	19/1
Mean (SD)	42.20 (9.53)	42.00 (8.60)
Median	40.98	39.86
Q1, Q3	35.08, 46.98	33.97, 50.50
Min, Max	29.5, 61.3	31.7, 56.4
Week 24		
n/nmiss	22/0	19/1
Mean (SD)	41.34 (9.34)	41.46 (8.19)
Median	38.67	37.99
Q1, Q3	35.35, 46.13	34.67, 49.30
Min, Max	28.1, 60.7	31.7, 56.2
Number of subjects included in analysis	21	19
Adjusted mean change (95% CI)	-0.910 (-1.476, -0.344)	-0.729 (-1.322, -0.136)
Difference (95% CI)	-0.181 (-0.950, 0.588)	
p-value	0.6355	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Week 0 = Randomization

14.2.2.5.2 Percentage Liver Fat, liver volume and total liver fat

Table 98 Analysis of covariance of change from baseline to week 24 in Liver volume (L). Full analysis set

Liver volume (L)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Week 0		
n/nmiss	25/0	22/2
Mean (SD)	1.89 (0.40)	1.79 (0.34)
Median	1.85	1.70
Q1, Q3	1.57, 2.18	1.55, 1.95
Min, Max	1.3, 2.7	1.1, 2.6
Week 24		
n/nmiss	23/2	20/4
Mean (SD)	1.95 (0.42)	1.91 (0.43)
Median	1.82	1.84
Q1, Q3	1.64, 2.22	1.59, 2.14
Min, Max	1.4, 3.1	1.3, 3.2
Number of subjects included in analysis	23	19
Adjusted mean change (95% CI)	0.044 (-0.015, 0.103)	-0.012 (-0.076, 0.053)
Difference (95% CI)	0.056 (-0.030, 0.142)	
p-value	0.1964	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.

Table 99 Analysis of covariance of change from baseline to week 24 in Total liver fat (L) at week 24. Full analysis set

Total liver fat (L)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Week 0		
n/nmiss	25/0	22/2
Mean (SD)	0.23 (0.26)	0.18 (0.19)
Median	0.17	0.12
Q1, Q3	0.04, 0.26	0.04, 0.27
Min, Max	0.0, 1.2	0.0, 0.7
Week 24		
n/nmiss	22/3	20/4
Mean (SD)	0.23 (0.30)	0.22 (0.25)
Median	0.11	0.11
Q1, Q3	0.04, 0.26	0.04, 0.34
Min, Max	0.0, 1.4	0.0, 0.9
Number of subjects included in analysis	22	19
Adjusted mean change (95% CI)	-0.020 (-0.054, 0.015)	-0.014 (-0.051, 0.023)
Difference (95% CI)	-0.006 (-0.056, 0.044)	
p-value	0.8119	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.

Table 100 Analysis of covariance of change from baseline to week 24 in Liver fat (%). Per-protocol analysis set

Liver fat (%)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Week 0		
n/nmiss	22/0	20/0
Mean (SD)	11.19 (11.22)	10.23 (8.92)
Median	6.25	7.30
Q1, Q3	2.90, 16.50	2.50, 17.80
Min, Max	0.9, 45.3	0.9, 26.5
Week 24		
n/nmiss	21/1	20/0
Mean (SD)	10.10 (10.85)	9.95 (9.39)
Median	5.90	6.15
Q1, Q3	2.80, 15.90	2.15, 16.95
Min, Max	1.2, 45.4	1.0, 33.0
Number of subjects included in analysis	21	20
Adjusted mean change (95% CI)	-1.38 (-2.78, 0.01)	-0.31 (-1.73, 1.11)
Difference (95% CI)	-1.07 (-3.04, 0.89)	
p-value	0.2765	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Week 0 = Randomization

Table 101 Analysis of covariance of change from baseline to week 24 in Liver volume (L). Per-protocol analysis set

Liver volume (L)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Week 0		
n/nmiss	22/0	19/1
Mean (SD)	1.90 (0.40)	1.85 (0.32)
Median	1.84	1.80
Q1, Q3	1.57, 2.26	1.57, 2.09
Min, Max	1.3, 2.7	1.5, 2.6
Week 24		
n/nmiss	22/0	20/0
Mean (SD)	1.95 (0.43)	1.91 (0.43)
Median	1.81	1.84
Q1, Q3	1.64, 2.22	1.59, 2.14
Min, Max	1.4, 3.1	1.3, 3.2
Number of subjects included in analysis	22	19
Adjusted mean change (95% CI)	0.042 (-0.020, 0.105)	-0.012 (-0.078, 0.053)
Difference (95% CI)	0.055 (-0.033, 0.143)	
p-value	0.2161	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Week 0 = Randomization

Table 102 Analysis of covariance of change from baseline to week 24 in total Liver fat (L). Per-protocol analysis set

Total liver fat (L)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Week 0		
n/nmiss	22/0	19/1
Mean (SD)	0.24 (0.28)	0.20 (0.20)
Median	0.14	0.11
Q1, Q3	0.04, 0.39	0.04, 0.29
Min, Max	0.0, 1.2	0.0, 0.7
Week 24		
n/nmiss	21/1	20/0
Mean (SD)	0.23 (0.31)	0.22 (0.25)
Median	0.10	0.11
Q1, Q3	0.04, 0.26	0.04, 0.34
Min, Max	0.0, 1.4	0.0, 0.9
Number of subjects included in analysis	21	19
Adjusted mean change (95% CI)	-0.020 (-0.056, 0.016)	-0.014 (-0.052, 0.024)
Difference (95% CI)	-0.006 (-0.057, 0.046)	
p-value	0.8196	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.

14.2.2.5.3 Body Fat as Measured by Bioimpedance

Table 103 Mixed model for repeated measures of change from baseline in Body fat (%) at week 24 as measured by bioimpedance. Full analysis set

Body fat (%)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Week 0 (Baseline)		
n/nmiss	25/0	24/0
Mean (SD)	41.71 (6.68)	39.25 (5.99)
Median	43.70	40.60
Q1, Q3	35.40, 47.00	35.10, 44.15
Min, Max	27.9, 50.3	27.2, 47.8
Week 12		
n/nmiss	23/2	21/3
Mean (SD)	41.33 (7.31)	39.52 (5.75)
Median	42.30	41.50
Q1, Q3	35.10, 48.10	35.60, 43.40
Min, Max	25.9, 51.6	27.8, 47.4
Week 24		
n/nmiss	23/2	20/4
Mean (SD)	40.90 (7.23)	39.25 (5.98)
Median	40.80	40.40
Q1, Q3	34.80, 46.90	34.90, 44.00
Min, Max	24.2, 51.4	28.0, 47.8
Number of subjects included in analysis	25	24
Adjusted mean change (95% CI)	-0.92 (-1.75, -0.08)	0.05 (-0.90, 0.99)
Difference (95% CI)	-0.96 (-2.21, 0.29)	
p-value	0.1283	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
A mixed model for repeated measures (MMRM) adjusted for treatment, week, treatment*week, gender and baseline body fat (%) was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.

Table 104 Mixed model for repeated measures of change from baseline in Body fat (%) at week 24 as measured by bioimpedance. Per-protocol analysis set

Body fat (%)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Week 0 (Baseline)		
n/nmiss	22/0	20/0
Mean (SD)	42.15 (6.65)	39.26 (5.71)
Median	43.80	40.60
Q1, Q3	35.90, 47.70	35.10, 43.50
Min, Max	27.9, 50.3	27.9, 47.8
Week 12		
n/nmiss	22/0	20/0
Mean (SD)	41.75 (7.19)	39.22 (5.72)
Median	42.40	41.45
Q1, Q3	36.00, 48.10	34.40, 43.20
Min, Max	25.9, 51.6	27.8, 47.4
Week 24		
n/nmiss	22/0	20/0
Mean (SD)	41.28 (7.17)	39.25 (5.98)
Median	41.20	40.40
Q1, Q3	37.20, 46.90	34.90, 44.00
Min, Max	24.2, 51.4	28.0, 47.8
Number of subjects included in analysis	22	20
Adjusted mean change (95% CI)	-0.91 (-1.79, -0.03)	0.02 (-0.96, 1.00)
Difference (95% CI)	-0.93 (-2.24, 0.37)	
p-value	0.1556	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
A mixed model for repeated measures (MMRM) adjusted for treatment, week, treatment*week, gender and baseline body fat (%) was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Source: G:\StudData\Uppsala University\Dapalost\BIS\SASprog\DDP\BIS\Tables\Exploratory - Body fat.sas

Figure 20 **Body fat (%) series plot by week. Full analysis set**

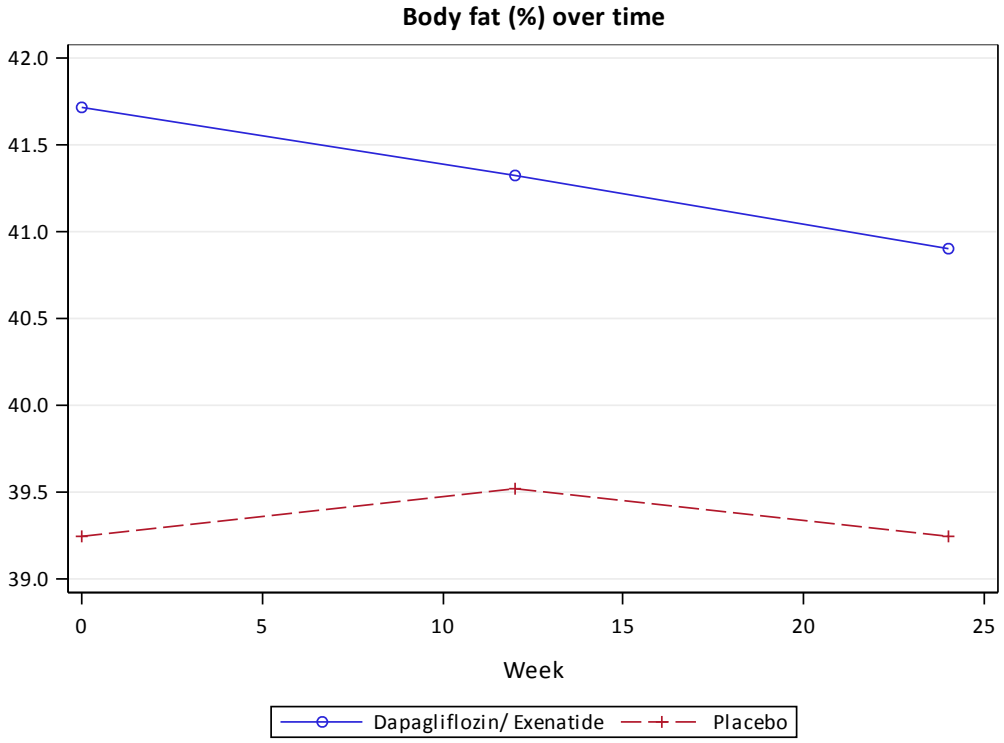
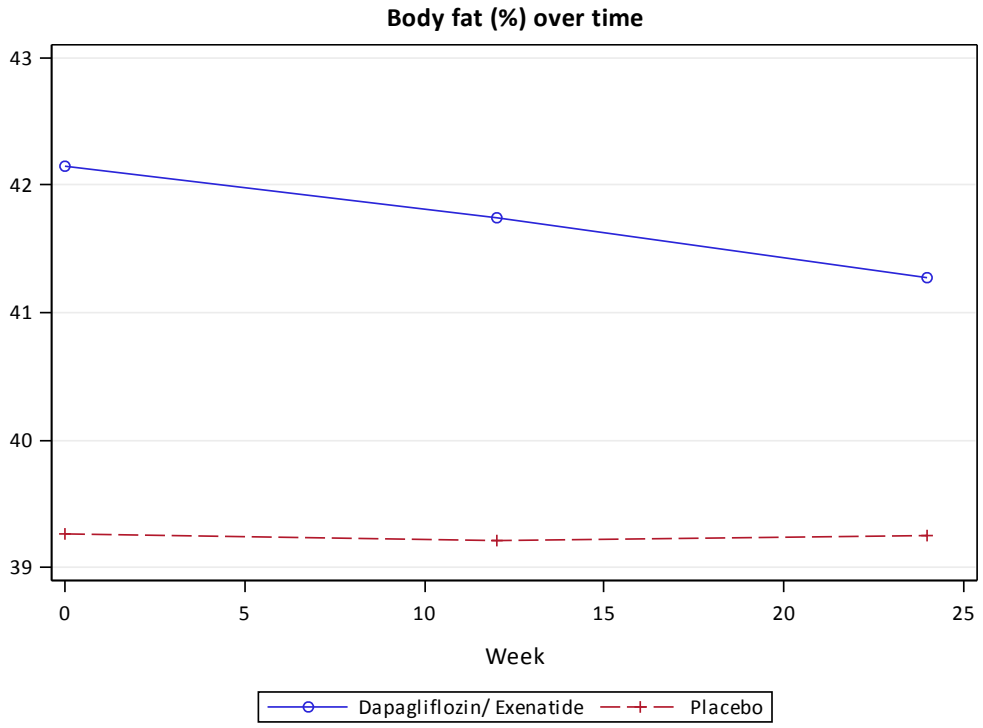


Figure 21 **Body fat (%) series plot by week. Per-protocol analysis set**



14.2.2.6 Glucose Tolerance, Insulin Secretion, Insulin Sensitivity and Lipolysis Regulation

14.2.2.6.1 Haemoglobin A1c

Table 105 Mixed model for repeated measures of change from baseline in HbA1c (mmol/mol). Full analysis set

HbA1c (mmol/mol)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Week -2(-1)		
n/nmiss	25/0	24/0
Mean (SD)	37.16 (3.87)	38.08 (3.32)
Median	37.00	37.50
Q1, Q3	35.00, 40.00	36.00, 40.00
Min, Max	29.0, 47.0	33.0, 49.0
Week 12		
n/nmiss	23/2	21/3
Mean (SD)	34.78 (3.34)	37.48 (3.39)
Median	34.00	37.00
Q1, Q3	32.00, 37.00	36.00, 39.00
Min, Max	28.0, 42.0	32.0, 47.0
Adjusted mean change (95% CI)	-2.6 (-3.5, -1.7)	-0.4 (-1.3, 0.6)
Difference (95% CI)	-2.3 (-3.6, -1.0)	
p-value	0.0010	
Week 24		
n/nmiss	22/3	20/4
Mean (SD)	33.32 (4.02)	36.25 (3.55)
Median	33.00	36.00
Q1, Q3	31.00, 36.00	33.00, 38.00
Min, Max	27.0, 43.0	32.0, 47.0
Adjusted mean change (95% CI)	-3.9 (-4.7, -3.1)	-1.6 (-2.5, -0.7)
Difference (95% CI)	-2.3 (-3.5, -1.1)	
p-value	0.0004	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
A mixed model for repeated measures (MMRM) adjusted for treatment, week, treatment*week, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Source: G:\StudData\Uppsala University\Dapalost\BIS\SASprog\DDP\BIS\Tables\Exploratory - Extended MMRM.sas

Table 106 Mixed model for repeated measures of change from baseline in HbA1c (mmol/mol). Per-protocol analysis set

HbA1c (mmol/mol)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Week -2(-1)		
n/nmiss	22/0	20/0
Mean (SD)	37.41 (3.80)	37.90 (3.61)
Median	36.50	37.00
Q1, Q3	35.00, 40.00	35.50, 40.00
Min, Max	29.0, 47.0	33.0, 49.0
Week 12		
n/nmiss	22/0	20/0
Mean (SD)	34.73 (3.41)	37.50 (3.47)
Median	34.00	37.50
Q1, Q3	32.00, 37.00	35.50, 39.50
Min, Max	28.0, 42.0	32.0, 47.0
Adjusted mean change (95% CI)	-2.7 (-3.6, -1.8)	-0.3 (-1.3, 0.6)
Difference (95% CI)	-2.4 (-3.7, -1.0)	
p-value	0.0011	
Week 24		
n/nmiss	21/1	20/0
Mean (SD)	33.29 (4.11)	36.25 (3.55)
Median	32.00	36.00
Q1, Q3	31.00, 36.00	33.00, 38.00
Min, Max	27.0, 43.0	32.0, 47.0
Adjusted mean change (95% CI)	-3.9 (-4.8, -3.1)	-1.6 (-2.5, -0.7)
Difference (95% CI)	-2.4 (-3.6, -1.1)	
p-value	0.0004	

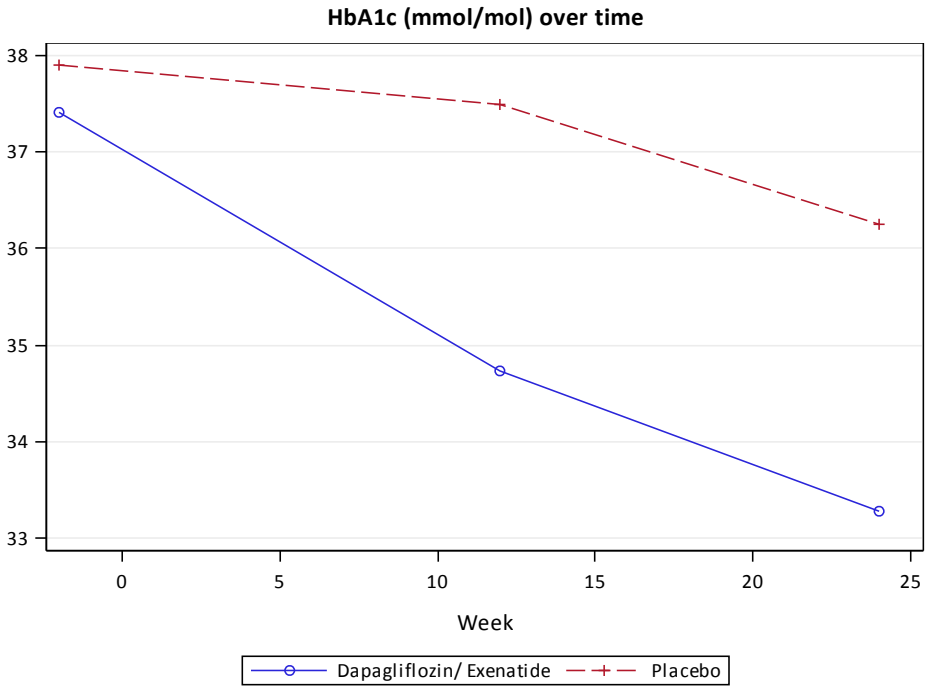
n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
A mixed model for repeated measures (MMRM) adjusted for treatment, week, treatment*week, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Source: G:\StudData\Uppsala University\Dapalost\BIS\SASprog\DDP\BIS\Tables\Exploratory - Extended MMRM.sas

Table 107 Mixed model for repeated measures of change from baseline in HbA1c (mmol/mol) at week 24. Per-protocol analysis set

HbA1c (mmol/mol)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Screening		
n/nmiss	22/0	20/0
Mean (SD)	37.41 (3.80)	37.90 (3.61)
Median	36.50	37.00
Q1, Q3	35.00, 40.00	35.50, 40.00
Min, Max	29.0, 47.0	33.0, 49.0
Week 12		
n/nmiss	22/0	20/0
Mean (SD)	34.73 (3.41)	37.50 (3.47)
Median	34.00	37.50
Q1, Q3	32.00, 37.00	35.50, 39.50
Min, Max	28.0, 42.0	32.0, 47.0
Week 24		
n/nmiss	21/1	20/0
Mean (SD)	33.29 (4.11)	36.25 (3.55)
Median	32.00	36.00
Q1, Q3	31.00, 36.00	33.00, 38.00
Min, Max	27.0, 43.0	32.0, 47.0
Number of subjects included in analysis	22	20
Adjusted mean change (95% CI)	-3.9 (-4.8, -3.1)	-1.6 (-2.5, -0.7)
Difference (95% CI)	-2.4 (-3.6, -1.1)	
p-value	0.0004	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
A mixed model for repeated measures (MMRM) adjusted for treatment, week, treatment*week, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

Figure 22 HbA1c (mmol/mol) series plot by week. Per-protocol analysis set



14.2.2.6.2 Glucose

Table 108 Analysis of covariance of change from baseline to week 24 of Glucose (mmol/L) at time 0 min during the OGTT. Per-protocol analysis set

Glucose (mmol/L)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Screening		
n/nmiss	22/0	20/0
Mean (SD)	5.95 (0.64)	5.83 (0.43)
Median	5.85	5.75
Q1, Q3	5.40, 6.30	5.55, 6.10
Min, Max	5.0, 7.2	5.1, 6.6
Week 24		
n/nmiss	22/0	20/0
Mean (SD)	5.48 (0.53)	6.08 (0.69)
Median	5.40	5.95
Q1, Q3	5.20, 5.70	5.70, 6.40
Min, Max	4.7, 7.1	5.1, 8.3
Number of subjects included in analysis	22	20
Adjusted mean change (95% CI)	-0.42 (-0.62, -0.22)	0.25 (0.04, 0.46)
Difference (95% CI)	-0.67 (-0.95, -0.38)	
p-value	<.0001	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

Table 109 Mixed model for repeated measures of change from baseline in Fasting plasma glucose (mmol/L) at week 24. Full analysis set

Fasting plasma glucose (mmol/L)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Screening		
n/nmiss	25/0	24/0
Mean (SD)	5.90 (0.63)	5.83 (0.43)
Median	5.80	5.75
Q1, Q3	5.40, 6.10	5.50, 6.10
Min, Max	5.0, 7.2	5.1, 6.6
Week 12		
n/nmiss	23/2	21/3
Mean (SD)	5.69 (0.55)	6.09 (0.53)
Median	5.70	5.90
Q1, Q3	5.20, 6.00	5.70, 6.50
Min, Max	4.7, 6.8	5.6, 7.6
Week 24		
n/nmiss	23/2	20/4
Mean (SD)	5.47 (0.52)	6.08 (0.69)
Median	5.40	5.95
Q1, Q3	5.20, 5.70	5.70, 6.40
Min, Max	4.7, 7.1	5.1, 8.3
Number of subjects included in analysis	25	24
Adjusted mean change (95% CI)	-0.43 (-0.61, -0.24)	0.25 (0.05, 0.45)
Difference (95% CI)	-0.67 (-0.94, -0.40)	
p-value	<.0001	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
A mixed model for repeated measures (MMRM) adjusted for treatment, week, treatment*week, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.

Table 110 Mixed model for repeated measures of change from baseline in Fasting plasma glucose (mmol/L) at week 24. Per-protocol analysis set

Fasting plasma glucose (mmol/L)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Screening		
n/nmiss	22/0	20/0
Mean (SD)	5.95 (0.64)	5.83 (0.43)
Median	5.85	5.75
Q1, Q3	5.40, 6.30	5.55, 6.10
Min, Max	5.0, 7.2	5.1, 6.6
Week 12		
n/nmiss	22/0	20/0
Mean (SD)	5.69 (0.56)	6.07 (0.53)
Median	5.70	5.85
Q1, Q3	5.20, 6.00	5.65, 6.40
Min, Max	4.7, 6.8	5.6, 7.6
Week 24		
n/nmiss	22/0	20/0
Mean (SD)	5.48 (0.53)	6.08 (0.69)
Median	5.40	5.95
Q1, Q3	5.20, 5.70	5.70, 6.40
Min, Max	4.7, 7.1	5.1, 8.3
Number of subjects included in analysis	22	20
Adjusted mean change (95% CI)	-0.43 (-0.63, -0.23)	0.24 (0.04, 0.45)
Difference (95% CI)	-0.67 (-0.96, -0.39)	
p-value	<.0001	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
A mixed model for repeated measures (MMRM) adjusted for treatment, week, treatment*week, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.

Figure 23 Fasting plasma glucose (mmol/L) series plot by week. Per-protocol analysis set

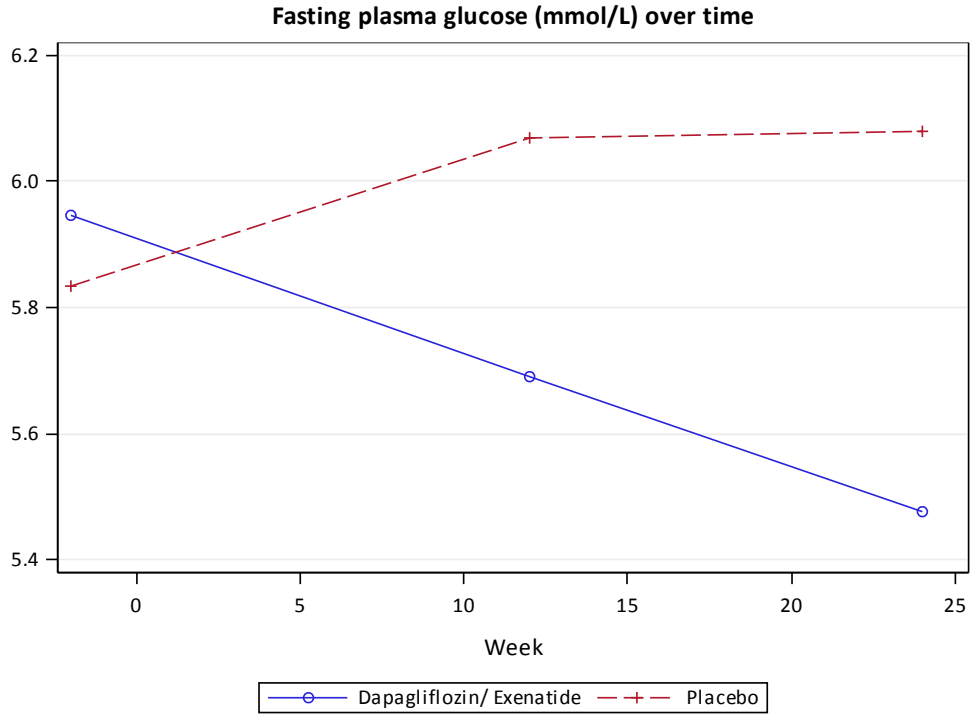


Table 111 Analysis of covariance of change from baseline to week 24 of Glucose (mmol/L) at time 120 min during the OGTT. Per-protocol analysis set

Glucose (mmol/L)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Screening		
n/nmiss	22/0	20/0
Mean (SD)	7.99 (2.27)	7.19 (1.13)
Median	7.60	7.10
Q1, Q3	6.30, 10.00	6.70, 8.05
Min, Max	4.3, 12.8	4.8, 9.4
Week 24		
n/nmiss	22/0	20/0
Mean (SD)	6.06 (1.78)	7.42 (1.91)
Median	5.60	6.90
Q1, Q3	4.70, 7.00	6.10, 8.50
Min, Max	3.8, 10.8	4.3, 12.5
Number of subjects included in analysis	22	20
Adjusted mean change (95% CI)	-1.59 (-2.42, -0.77)	-0.09 (-0.94, 0.77)
Difference (95% CI)	-1.51 (-2.70, -0.32)	
p-value	0.0145	

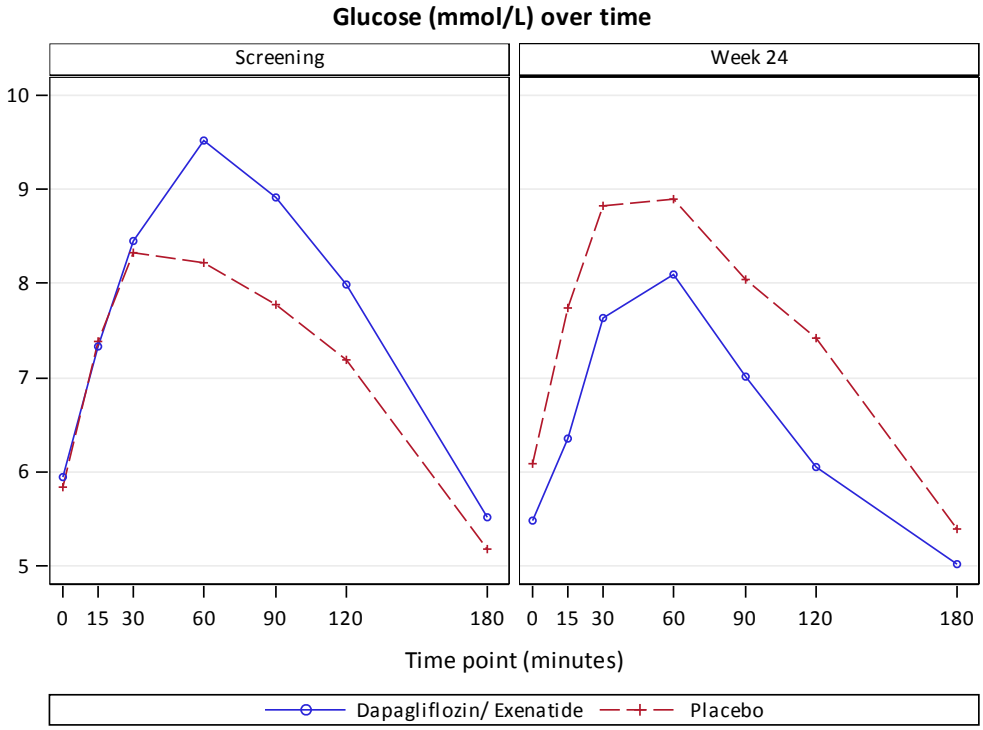
n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

Table 112 Analysis of covariance of change from baseline to week 24 in Glucose AUC (mmol/L x 180 min). Per-protocol analysis set

Glucose AUC (mmol/L x 180 min)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Screening		
n/nmiss	21/1	20/0
Mean (SD)	1440.86 (305.37)	1300.13 (169.06)
95% CI for the mean	(1301.85, 1579.86)	(1221.00, 1379.25)
Geometric mean	1407.790	1289.770
%CV	21.2%	13.0%
Median	1522.50	1270.88
Q1, Q3	1229.25, 1638.75	1168.88, 1408.88
Min, Max	851.3, 1936.5	992.3, 1606.5
Week 24		
n/nmiss	21/1	20/0
Mean (SD)	1189.07 (235.77)	1364.03 (271.32)
95% CI for the mean	(1081.75, 1296.39)	(1237.04, 1491.01)
Geometric mean	1168.200	1341.280
%CV	19.8%	19.9%
Median	1152.75	1299.75
Q1, Q3	1011.00, 1357.50	1191.00, 1468.13
Min, Max	899.3, 1674.8	995.3, 2193.8
Number of subjects included in analysis	20	20
Adjusted mean change (95% CI)	-191.10 (-297.13, -85.08)	34.24 (-69.36, 137.84)
Difference (95% CI)	-225.34 (-374.05, -76.64)	
p-value	0.0040	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
CV = coefficient of variation.
CI = Confidence interval.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
Screening = week -2-(-1)

Figure 24 Glucose (mmol/L) series plots during the OGTTs. Per-protocol analysis set



14.2.2.6.3 Impaired Fasting Glucose

Table 113 IFG category. Per-protocol analysis set

IFG	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Screening		
Normal	7 (31.8%)	5 (25.0%)
Raised	15 (68.2%)	15 (75.0%)
Week 24		
Normal	14 (63.6%)	3 (15.0%)
Raised	8 (36.4%)	17 (85.0%)
Shift from screening to week 24		
Normal, no change	7 (31.8%)	2 (10.0%)
Normal to raised	0	3 (15.0%)
Raised to normal	7 (31.8%)	1 (5.0%)
Raised, no change	8 (36.4%)	14 (70.0%)
p-value[1]	0.0082	0.3173
p-value[2]	0.0011	

[1]P-value of difference between baseline and week 24 based on a paired McNemar test.
[2]P-value of difference between treatments at week 24 based on a Cochran-Mantel-Haenszel test adjusted for baseline IFG category.
Screening = baseline

14.2.2.6.4 Impaired Glucose Tolerance

Table 114 IGT category. Per-protocol analysis set

IGT	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Screening		
Normal	11 (50.0%)	13 (65.0%)
Raised	11 (50.0%)	7 (35.0%)
Week 24		
Normal	18 (81.8%)	12 (60.0%)
Raised	4 (18.2%)	8 (40.0%)
Shift from screening to week 24		
Normal, no change	10 (45.5%)	9 (45.0%)
Normal to raised	1 (4.5%)	4 (20.0%)
Raised to normal	8 (36.4%)	3 (15.0%)
Raised, no change	3 (13.6%)	4 (20.0%)
p-value[1]	0.0196	0.7055
p-value[2]	0.0763	

[1]P-value of difference between baseline and week 24 based on a paired McNemar test.
[2]P-value of difference between treatments at week 24 based on a Cochran-Mantel-Haenszel test adjusted for baseline IGT.
Screening = baseline

14.2.2.6.5 Impaired Fasting Glucose/Impaired Glucose Tolerance

Table 115 Any IFG and/or IGT category. Per-protocol analysis set

Any IFG/IGT	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Screening		
Normal	6 (27.3%)	3 (15.0%)
Raised	16 (72.7%)	17 (85.0%)
Week 24		
Normal	14 (63.6%)	3 (15.0%)
Raised	8 (36.4%)	17 (85.0%)
Shift from screening to week 24		
Normal to raised	0	1 (5.0%)
Normal, no change	6 (27.3%)	2 (10.0%)
Raised to normal	8 (36.4%)	1 (5.0%)
Raised, no change	8 (36.4%)	16 (80.0%)
p-value[1]	0.0047	1.0000
p-value[2]	0.0019	

[1]P-value of difference between baseline and week 24 based on a paired McNemar test.
[2]P-value of difference between treatments at week 24 based on a Cochran-Mantel-Haenszel test adjusted for baseline IFG/IGT category.
Screening = baseline

14.2.2.6.6 Insulin

Table 116 Analysis of covariance of change from baseline to week 24 of Insulin (mU/L) at time 0 min during the OGTT. Full analysis set

Insulin (mU/L)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Screening		
n/nmiss	25/0	24/0
Mean (SD)	13.47 (6.49)	15.11 (8.59)
Median	11.40	12.95
Q1, Q3	9.20, 18.30	9.90, 17.50
Min, Max	3.9, 27.0	5.9, 41.0
Week 24		
n/nmiss	23/2	20/4
Mean (SD)	15.14 (13.92)	16.30 (11.65)
Median	13.60	13.40
Q1, Q3	7.60, 16.00	7.40, 22.50
Min, Max	3.1, 72.0	4.0, 50.0
Number of subjects included in analysis	23	20
Adjusted mean change (95% CI)	1.79 (-2.44, 6.02)	1.42 (-3.13, 5.97)
Difference (95% CI)	0.37 (-5.78, 6.52)	
p-value	0.9039	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

Table 117 Analysis of covariance of change from baseline to week 24 of Insulin (mU/L) at time 120 min during the OGTT. Full analysis set

Insulin (mU/L)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Screening		
n/nmiss	25/0	24/0
Mean (SD)	86.83 (80.60)	99.42 (83.92)
Median	62.00	75.00
Q1, Q3	44.00, 98.00	47.00, 123.00
Min, Max	13.8, 408.0	22.0, 400.0
Week 24		
n/nmiss	23/2	20/4
Mean (SD)	67.78 (59.12)	89.55 (79.41)
Median	60.00	72.00
Q1, Q3	15.80, 106.00	47.50, 107.50
Min, Max	4.6, 238.0	26.0, 399.0
Number of subjects included in analysis	23	20
Adjusted mean change (95% CI)	-21.98 (-44.20, 0.24)	-4.68 (-28.44, 19.08)
Difference (95% CI)	-17.29 (-49.48, 14.89)	
p-value	0.2837	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

Table 118 Analysis of covariance of change from baseline to week 24 of Insulin (mU/L) at time 0 min during the OGTT. Per-protocol analysis set

Insulin (mU/L)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Screening		
n/nmiss	22/0	20/0
Mean (SD)	13.63 (6.52)	15.36 (9.14)
Median	11.10	12.45
Q1, Q3	9.20, 18.30	9.90, 17.50
Min, Max	4.2, 27.0	6.5, 41.0
Week 24		
n/nmiss	22/0	20/0
Mean (SD)	15.18 (14.24)	16.30 (11.65)
Median	13.10	13.40
Q1, Q3	7.60, 16.00	7.40, 22.50
Min, Max	3.1, 72.0	4.0, 50.0
Number of subjects included in analysis	22	20
Adjusted mean change (95% CI)	2.24 (-2.14, 6.61)	1.47 (-3.11, 6.05)
Difference (95% CI)	0.77 (-5.48, 7.02)	
p-value	0.8052	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

Table 119 Analysis of covariance of change from baseline to week 24 of Insulin (mU/L) at time 120 min during the OGTT. Per-protocol analysis set

Insulin (mU/L)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Screening		
n/nmiss	22/0	20/0
Mean (SD)	89.31 (84.82)	98.35 (89.89)
Median	61.50	71.00
Q1, Q3	44.00, 98.00	46.00, 102.50
Min, Max	13.8, 408.0	22.0, 400.0
Week 24		
n/nmiss	22/0	20/0
Mean (SD)	68.32 (60.45)	89.55 (79.41)
Median	64.50	72.00
Q1, Q3	15.80, 106.00	47.50, 107.50
Min, Max	4.6, 238.0	26.0, 399.0
Number of subjects included in analysis	22	20
Adjusted mean change (95% CI)	-19.91 (-42.96, 3.15)	-4.29 (-28.24, 19.66)
Difference (95% CI)	-15.62 (-48.42, 17.18)	
p-value	0.3411	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

Figure 25 Insulin (mU/L) series plots during the OGTTs. Per-protocol analysis set

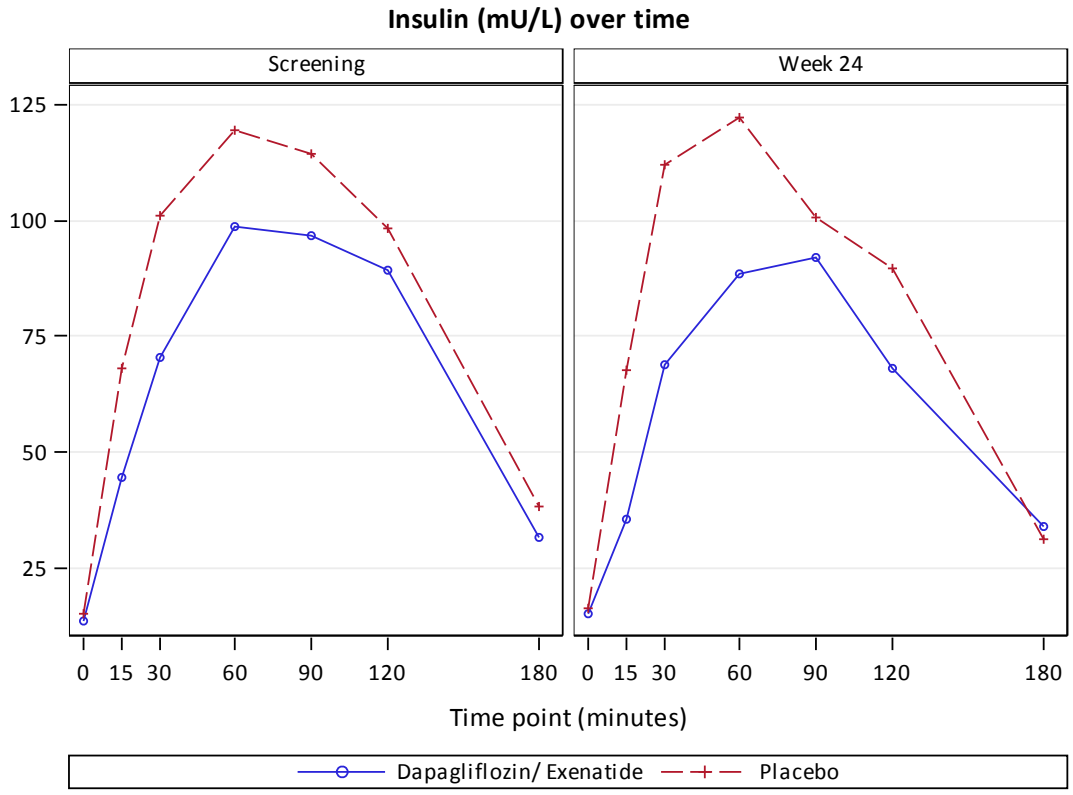


Table 120 Analysis of covariance of change from baseline to week 24 in Insulin AUC (mU/L x 180 min). Full analysis set

Insulin AUC (mU/L x 180 min)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Screening		
n/nmiss	24/1	24/0
Mean (SD)	12941.78 (8572.19)	15656.34 (9883.35)
95% CI for the mean	(9322.06, 16561.50)	(11482.97, 19829.72)
Geometric mean	10680.890	13661.030
%CV	66.2%	63.1%
Median	10659.00	13732.13
Q1, Q3	6671.63, 16946.63	10213.13, 18185.25
Min, Max	3792.8, 38242.5	5242.5, 53407.5
Week 24		
n/nmiss	21/4	20/4
Mean (SD)	11682.14 (7016.30)	15311.21 (8302.88)
95% CI for the mean	(8488.36, 14875.93)	(11425.35, 19197.08)
Geometric mean	9895.610	13463.840
%CV	60.1%	54.2%
Median	10044.00	14678.63
Q1, Q3	7114.50, 14212.50	8885.63, 20201.25
Min, Max	3267.8, 30031.5	4840.5, 41505.0
Number of subjects included in analysis	20	20
Adjusted mean change (95% CI)	-1619.30 (-4009.78, 771.17)	285.46 (-2109.49, 2680.42)
Difference (95% CI)	-1904.77 (-5270.66, 1461.13)	
p-value	0.2587	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
CV = coefficient of variation.
CI = Confidence interval.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
Screening = week -2-(-1)

Table 121 Analysis of covariance of change from baseline to week 24 in Insulin AUC (mU/L x 180 min). Per-protocol analysis

Insulin AUC (mU/L x 180 min)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Screening		
n/nmiss	21/1	20/0
Mean (SD)	13324.04 (8978.99)	15998.74 (10717.85)
95% CI for the mean	(9236.85, 17411.22)	(10982.63, 21014.85)
Geometric mean	10922.010	13684.400
%CV	67.4%	67.0%
Median	8922.00	13927.50
Q1, Q3	6797.25, 18872.25	9668.25, 18185.25
Min, Max	3792.8, 38242.5	5242.5, 53407.5
Week 24		
n/nmiss	20/2	20/0
Mean (SD)	11764.05 (7188.27)	15311.21 (8302.88)
95% CI for the mean	(8399.84, 15128.26)	(11425.35, 19197.08)
Geometric mean	9888.250	13463.840
%CV	61.1%	54.2%
Median	10143.00	14678.63
Q1, Q3	6854.25, 14432.25	8885.63, 20201.25
Min, Max	3267.8, 30031.5	4840.5, 41505.0
Number of subjects included in analysis	19	20
Adjusted mean change (95% CI)	-1351.04 (-3830.04, 1127.97)	308.95 (-2095.53, 2713.43)
Difference (95% CI)	-1659.99 (-5083.27, 1763.30)	
p-value	0.3317	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
CV = coefficient of variation.
CI = Confidence interval.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
Screening = week -2-(-1)

14.2.2.6.7 Quantitative Insulin Sensitivity Check Index

Table 122 Analysis of covariance of change from baseline to week 24 in the QUICKI index. Full analysis set

Quicki index	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Screening		
n/nmiss	25/0	24/0
Mean (SD)	0.32 (0.03)	0.32 (0.02)
Median	0.33	0.32
Q1, Q3	0.30, 0.34	0.31, 0.33
Min, Max	0.3, 0.4	0.3, 0.4
Week 24		
n/nmiss	23/2	20/4
Mean (SD)	0.33 (0.04)	0.32 (0.03)
Median	0.33	0.32
Q1, Q3	0.31, 0.35	0.30, 0.35
Min, Max	0.3, 0.4	0.3, 0.4
Number of subjects included in analysis	23	20
Adjusted mean change (95% CI)	0.007 (-0.005, 0.019)	0.000 (-0.012, 0.013)
Difference (95% CI)	0.007 (-0.010, 0.024)	
p-value	0.4323	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

Table 123 Analysis of covariance of change from baseline to week 24 in the QUICKI index. Per-protocol analysis set

Quicki index	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Screening		
n/nmiss	22/0	20/0
Mean (SD)	0.32 (0.02)	0.32 (0.02)
Median	0.33	0.32
Q1, Q3	0.30, 0.34	0.31, 0.33
Min, Max	0.3, 0.4	0.3, 0.4
Week 24		
n/nmiss	22/0	20/0
Mean (SD)	0.33 (0.04)	0.32 (0.03)
Median	0.33	0.32
Q1, Q3	0.31, 0.35	0.30, 0.35
Min, Max	0.3, 0.4	0.3, 0.4
Number of subjects included in analysis	22	20
Adjusted mean change (95% CI)	0.007 (-0.006, 0.019)	0.000 (-0.013, 0.013)
Difference (95% CI)	0.006 (-0.011, 0.024)	
p-value	0.4606	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.

14.2.2.6.8 Revised Quantitative Insulin Sensitivity Check Index

Table 124 Analysis of covariance of change from baseline to week 24 in the Revised QUICKI index. Full analysis set

Revised Quicki index	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Screening		
n/nmiss	23/2	20/4
Mean (SD)	0.19 (0.01)	0.18 (0.01)
Median	0.18	0.18
Q1, Q3	0.18, 0.19	0.18, 0.19
Min, Max	0.2, 0.2	0.2, 0.2
Week 24		
n/nmiss	23/2	20/4
Mean (SD)	0.19 (0.01)	0.19 (0.01)
Median	0.19	0.19
Q1, Q3	0.18, 0.19	0.18, 0.20
Min, Max	0.2, 0.2	0.2, 0.2
Number of subjects included in analysis	23	20
Adjusted mean change (95% CI)	0.001 (-0.003, 0.005)	0.002 (-0.003, 0.006)
Difference (95% CI)	-0.001 (-0.007, 0.005)	
p-value	0.7378	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

Table 125 Analysis of covariance of change from baseline to week 24 in the Revised QUICKI index. Per-protocol analysis set

Revised Quicki index	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Screening		
n/nmiss	22/0	20/0
Mean (SD)	0.19 (0.01)	0.18 (0.01)
Median	0.19	0.18
Q1, Q3	0.18, 0.19	0.18, 0.19
Min, Max	0.2, 0.2	0.2, 0.2
Week 24		
n/nmiss	22/0	20/0
Mean (SD)	0.19 (0.01)	0.19 (0.01)
Median	0.19	0.19
Q1, Q3	0.18, 0.19	0.18, 0.20
Min, Max	0.2, 0.2	0.2, 0.2
Number of subjects included in analysis	22	20
Adjusted mean change (95% CI)	0.001 (-0.004, 0.005)	0.002 (-0.003, 0.006)
Difference (95% CI)	-0.001 (-0.007, 0.005)	
p-value	0.7376	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.

14.2.2.6.9 Matsuda Index Adjusted for Urinary Glucose Excretion

Table 126 Analysis of covariance of change from baseline to week 24 in the weighted Matsuda index adjusted for urinary glucose excretion (UGE). Full analysis set

Weighted UGE-adjusted Matsuda index	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Screening		
n/nmiss	24/1	24/0
Mean (SD)	3.69 (2.26)	3.08 (1.55)
Median	3.30	2.68
Q1, Q3	2.02, 4.95	1.96, 3.75
Min, Max	0.9, 10.5	0.7, 7.1
Week 24		
n/nmiss	20/5	20/4
Mean (SD)	4.55 (3.31)	3.26 (2.25)
Median	3.65	2.62
Q1, Q3	2.69, 4.98	1.80, 4.14
Min, Max	0.6, 13.2	0.7, 9.5
Number of subjects included in analysis	19	20
Adjusted mean change (95% CI)	0.86 (0.08, 1.65)	0.25 (-0.52, 1.03)
Difference (95% CI)	0.61 (-0.48, 1.70)	
p-value	0.2658	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.

Table 127 Analysis of covariance of change from baseline to week 24 in the weighted Matsuda index adjusted for UGE. Per-protocol analysis set

Weighted UGE-adjusted Matsuda index	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Screening		
n/nmiss	21/1	20/0
Mean (SD)	3.49 (1.82)	3.08 (1.62)
Median	3.75	2.68
Q1, Q3	1.77, 4.82	1.96, 3.75
Min, Max	0.9, 6.6	0.7, 7.1
Week 24		
n/nmiss	19/3	20/0
Mean (SD)	4.63 (3.38)	3.26 (2.25)
Median	3.67	2.62
Q1, Q3	2.50, 5.39	1.80, 4.14
Min, Max	0.6, 13.2	0.7, 9.5
Number of subjects included in analysis	18	20
Adjusted mean change (95% CI)	0.85 (0.03, 1.68)	0.26 (-0.52, 1.05)
Difference (95% CI)	0.59 (-0.53, 1.72)	
p-value	0.2927	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.

14.2.2.6.10 Insulinogenic Index

Table 128 Analysis of covariance of change from baseline to week 24 in the Insulinogenic index. Full analysis set

Insulinogenic index	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Screening		
n/nmiss	25/0	24/0
Mean (SD)	19.34 (31.16)	36.03 (21.60)
Median	20.62	29.66
Q1, Q3	9.63, 31.75	19.54, 43.10
Min, Max	-85.3, 98.4	14.1, 97.5
Week 24		
n/nmiss	22/3	20/4
Mean (SD)	27.97 (18.04)	38.98 (27.42)
Median	23.99	32.21
Q1, Q3	17.56, 35.00	17.58, 50.75
Min, Max	5.6, 81.3	9.8, 96.5
Number of subjects included in analysis	22	20
Adjusted mean change (95% CI)	2.947 (-6.627, 12.520)	10.377 (0.366, 20.389)
Difference (95% CI)	-7.431 (-21.497, 6.636)	
p-value	0.2916	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening=week -2-(-1)

Table 129 Analysis of covariance of change from baseline to week 24 in the Insulinogenic index. Per-protocol analysis set

Insulinogenic index	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Screening		
n/nmiss	22/0	20/0
Mean (SD)	18.12 (32.91)	37.83 (23.27)
Median	19.74	37.76
Q1, Q3	9.29, 31.75	19.38, 45.66
Min, Max	-85.3, 98.4	14.1, 97.5
Week 24		
n/nmiss	21/1	20/0
Mean (SD)	25.43 (13.88)	38.98 (27.42)
Median	23.63	32.21
Q1, Q3	17.56, 30.22	17.58, 50.75
Min, Max	5.6, 62.0	9.8, 96.5
Number of subjects included in analysis	21	20
Adjusted mean change (95% CI)	0.710 (-8.844, 10.263)	10.714 (1.049, 20.379)
Difference (95% CI)	-10.005 (-23.809, 3.800)	
p-value	0.1504	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval
Screening=week -2-(-1)

14.2.2.6.11 C-peptide

Table 130 Analysis of covariance of change from baseline to week 24 of C-peptide (nmol/L) at time 0 min during the OGTT. Full analysis set

C-peptide (nmol/L)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Screening		
n/nmiss	25/0	24/0
Mean (SD)	1.06 (0.38)	1.03 (0.30)
Median	0.96	1.07
Q1, Q3	0.80, 1.28	0.80, 1.18
Min, Max	0.4, 2.0	0.5, 1.7
Week 24		
n/nmiss	23/2	20/4
Mean (SD)	1.21 (0.54)	1.09 (0.38)
Median	1.04	1.05
Q1, Q3	0.84, 1.47	0.80, 1.37
Min, Max	0.6, 2.7	0.5, 2.0
Number of subjects included in analysis	23	20
Adjusted mean change (95% CI)	0.122 (0.011, 0.233)	0.072 (-0.046, 0.189)
Difference (95% CI)	0.050 (-0.110, 0.210)	
p-value	0.5288	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

Table 131 Analysis of covariance of change from baseline to week 24 of C-peptide (nmol/L) at time 30 min during the OGTT. Full analysis set

C-peptide (nmol/L)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Screening		
n/nmiss	25/0	20/4
Mean (SD)	2.49 (0.82)	3.00 (0.68)
Median	2.60	3.00
Q1, Q3	1.95, 3.10	2.55, 3.45
Min, Max	0.9, 4.0	1.7, 4.3
Week 24		
n/nmiss	22/3	20/4
Mean (SD)	2.56 (0.94)	2.98 (0.98)
Median	2.40	2.90
Q1, Q3	1.79, 3.00	2.30, 3.55
Min, Max	1.1, 4.7	1.5, 4.8
Number of subjects included in analysis	22	17
Adjusted mean change (95% CI)	0.020 (-0.318, 0.357)	0.164 (-0.228, 0.555)
Difference (95% CI)	-0.144 (-0.667, 0.380)	
p-value	0.5809	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

Table 132 Analysis of covariance of change from baseline to week 24 of C-peptide (nmol/L) at time 60 min during the OGTT. Full analysis set

C-peptide (nmol/L)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Screening		
n/nmiss	25/0	23/1
Mean (SD)	3.41 (1.26)	3.59 (0.84)
Median	3.20	3.60
Q1, Q3	2.60, 4.00	3.00, 4.10
Min, Max	1.2, 6.4	1.9, 5.2
Week 24		
n/nmiss	23/2	20/4
Mean (SD)	3.63 (1.64)	3.74 (1.03)
Median	3.30	3.55
Q1, Q3	2.50, 4.20	3.20, 4.45
Min, Max	1.4, 8.2	1.8, 5.9
Number of subjects included in analysis	23	19
Adjusted mean change (95% CI)	0.134 (-0.216, 0.483)	0.238 (-0.144, 0.620)
Difference (95% CI)	-0.104 (-0.617, 0.408)	
p-value	0.6829	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

Table 133 Analysis of covariance of change from baseline to week 24 of C-peptide (nmol/L) at time 0 min during the OGTT. Per-protocol analysis set

C-peptide (nmol/L)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Screening		
n/nmiss	22/0	20/0
Mean (SD)	1.08 (0.38)	1.02 (0.32)
Median	0.94	0.97
Q1, Q3	0.80, 1.30	0.80, 1.25
Min, Max	0.5, 2.0	0.5, 1.7
Week 24		
n/nmiss	22/0	20/0
Mean (SD)	1.20 (0.55)	1.09 (0.38)
Median	1.04	1.05
Q1, Q3	0.84, 1.47	0.80, 1.37
Min, Max	0.6, 2.7	0.5, 2.0
Number of subjects included in analysis	22	20
Adjusted mean change (95% CI)	0.129 (0.014, 0.244)	0.072 (-0.047, 0.191)
Difference (95% CI)	0.057 (-0.106, 0.220)	
p-value	0.4841	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

Table 134 Analysis of covariance of change from baseline to week 24 of C-peptide (nmol/L) at time 30 min during the OGTT. Per-protocol analysis set

C-peptide (nmol/L)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Screening		
n/nmiss	22/0	17/3
Mean (SD)	2.46 (0.81)	2.98 (0.73)
Median	2.55	3.00
Q1, Q3	1.95, 3.00	2.30, 3.40
Min, Max	0.9, 4.0	1.7, 4.3
Week 24		
n/nmiss	21/1	20/0
Mean (SD)	2.57 (0.96)	2.98 (0.98)
Median	2.40	2.90
Q1, Q3	1.79, 3.00	2.30, 3.55
Min, Max	1.1, 4.7	1.5, 4.8
Number of subjects included in analysis	21	17
Adjusted mean change (95% CI)	0.082 (-0.262, 0.427)	0.165 (-0.223, 0.554)
Difference (95% CI)	-0.083 (-0.609, 0.443)	
p-value	0.7504	

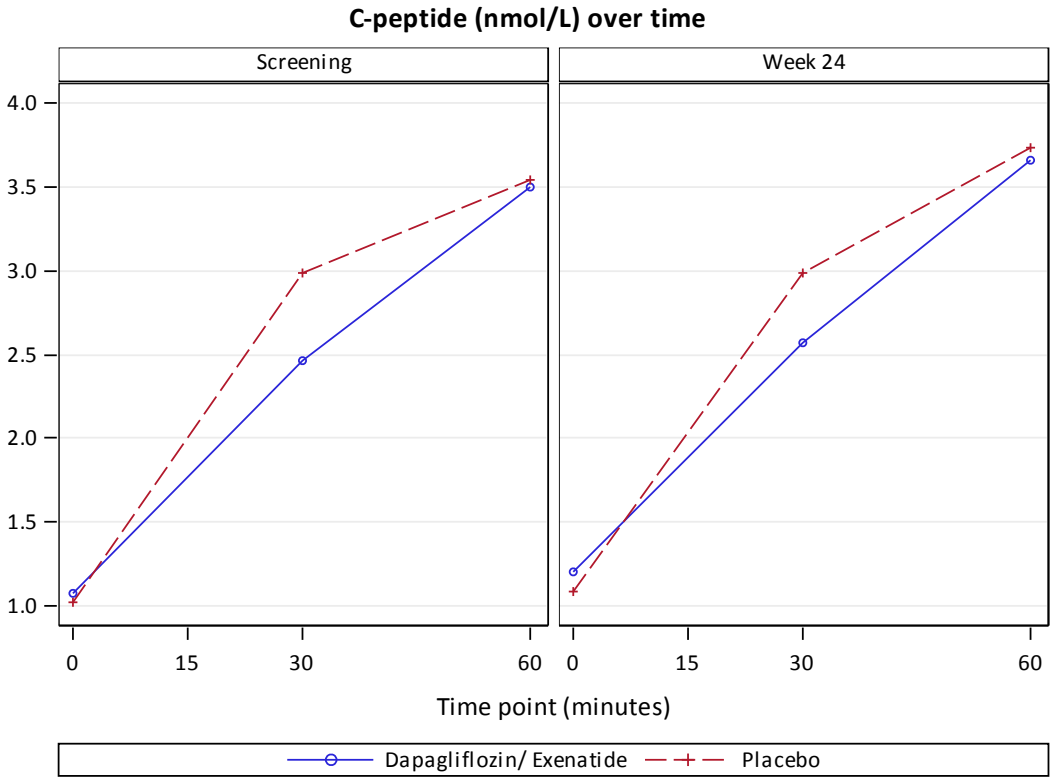
n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

Table 135 Analysis of covariance of change from baseline to week 24 of C-peptide (nmol/L) at time 60 min during the OGTT. Per-protocol analysis set

C-peptide (nmol/L)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Screening		
n/nmiss	22/0	19/1
Mean (SD)	3.49 (1.30)	3.54 (0.92)
Median	3.35	3.60
Q1, Q3	2.60, 4.30	2.60, 4.20
Min, Max	1.2, 6.4	1.9, 5.2
Week 24		
n/nmiss	22/0	20/0
Mean (SD)	3.66 (1.68)	3.74 (1.03)
Median	3.40	3.55
Q1, Q3	2.50, 4.20	3.20, 4.45
Min, Max	1.4, 8.2	1.8, 5.9
Number of subjects included in analysis	22	19
Adjusted mean change (95% CI)	0.162 (-0.202, 0.525)	0.241 (-0.144, 0.627)
Difference (95% CI)	-0.079 (-0.602, 0.443)	
p-value	0.7598	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

Figure 26 C-peptide (nmol/L) series plots during the OGTTs. Per-protocol analysis set



14.2.2.6.12 Glucagon

Table 136 Analysis of covariance of change from baseline to week 24 of Glucagon (pmol/L) at time 0 min during the OGTT. Full analysis set

Glucagon (pmol/L)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Screening		
n/nmiss	23/2	20/4
Mean (SD)	9.99 (6.63)	8.34 (4.66)
Median	8.18	7.30
Q1, Q3	5.09, 13.02	4.72, 10.88
Min, Max	2.5, 28.8	1.4, 17.1
Week 24		
n/nmiss	21/4	20/4
Mean (SD)	11.70 (7.84)	13.11 (8.17)
Median	9.31	11.03
Q1, Q3	5.38, 15.59	7.53, 17.48
Min, Max	3.4, 30.9	1.1, 33.6
Number of subjects included in analysis	21	20
Adjusted mean change (95% CI)	2.717 (0.095, 5.339)	5.004 (2.369, 7.640)
Difference (95% CI)	-2.288 (-5.959, 1.384)	
p-value	0.2147	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

Table 137 Analysis of covariance of change from baseline to week 24 of Glucagon (pmol/L) at time 120 min during the OGTT. Full analysis set

Glucagon (pmol/L)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Screening		
n/nmiss	23/2	20/4
Mean (SD)	3.14 (3.54)	3.37 (2.28)
Median	1.84	2.99
Q1, Q3	1.24, 3.77	1.59, 4.68
Min, Max	0.2, 16.5	0.1, 8.3
Week 24		
n/nmiss	21/4	20/4
Mean (SD)	6.91 (6.02)	5.18 (3.89)
Median	5.02	3.93
Q1, Q3	2.41, 9.85	2.18, 9.51
Min, Max	0.0, 23.1	0.0, 11.3
Number of subjects included in analysis	21	20
Adjusted mean change (95% CI)	3.761 (1.560, 5.963)	1.954 (-0.291, 4.200)
Difference (95% CI)	1.807 (-1.297, 4.911)	
p-value	0.2457	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

Table 138 Analysis of covariance of change from baseline to week 24 of Glucagon (pmol/L) at time 0 min during the OGTT. Per-protocol analysis set

Glucagon (pmol/L)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Screening		
n/nmiss	22/0	20/0
Mean (SD)	9.55 (6.44)	8.34 (4.66)
Median	7.77	7.30
Q1, Q3	5.09, 12.69	4.72, 10.88
Min, Max	2.5, 28.8	1.4, 17.1
Week 24		
n/nmiss	20/2	20/0
Mean (SD)	11.58 (8.02)	13.11 (8.17)
Median	8.49	11.03
Q1, Q3	5.32, 17.13	7.53, 17.48
Min, Max	3.4, 30.9	1.1, 33.6
Number of subjects included in analysis	20	20
Adjusted mean change (95% CI)	3.196 (0.580, 5.813)	5.045 (2.485, 7.604)
Difference (95% CI)	-1.848 (-5.441, 1.745)	
p-value	0.3038	

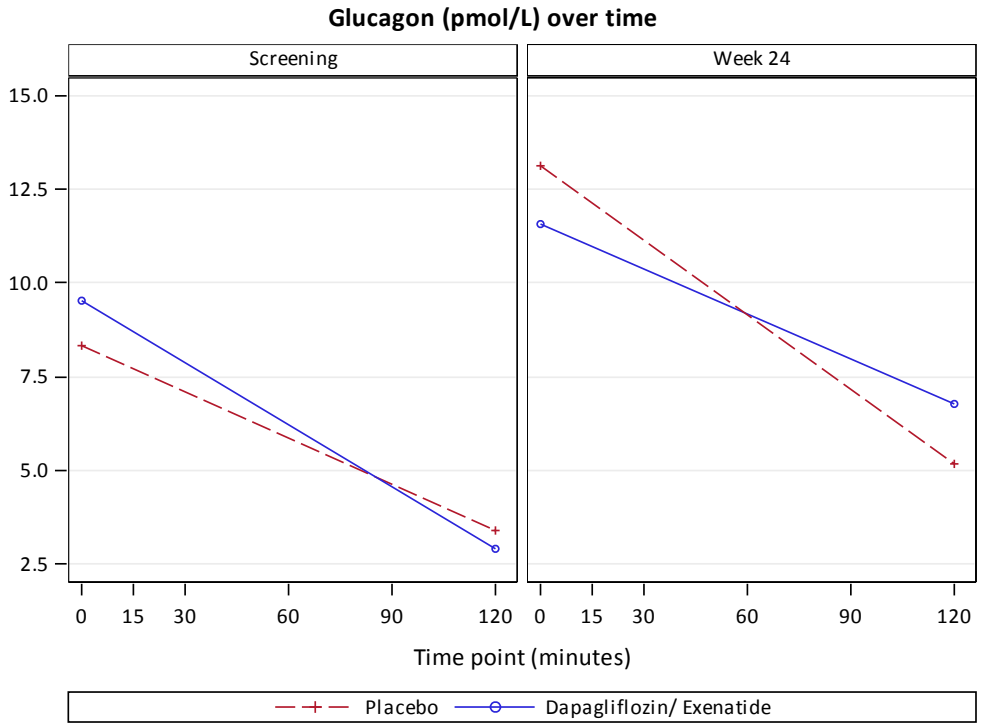
n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.

Table 139 Analysis of covariance of change from baseline to week 24 of Glucagon (pmol/L) at time 120 min during the OGTT. Per-protocol analysis set

Glucagon (pmol/L)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Screening		
n/nmiss	22/0	20/0
Mean (SD)	2.91 (3.45)	3.37 (2.28)
Median	1.74	2.99
Q1, Q3	1.24, 3.65	1.59, 4.68
Min, Max	0.2, 16.5	0.1, 8.3
Week 24		
n/nmiss	20/2	20/0
Mean (SD)	6.76 (6.13)	5.18 (3.89)
Median	5.02	3.93
Q1, Q3	2.22, 9.79	2.18, 9.51
Min, Max	0.0, 23.1	0.0, 11.3
Number of subjects included in analysis	20	20
Adjusted mean change (95% CI)	3.827 (1.519, 6.134)	2.015 (-0.268, 4.298)
Difference (95% CI)	1.812 (-1.384, 5.007)	
p-value	0.2578	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

Figure 27 Glucagon (pmol/L) series plots during the OGTTs. Per-protocol analysis set



14.2.2.6.13 Glycerol

Table 140 Analysis of covariance of change from baseline to week 24 of Glycerol (µmol/L) at time 0 min during the OGTT. Full analysis set

Glycerol (µmol/L)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Screening		
n/nmiss	23/2	20/4
Mean (SD)	120.04 (40.30)	116.70 (42.27)
Median	115.00	101.50
Q1, Q3	93.00, 152.00	87.00, 140.00
Min, Max	58.0, 233.0	70.0, 233.0
Week 24		
n/nmiss	23/2	20/4
Mean (SD)	92.74 (39.77)	95.35 (27.60)
Median	74.00	92.00
Q1, Q3	61.00, 124.00	78.00, 116.50
Min, Max	48.0, 184.0	36.0, 141.0
Number of subjects included in analysis	23	20
Adjusted mean change (95% CI)	-25.3 (-38.3, -12.3)	-21.2 (-35.1, -7.2)
Difference (95% CI)	-4.1 (-23.0, 14.7)	
p-value	0.6605	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

Table 141 Analysis of covariance of change from baseline to week 24 of Glycerol (µmol/L) at time 30 min during the OGTT. Full analysis set

Glycerol (µmol/L)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Screening		
n/nmiss	23/2	20/4
Mean (SD)	81.57 (24.25)	82.10 (27.15)
Median	77.00	85.00
Q1, Q3	66.00, 100.00	58.00, 100.50
Min, Max	44.0, 128.0	39.0, 144.0
Week 24		
n/nmiss	23/2	20/4
Mean (SD)	93.13 (38.96)	74.65 (26.71)
Median	79.00	73.50
Q1, Q3	63.00, 128.00	53.00, 91.00
Min, Max	43.0, 182.0	28.0, 130.0
Number of subjects included in analysis	23	20
Adjusted mean change (95% CI)	13.3 (0.1, 26.6)	-5.6 (-19.8, 8.5)
Difference (95% CI)	18.9 (-0.2, 38.1)	
p-value	0.0524	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

Table 142 Analysis of covariance of change from baseline to week 24 of Glycerol (µmol/L) at time 60 min during the OGTT. Full analysis set

Glycerol (µmol/L)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Screening		
n/nmiss	23/2	20/4
Mean (SD)	71.78 (23.25)	71.10 (26.21)
Median	70.00	60.00
Q1, Q3	60.00, 81.00	51.50, 86.00
Min, Max	35.0, 118.0	39.0, 125.0
Week 24		
n/nmiss	23/2	20/4
Mean (SD)	85.83 (62.00)	72.70 (40.33)
Median	64.00	61.50
Q1, Q3	48.00, 93.00	46.50, 88.00
Min, Max	43.0, 307.0	21.0, 212.0
Number of subjects included in analysis	23	20
Adjusted mean change (95% CI)	16.8 (-3.8, 37.3)	4.1 (-17.9, 26.0)
Difference (95% CI)	12.7 (-17.0, 42.5)	
p-value	0.3927	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

Table 143 Analysis of covariance of change from baseline to week 24 of Glycerol (µmol/L) at time 120 min during the OGTT. Full analysis set

Glycerol (µmol/L)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Screening		
n/nmiss	23/2	20/4
Mean (SD)	69.57 (26.97)	63.35 (25.48)
Median	60.00	56.50
Q1, Q3	52.00, 87.00	43.50, 84.50
Min, Max	32.0, 153.0	28.0, 110.0
Week 24		
n/nmiss	23/2	20/4
Mean (SD)	68.04 (33.48)	63.50 (24.64)
Median	65.00	54.00
Q1, Q3	41.00, 83.00	49.00, 77.50
Min, Max	26.0, 163.0	23.0, 112.0
Number of subjects included in analysis	23	20
Adjusted mean change (95% CI)	2.0 (-9.9, 13.9)	-0.2 (-12.9, 12.5)
Difference (95% CI)	2.2 (-15.1, 19.5)	
p-value	0.7978	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

Table 144 Analysis of covariance of change from baseline to week 24 of Glycerol (µmol/L) at time 0 min during the OGTT. Per-protocol analysis set

Glycerol (µmol/L)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Screening		
n/nmiss	22/0	20/0
Mean (SD)	121.55 (40.58)	116.70 (42.27)
Median	115.00	101.50
Q1, Q3	94.00, 152.00	87.00, 140.00
Min, Max	58.0, 233.0	70.0, 233.0
Week 24		
n/nmiss	22/0	20/0
Mean (SD)	92.41 (40.67)	95.35 (27.60)
Median	71.50	92.00
Q1, Q3	61.00, 124.00	78.00, 116.50
Min, Max	48.0, 184.0	36.0, 141.0
Number of subjects included in analysis	22	20
Adjusted mean change (95% CI)	-26.6 (-40.1, -13.0)	-21.7 (-35.8, -7.5)
Difference (95% CI)	-4.9 (-24.2, 14.3)	
p-value	0.6078	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

Table 145 Analysis of covariance of change from baseline to week 24 of Glycerol (µmol/L) at time 30 min during the OGTT. Per-protocol analysis set

Glycerol (µmol/L)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Screening		
n/nmiss	22/0	20/0
Mean (SD)	81.82 (24.79)	82.10 (27.15)
Median	77.50	85.00
Q1, Q3	66.00, 100.00	58.00, 100.50
Min, Max	44.0, 128.0	39.0, 144.0
Week 24		
n/nmiss	22/0	20/0
Mean (SD)	91.59 (39.16)	74.65 (26.71)
Median	77.00	73.50
Q1, Q3	63.00, 128.00	53.00, 91.00
Min, Max	43.0, 182.0	28.0, 130.0
Number of subjects included in analysis	22	20
Adjusted mean change (95% CI)	11.8 (-1.9, 25.5)	-5.9 (-20.1, 8.3)
Difference (95% CI)	17.7 (-1.8, 37.1)	
p-value	0.0735	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

Table 146 Analysis of covariance of change from baseline to week 24 of Glycerol (µmol/L) at time 60 min during the OGTT. Per-protocol analysis set

Glycerol (µmol/L)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Screening		
n/nmiss	22/0	20/0
Mean (SD)	70.09 (22.30)	71.10 (26.21)
Median	69.00	60.00
Q1, Q3	60.00, 80.00	51.50, 86.00
Min, Max	35.0, 118.0	39.0, 125.0
Week 24		
n/nmiss	22/0	20/0
Mean (SD)	83.86 (62.72)	72.70 (40.33)
Median	62.00	61.50
Q1, Q3	48.00, 83.00	46.50, 88.00
Min, Max	43.0, 307.0	21.0, 212.0
Number of subjects included in analysis	22	20
Adjusted mean change (95% CI)	17.2 (-4.3, 38.7)	4.2 (-18.1, 26.4)
Difference (95% CI)	13.0 (-17.5, 43.5)	
p-value	0.3929	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

Table 147 Analysis of covariance of change from baseline to week 24 of Glycerol (µmol/L) at time 120 min during the OGTT. Per-protocol analysis set

Glycerol (µmol/L)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Screening		
n/nmiss	22/0	20/0
Mean (SD)	69.91 (27.55)	63.35 (25.48)
Median	59.50	56.50
Q1, Q3	52.00, 87.00	43.50, 84.50
Min, Max	32.0, 153.0	28.0, 110.0
Week 24		
n/nmiss	22/0	20/0
Mean (SD)	67.77 (34.24)	63.50 (24.64)
Median	64.50	54.00
Q1, Q3	41.00, 83.00	49.00, 77.50
Min, Max	26.0, 163.0	23.0, 112.0
Number of subjects included in analysis	22	20
Adjusted mean change (95% CI)	2.0 (-10.4, 14.4)	-0.3 (-13.2, 12.7)
Difference (95% CI)	2.3 (-15.4, 20.0)	
p-value	0.7980	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

Figure 28 Glycerol (µmol/L) series plots during the OGTTs. Per-protocol analysis set

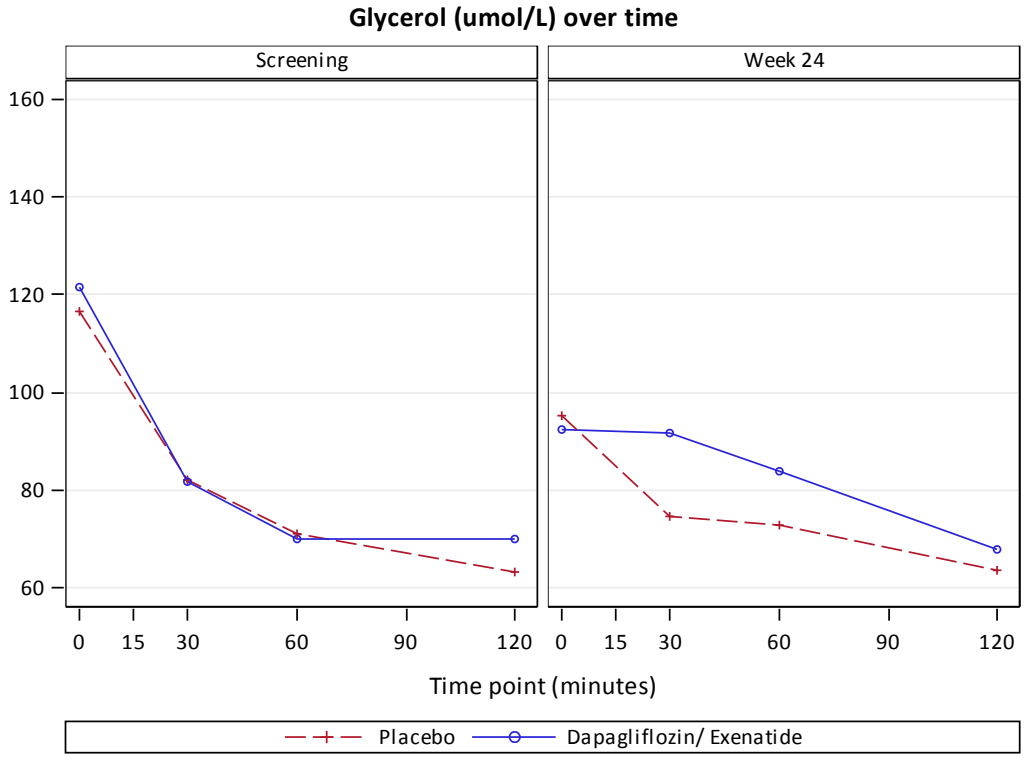


Table 148 Analysis of covariance of change from baseline to week 24 in Glycerol AUC (µmol/L x 120 min). Full analysis set

Glycerol AUC (umol/L x 120 min)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Screening		
n/nmiss	23/2	20/4
Mean (SD)	9564.78 (2682.39)	9313.50 (3031.19)
95% CI for the mean	(8404.83, 10724.74)	(7894.86, 10732.14)
Geometric mean	9192.620	8889.260
%CV	28.0%	32.5%
Median	9420.00	8085.00
Q1, Q3	7785.00, 11625.00	7395.00, 11527.50
Min, Max	5085.0, 15375.0	5415.0, 15450.0
Week 24		
n/nmiss	23/2	20/4
Mean (SD)	10088.48 (5004.50)	8846.25 (3238.02)
95% CI for the mean	(7924.37, 12252.59)	(7330.81, 10361.69)
Geometric mean	9238.080	8317.560
%CV	49.6%	36.6%
Median	7590.00	8572.50
Q1, Q3	6915.00, 11790.00	6907.50, 10177.50
Min, Max	5580.0, 26070.0	3015.0, 18690.0
Number of subjects included in analysis	23	20
Adjusted mean change (95% CI)	831.03 (-771.98, 2434.05)	-243.62 (-1960.81, 1473.56)
Difference (95% CI)	1074.66 (-1247.60, 3396.92)	
p-value	0.3550	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
CV = coefficient of variation.
CI = Confidence interval.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
Screening = week -2-(-1)

Table 149 Analysis of covariance of change from baseline to week 24 in Glycerol AUC (µmol/L x 120 min). Per-protocol analysis set

Glycerol AUC (umol/L x 120 min)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Screening		
n/nmiss	22/0	20/0
Mean (SD)	9529.09 (2739.92)	9313.50 (3031.19)
95% CI for the mean	(8314.28, 10743.90)	(7894.86, 10732.14)
Geometric mean	9143.200	8889.260
%CV	28.8%	32.5%
Median	9382.50	8085.00
Q1, Q3	7785.00, 11625.00	7395.00, 11527.50
Min, Max	5085.0, 15375.0	5415.0, 15450.0
Week 24		
n/nmiss	22/0	20/0
Mean (SD)	9940.91 (5070.79)	8846.25 (3238.02)
95% CI for the mean	(7692.65, 12189.17)	(7330.81, 10361.69)
Geometric mean	9085.220	8317.560
%CV	51.0%	36.6%
Median	7582.50	8572.50
Q1, Q3	6915.00, 10875.00	6907.50, 10177.50
Min, Max	5580.0, 26070.0	3015.0, 18690.0
Number of subjects included in analysis	22	20
Adjusted mean change (95% CI)	776.40 (-896.04, 2448.85)	-247.07 (-1986.46, 1492.31)
Difference (95% CI)	1023.48 (-1353.32, 3400.28)	
p-value	0.3888	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
CV = coefficient of variation.
CI = Confidence interval.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 150 Analysis of covariance of change from baseline to week 24 in Glycerol (µmol/L/min) incremental area under curve. Full analysis set

Glycerol (µmol/L/min)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Screening		
n/nmiss	23/2	20/4
Mean (SD)	-4840.43 (3608.68)	-4690.50 (2859.01)
95% CI for the mean	(-6400.94, -3279.93)	(-6028.56, -3352.44)
%CV	-74.6%	-61.0%
Median	-4905.00	-4650.00
Q1, Q3	-6975.00, -1875.00	-6225.00, -2325.00
Min, Max	-12585.0, 840.0	-12510.0, -675.0
Week 24		
n/nmiss	23/2	20/4
Mean (SD)	-1040.22 (3576.02)	-2595.75 (2943.12)
95% CI for the mean	(-2586.60, 506.17)	(-3973.17, -1218.33)
%CV	-343.8%	-113.4%
Median	-1290.00	-2797.50
Q1, Q3	-2205.00, 75.00	-4852.50, -735.00
Min, Max	-7305.0, 10830.0	-7590.0, 3390.0
Number of subjects included in analysis		
Number of subjects included in analysis	23	20
Adjusted mean change (95% CI)	3945.8 (2609.6, 5282.0)	2350.4 (919.4, 3781.4)
Difference (95% CI)	1595.4 (-334.2, 3525.0)	
p-value	0.1025	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

Table 151 Analysis of covariance of change from baseline to week 24 in Glycerol (µmol/L/min) incremental area under curve. Per-protocol analysis set

Glycerol (µmol/L/min)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Screening		
n/nmiss	22/0	20/0
Mean (SD)	-5056.36 (3538.25)	-4690.50 (2859.01)
95% CI for the mean	(-6625.14, -3487.59)	(-6028.56, -3352.44)
%CV	-70.0%	-61.0%
Median	-4927.50	-4650.00
Q1, Q3	-6975.00, -2550.00	-6225.00, -2325.00
Min, Max	-12585.0, 840.0	-12510.0, -675.0
Week 24		
n/nmiss	22/0	20/0
Mean (SD)	-1148.18 (3621.60)	-2595.75 (2943.12)
95% CI for the mean	(-2753.91, 457.55)	(-3973.17, -1218.33)
%CV	-315.4%	-113.4%
Median	-1290.00	-2797.50
Q1, Q3	-2205.00, -165.00	-4852.50, -735.00
Min, Max	-7305.0, 10830.0	-7590.0, 3390.0
Number of subjects included in analysis		
Number of subjects included in analysis	22	20
Adjusted mean change (95% CI)	4014.5 (2620.7, 5408.3)	2443.5 (988.8, 3898.2)
Difference (95% CI)	1571.0 (-408.3, 3550.2)	
p-value	0.1164	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.

14.2.2.6.14 Free Fatty Acids

Table 152 Analysis of covariance of change from baseline to week 24 of FFA (µmol/L) at time 0 min during the OGTT. Full analysis set

Free fatty acid (FFA) (µmol/L)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Screening		
n/nmiss	23/2	20/4
Mean (SD)	218.43 (74.57)	200.95 (42.50)
Median	212.00	192.00
Q1, Q3	156.00, 303.00	165.00, 236.00
Min, Max	102.0, 332.0	145.0, 284.0
Week 24		
n/nmiss	23/2	20/4
Mean (SD)	214.78 (60.77)	193.85 (43.95)
Median	210.00	186.50
Q1, Q3	160.00, 258.00	167.50, 227.50
Min, Max	116.0, 339.0	101.0, 275.0
Number of subjects included in analysis	23	20
Adjusted mean change (95% CI)	-0.8 (-19.9, 18.3)	-13.5 (-34.2, 7.1)
Difference (95% CI)	12.8 (-15.2, 40.7)	
p-value	0.3607	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

Table 153 Analysis of covariance of change from baseline to week 24 of Free fatty acid (µmol/L) at time 0 min during the OGTT. Per-protocol analysis set

Free fatty acid (FFA) (µmol/L)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Screening		
n/nmiss	22/0	20/0
Mean (SD)	220.14 (75.87)	200.95 (42.50)
Median	214.50	192.00
Q1, Q3	156.00, 303.00	165.00, 236.00
Min, Max	102.0, 332.0	145.0, 284.0
Week 24		
n/nmiss	22/0	20/0
Mean (SD)	215.59 (62.07)	193.85 (43.95)
Median	212.50	186.50
Q1, Q3	160.00, 258.00	167.50, 227.50
Min, Max	116.0, 339.0	101.0, 275.0
Number of subjects included in analysis	22	20
Adjusted mean change (95% CI)	-1.6 (-21.5, 18.4)	-13.9 (-34.9, 7.0)
Difference (95% CI)	12.4 (-16.3, 41.0)	
p-value	0.3870	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

Table 154 Analysis of covariance of change from baseline to week 24 of Free fatty acids (µmol/L) at time 30 min during the OGTT. Per-protocol analysis set

Free fatty acid (FFA) (µmol/L)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Screening		
n/nmiss	22/0	20/0
Mean (SD)	173.09 (81.43)	142.00 (52.45)
Median	177.00	133.50
Q1, Q3	100.00, 233.00	109.50, 185.50
Min, Max	61.0, 326.0	54.0, 243.0
Week 24		
n/nmiss	22/0	20/0
Mean (SD)	189.41 (60.48)	149.80 (37.67)
Median	192.00	149.50
Q1, Q3	144.00, 230.00	129.50, 175.50
Min, Max	79.0, 305.0	81.0, 235.0
Number of subjects included in analysis	22	20
Adjusted mean change (95% CI)	22.0 (5.4, 38.6)	-1.8 (-19.1, 15.6)
Difference (95% CI)	23.8 (-0.2, 47.7)	
p-value	0.0515	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

Table 155 Analysis of covariance of change from baseline to week 24 of Free fatty acids (µmol/L) at time 60 min during the OGTT. Per-protocol analysis set

Free fatty acid (FFA) (umol/L)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Screening		
n/nmiss	22/0	20/0
Mean (SD)	83.73 (51.37)	72.65 (46.61)
Median	80.00	64.00
Q1, Q3	40.00, 114.00	38.00, 95.50
Min, Max	19.0, 205.0	14.0, 191.0
Week 24		
n/nmiss	22/0	20/0
Mean (SD)	106.32 (50.21)	69.60 (37.04)
Median	96.00	51.00
Q1, Q3	73.00, 139.00	42.50, 97.50
Min, Max	26.0, 222.0	25.0, 140.0
Number of subjects included in analysis	22	20
Adjusted mean change (95% CI)	23.7 (9.3, 38.2)	-5.7 (-20.6, 9.2)
Difference (95% CI)	29.4 (8.9, 50.0)	
p-value	0.0061	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.

Table 156 Analysis of covariance of change from baseline to week 24 of Free fatty acids (µmol/L) at time 120 min during the OGTT. Per-protocol analysis set

Free fatty acid (FFA) (umol/L)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Screening		
n/nmiss	22/0	20/0
Mean (SD)	31.82 (22.76)	27.55 (23.38)
Median	24.00	21.00
Q1, Q3	17.00, 42.00	11.50, 30.00
Min, Max	1.0, 96.0	5.0, 99.0
Week 24		
n/nmiss	22/0	20/0
Mean (SD)	48.59 (36.58)	26.05 (18.69)
Median	35.00	19.00
Q1, Q3	24.00, 61.00	13.50, 31.50
Min, Max	4.0, 148.0	7.0, 70.0
Number of subjects included in analysis	22	20
Adjusted mean change (95% CI)	18.1 (6.0, 30.2)	-2.3 (-14.7, 10.2)
Difference (95% CI)	20.4 (3.2, 37.5)	
p-value	0.0212	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.

Figure 29 Free fatty acid (FFA) (umol/L) series plots during the OGTTs. Per-protocol analysis set

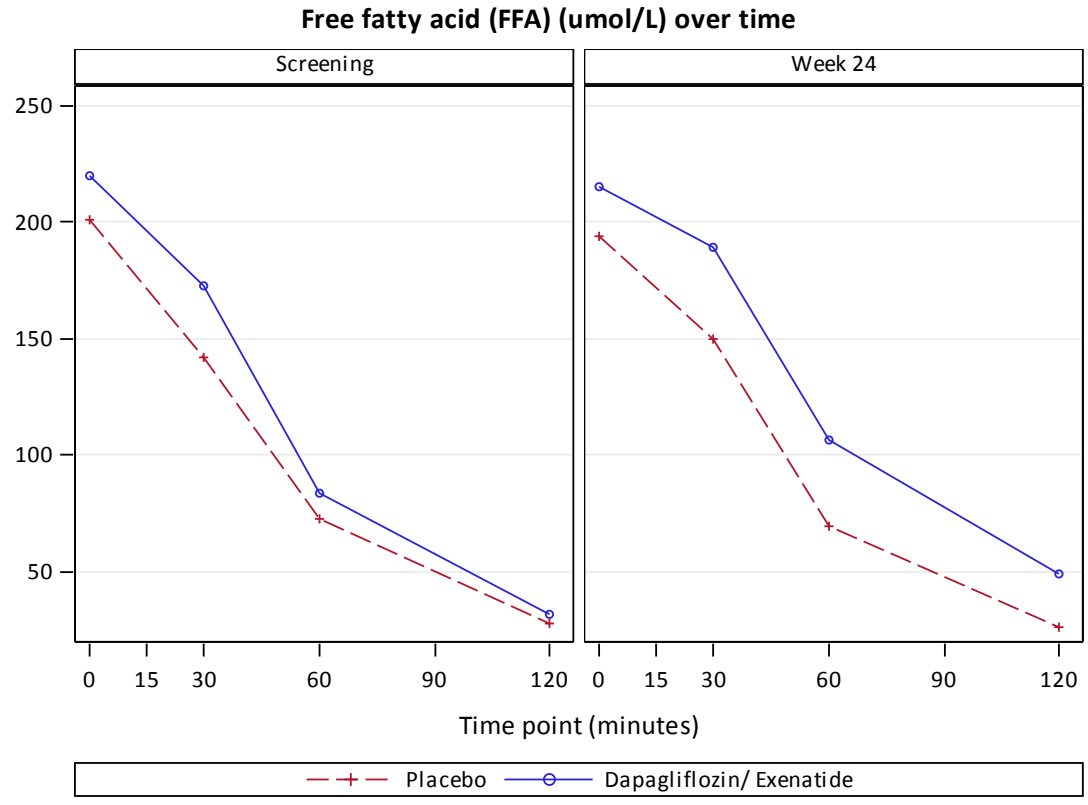


Table 157 Analysis of covariance of change from baseline to week 24 in Free fatty acid AUC (µmol/L x 120 min). Per-protocol analysis set

FFA AUC (umol/L x 120 min)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Screening		
n/nmiss	22/0	20/0
Mean (SD)	13217.05 (5733.85)	11370.00 (4233.28)
95% CI for the mean	(10674.80, 15759.29)	(9388.76, 13351.24)
Geometric mean	11979.160	10704.680
%CV	43.4%	37.2%
Median	12900.00	10740.00
Q1, Q3	8760.00, 16515.00	8197.50, 13177.50
Min, Max	4425.0, 26025.0	6120.0, 20820.0
Week 24		
n/nmiss	22/0	20/0
Mean (SD)	15158.18 (4834.57)	11315.25 (3240.50)
95% CI for the mean	(13014.65, 17301.71)	(9798.65, 12831.85)
Geometric mean	14379.140	10919.870
%CV	31.9%	28.6%
Median	14280.00	10237.50
Q1, Q3	11130.00, 19020.00	9202.50, 13080.00
Min, Max	6630.0, 25440.0	6900.0, 18660.0
Number of subjects included in analysis	22	20
Adjusted mean change (95% CI)	2176.56 (988.75, 3364.37)	-472.70 (-1707.10, 761.69)
Difference (95% CI)	2649.26 (945.71, 4352.81)	
p-value	0.0032	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
CV = coefficient of variation.
CI = Confidence interval.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
Screening = week -2-(-1)

Table 158 Analysis of covariance of change from baseline to week 24 in Free fatty acid (µmol/L/min) incremental area under curve. Full analysis set

Free fatty acid (µmol/L/min)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Screening		
n/nmiss	23/2	20/4
Mean (SD)	-13125.65 (5433.79)	-12744.00 (4820.45)
95% CI for the mean	(-15475.40, -10775.91)	(-15000.04, -10487.96)
%CV	-41.4%	-37.8%
Median	-13560.00	-13222.50
Q1, Q3	-16125.00, -8955.00	-15690.00, -8632.50
Min, Max	-23205.0, -2505.0	-24090.0, -4905.0
Week 24		
n/nmiss	23/2	20/4
Mean (SD)	-10516.96 (4483.01)	-11946.75 (4171.10)
95% CI for the mean	(-12455.56, -8578.36)	(-13898.88, -9994.62)
%CV	-42.6%	-34.9%
Median	-9900.00	-11985.00
Q1, Q3	-13890.00, -8070.00	-14100.00, -10162.50
Min, Max	-19200.0, -2325.0	-20790.0, -2745.0

Free fatty acid (µmol/L/min)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Number of subjects included in analysis		
Number of subjects included in analysis	23	20
Adjusted mean change (95% CI)	2760.9 (1010.6, 4511.2)	1269.9 (-607.1, 3147.0)
Difference (95% CI)	1491.0 (-1041.1, 4023.1)	
p-value	0.2408	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

Table 159 Analysis of covariance of change from baseline to week 24 in Free fatty acid (µmol/L/min) incremental area under curve. Per-protocol analysis set

Free fatty acid (µmol/L/min)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Screening		
n/nmiss	22/0	20/0
Mean (SD)	-13199.32 (5549.89)	-12744.00 (4820.45)
95% CI for the mean	(-15660.00, -10738.63)	(-15000.04, -10487.96)
%CV	-42.0%	-37.8%
Median	-13687.50	-13222.50
Q1, Q3	-16125.00, -8955.00	-15690.00, -8632.50
Min, Max	-23205.0, -2505.0	-24090.0, -4905.0
Week 24		
n/nmiss	22/0	20/0
Mean (SD)	-10712.73 (4486.75)	-11946.75 (4171.10)
95% CI for the mean	(-12702.04, -8723.41)	(-13898.88, -9994.62)
%CV	-41.9%	-34.9%
Median	-10177.50	-11985.00
Q1, Q3	-13890.00, -8310.00	-14100.00, -10162.50
Min, Max	-19200.0, -2325.0	-20790.0, -2745.0
Number of subjects included in analysis		
Number of subjects included in analysis	22	20
Adjusted mean change (95% CI)	2660.6 (840.4, 4480.8)	1283.4 (-612.5, 3179.3)
Difference (95% CI)	1377.1 (-1205.9, 3960.2)	
p-value	0.2873	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

14.2.2.6.15 Ketones

Table 160 Analysis of covariance of change from baseline to week 24 of Ketones (mmol/L) at time 0 min during the OGTT. Full analysis set

Ketones (mmol/L)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Screening		
n/nmiss	25/0	24/0
Mean (SD)	0.23 (0.11)	0.21 (0.07)
Median	0.20	0.20
Q1, Q3	0.20, 0.30	0.20, 0.20
Min, Max	0.1, 0.6	0.1, 0.4
Week 24		
n/nmiss	23/2	20/4
Mean (SD)	0.23 (0.10)	0.18 (0.11)
Median	0.20	0.10
Q1, Q3	0.10, 0.30	0.10, 0.25
Min, Max	0.1, 0.4	0.1, 0.4
Number of subjects included in analysis	23	20
Adjusted mean change (95% CI)	0.01 (-0.03, 0.06)	-0.03 (-0.08, 0.01)
Difference (95% CI)	0.05 (-0.02, 0.11)	
p-value	0.1488	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

Table 161 Analysis of covariance of change from baseline to week 24 of Ketones (mmol/L) at time 120 min during the OGTT. Full analysis set

Ketones (mmol/L)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Screening		
n/nmiss	21/4	23/1
Mean (SD)	0.17 (0.06)	0.16 (0.05)
Median	0.20	0.20
Q1, Q3	0.10, 0.20	0.10, 0.20
Min, Max	0.1, 0.3	0.1, 0.2
Week 24		
n/nmiss	23/2	20/4
Mean (SD)	0.17 (0.08)	0.14 (0.05)
Median	0.20	0.10
Q1, Q3	0.10, 0.20	0.10, 0.20
Min, Max	0.1, 0.4	0.1, 0.2
Number of subjects included in analysis	19	19
Adjusted mean change (95% CI)	0.01 (-0.02, 0.04)	-0.02 (-0.05, 0.02)
Difference (95% CI)	0.02 (-0.02, 0.07)	
p-value	0.2841	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

Table 162 Analysis of covariance of change from baseline to week 24 of Ketones (mmol/L) at time 0 min during the OGTT. Per-protocol set

Ketones (mmol/L)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Screening		
n/nmiss	22/0	20/0
Mean (SD)	0.22 (0.10)	0.20 (0.06)
Median	0.20	0.20
Q1, Q3	0.20, 0.20	0.20, 0.20
Min, Max	0.1, 0.6	0.1, 0.4
Week 24		
n/nmiss	22/0	20/0
Mean (SD)	0.23 (0.09)	0.18 (0.11)
Median	0.20	0.10
Q1, Q3	0.20, 0.30	0.10, 0.25
Min, Max	0.1, 0.4	0.1, 0.4
Number of subjects included in analysis	22	20
Adjusted mean change (95% CI)	0.02 (-0.03, 0.06)	-0.03 (-0.08, 0.01)
Difference (95% CI)	0.05 (-0.01, 0.12)	
p-value	0.1014	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

Table 163 Analysis of covariance of change from baseline to week 24 of Ketones (mmol/L) at time 120 min during the OGTT. Per-protocol set

Ketones (mmol/L)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Screening		
n/nmiss	18/4	19/1
Mean (SD)	0.16 (0.05)	0.15 (0.05)
Median	0.20	0.20
Q1, Q3	0.10, 0.20	0.10, 0.20
Min, Max	0.1, 0.2	0.1, 0.2
Week 24		
n/nmiss	22/0	20/0
Mean (SD)	0.18 (0.08)	0.14 (0.05)
Median	0.20	0.10
Q1, Q3	0.10, 0.20	0.10, 0.20
Min, Max	0.1, 0.4	0.1, 0.2
Number of subjects included in analysis	18	19
Adjusted mean change (95% CI)	0.01 (-0.02, 0.05)	-0.02 (-0.05, 0.02)
Difference (95% CI)	0.03 (-0.02, 0.07)	
p-value	0.2257	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

Figure 30 Ketones (mmol/L) series plots during the OGTTs. Per-protocol analysis set

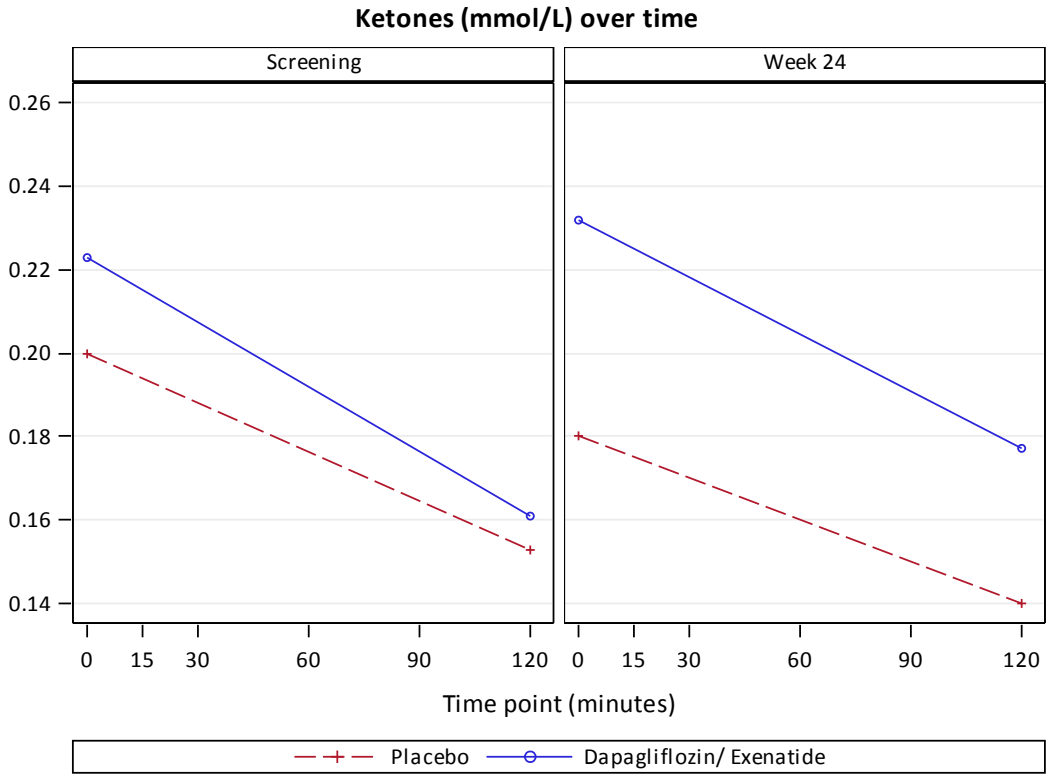


Table 164 Analysis of covariance of ketones (mmol/L) delta-delta at week 24. Full analysis set

Delta-delta	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Number of subjects included in analysis	19	19
Adjusted mean change (95% CI)	-0.003 (-0.055, 0.050)	0.007 (-0.046, 0.060)
Difference (95% CI)	-0.010 (-0.084, 0.065)	
p-value	0.7930	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline ketone value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Source: G:\StudData\Uppsala University\Dapalost\BIS\SASprog\DDP\BIS\Tables\Exploratory - Delta-delta Ketones.sas

Table 165 Analysis of covariance of ketones (µmol/L) delta-delta at week 24. Per-protocol analysis set

Delta-delta	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Number of subjects included in analysis	18	19
Adjusted mean change (95% CI)	0.001 (-0.055, 0.056)	0.009 (-0.045, 0.063)
Difference (95% CI)	-0.008 (-0.086, 0.070)	
p-value	0.8316	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
An analysis of covariance (ANCOVA) model adjusted for treatment, gender and baseline ketone value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Source: G:\StudData\Uppsala University\Dapalost\BIS\SASprog\DDP\BIS\Tables\Exploratory - Delta-delta Ketones.sas

14.2.2.7 Blood Lipid Profile

14.2.2.7.1 Total Cholesterol, Low-density Lipoprotein Cholesterol and High-density Lipoprotein Cholesterol

Table 166 Mixed model for repeated measures of change from baseline in Total cholesterol (mmol/L) at week 24. Full analysis set

Total cholesterol (TC) (mmol/L)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Screening		
n/nmiss	25/0	24/0
Mean (SD)	5.34 (1.00)	5.35 (0.95)
Median	5.30	5.45
Q1, Q3	4.80, 5.90	4.80, 5.80
Min, Max	3.1, 7.4	3.6, 7.9
Week 12		
n/nmiss	23/2	21/3
Mean (SD)	4.98 (0.87)	5.36 (1.22)
Median	4.90	5.40
Q1, Q3	4.60, 5.50	4.60, 6.10
Min, Max	3.1, 7.4	3.5, 8.4
Week 24		
n/nmiss	22/3	19/5
Mean (SD)	5.19 (1.09)	5.08 (1.18)
Median	5.15	5.00
Q1, Q3	4.50, 5.50	4.30, 5.80
Min, Max	3.1, 7.8	3.5, 8.6
Number of subjects included in analysis	25	24
Adjusted mean change (95% CI)	-0.17 (-0.42, 0.09)	-0.26 (-0.54, 0.01)
Difference (95% CI)	0.10 (-0.27, 0.47)	
p-value	0.5955	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
A mixed model for repeated measures (MMRM) adjusted for treatment, week, treatment*week, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

Table 167 Mixed model for repeated measures of change from baseline in Total cholesterol (mmol/L) at week 24. Per-protocol analysis set

Total cholesterol (TC) (mmol/L)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Screening		
n/nmiss	22/0	20/0
Mean (SD)	5.31 (1.06)	5.32 (0.97)
Median	5.15	5.35
Q1, Q3	4.70, 5.90	4.80, 5.70
Min, Max	3.1, 7.4	3.6, 7.9
Week 12		
n/nmiss	22/0	20/0
Mean (SD)	4.98 (0.89)	5.31 (1.23)
Median	4.85	5.40
Q1, Q3	4.60, 5.50	4.35, 5.95
Min, Max	3.1, 7.4	3.5, 8.4
Week 24		
n/nmiss	21/1	19/1
Mean (SD)	5.19 (1.12)	5.08 (1.18)
Median	5.10	5.00
Q1, Q3	4.50, 5.50	4.30, 5.80
Min, Max	3.1, 7.8	3.5, 8.6
Number of subjects included in analysis	22	20
Adjusted mean change (95% CI)	-0.15 (-0.42, 0.11)	-0.27 (-0.55, 0.01)
Difference (95% CI)	0.11 (-0.27, 0.49)	
p-value	0.5440	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
A mixed model for repeated measures (MMRM) adjusted for treatment, week, treatment*week, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

Table 168 Mixed model for repeated measures of change from baseline in Low-density lipoprotein cholesterol at week 24. Full analysis set

Low-density lipoprotein cholesterol (LDL-C) (mmol/L)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Screening		
n/nmiss	25/0	24/0
Mean (SD)	3.52 (0.91)	3.44 (0.89)
Median	3.40	3.50
Q1, Q3	3.10, 4.00	2.85, 3.85
Min, Max	1.9, 5.6	2.2, 5.7
Week 12		
n/nmiss	23/2	21/3
Mean (SD)	3.17 (0.72)	3.38 (1.01)
Median	3.10	3.30
Q1, Q3	2.70, 3.40	2.70, 4.00
Min, Max	2.0, 5.2	1.4, 5.7
Week 24		
n/nmiss	22/3	20/4
Mean (SD)	3.29 (0.84)	3.17 (1.05)
Median	3.25	3.15
Q1, Q3	2.70, 3.70	2.35, 3.70
Min, Max	1.7, 5.2	1.6, 6.3
Number of subjects included in analysis	25	24
Adjusted mean change (95% CI)	-0.17 (-0.38, 0.04)	-0.22 (-0.44, -0.00)
Difference (95% CI)	0.05 (-0.25, 0.35)	
p-value	0.7266	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
A mixed model for repeated measures (MMRM) adjusted for treatment, week, treatment*week, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

Table 169 Mixed model for repeated measures of change from baseline in Low-density lipoprotein cholesterol (mmol/L) at week 24. Per-protocol analysis set

Low-density lipoprotein cholesterol (LDL-C) (mmol/L)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Screening		
n/nmiss	22/0	20/0
Mean (SD)	3.49 (0.97)	3.38 (0.88)
Median	3.25	3.45
Q1, Q3	2.70, 4.00	2.85, 3.70
Min, Max	1.9, 5.6	2.2, 5.7
Week 12		
n/nmiss	22/0	20/0
Mean (SD)	3.17 (0.73)	3.34 (1.02)
Median	3.05	3.30
Q1, Q3	2.70, 3.40	2.65, 3.90
Min, Max	2.0, 5.2	1.4, 5.7
Week 24		
n/nmiss	21/1	20/0
Mean (SD)	3.29 (0.86)	3.17 (1.05)
Median	3.10	3.15
Q1, Q3	2.70, 3.70	2.35, 3.70
Min, Max	1.7, 5.2	1.6, 6.3
Number of subjects included in analysis	22	20
Adjusted mean change (95% CI)	-0.15 (-0.37, 0.07)	-0.22 (-0.44, 0.01)
Difference (95% CI)	0.07 (-0.24, 0.38)	
p-value	0.6424	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
A mixed model for repeated measures (MMRM) adjusted for treatment, week, treatment*week, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

Table 170 Mixed model for repeated measures of change from baseline in High-density lipoprotein cholesterol at week 24. Full analysis set

High-density lipoprotein cholesterol (HDL-C) (mmol/L)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Screening		
n/nmiss	25/0	24/0
Mean (SD)	1.26 (0.28)	1.26 (0.31)
Median	1.20	1.30
Q1, Q3	1.10, 1.50	1.00, 1.45
Min, Max	0.9, 1.9	0.7, 2.0
Week 12		
n/nmiss	23/2	21/3
Mean (SD)	1.22 (0.28)	1.26 (0.32)
Median	1.20	1.20
Q1, Q3	1.00, 1.40	0.96, 1.40
Min, Max	0.8, 1.8	0.8, 2.1
Week 24		
n/nmiss	23/2	20/4
Mean (SD)	1.26 (0.25)	1.20 (0.31)
Median	1.30	1.20
Q1, Q3	1.10, 1.50	1.00, 1.35
Min, Max	0.8, 1.6	0.8, 1.9
Number of subjects included in analysis	25	24
Adjusted mean change (95% CI)	0.016 (-0.059, 0.091)	-0.073 (-0.152, 0.006)
Difference (95% CI)	0.089 (-0.018, 0.196)	
p-value	0.1005	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
A mixed model for repeated measures (MMRM) adjusted for treatment, week, treatment*week, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

Table 171 Mixed model for repeated measures of change from baseline in High-density lipoprotein cholesterol (mmol/L) at week 24. Per-protocol analysis set

High-density lipoprotein cholesterol (HDL-C) (mmol/L)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Screening		
n/nmiss	22/0	20/0
Mean (SD)	1.26 (0.27)	1.28 (0.32)
Median	1.20	1.30
Q1, Q3	1.10, 1.50	1.00, 1.55
Min, Max	0.9, 1.9	0.7, 2.0
Week 12		
n/nmiss	22/0	20/0
Mean (SD)	1.23 (0.28)	1.25 (0.33)
Median	1.20	1.20
Q1, Q3	1.00, 1.40	0.96, 1.45
Min, Max	0.8, 1.8	0.8, 2.1
Week 24		
n/nmiss	22/0	20/0
Mean (SD)	1.28 (0.25)	1.20 (0.31)
Median	1.30	1.20
Q1, Q3	1.10, 1.50	1.00, 1.35
Min, Max	0.8, 1.6	0.8, 1.9
Number of subjects included in analysis	22	20
Adjusted mean change (95% CI)	0.023 (-0.055, 0.101)	-0.075 (-0.155, 0.005)
Difference (95% CI)	0.098 (-0.012, 0.207)	
p-value	0.0793	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
A mixed model for repeated measures (MMRM) adjusted for treatment, week, treatment*week, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

14.2.2.7.2 Triglycerides

Table 172 Mixed model for repeated measures of change from baseline in Triglycerides (mmol/L) at week 24. Full analysis set

Triglycerides (TG) (mmol/L)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Screening		
n/nmiss	25/0	24/0
Mean (SD)	1.40 (0.57)	1.59 (0.59)
Median	1.35	1.59
Q1, Q3	1.02, 1.62	1.13, 1.92
Min, Max	0.5, 3.2	0.5, 3.0
Week 12		
n/nmiss	23/2	21/3
Mean (SD)	1.22 (0.43)	1.55 (0.71)
Median	1.21	1.37
Q1, Q3	0.86, 1.42	0.99, 2.02
Min, Max	0.6, 2.5	0.6, 3.3
Week 24		
n/nmiss	22/3	20/4
Mean (SD)	1.35 (0.57)	1.53 (0.71)
Median	1.19	1.43
Q1, Q3	0.99, 1.73	0.92, 1.97
Min, Max	0.5, 2.5	0.6, 3.1
Number of subjects included in analysis	25	24
Adjusted mean change (95% CI)	-0.096 (-0.287, 0.096)	-0.006 (-0.207, 0.195)
Difference (95% CI)	-0.090 (-0.367, 0.187)	
p-value	0.5158	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
A mixed model for repeated measures (MMRM) adjusted for treatment, week, treatment*week, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

Table 173 Mixed model for repeated measures of change from baseline in Triglycerides (mmol/L) at week 24. Per-protocol analysis set

Triglycerides (TG) (mmol/L)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Screening		
n/nmiss	22/0	20/0
Mean (SD)	1.44 (0.59)	1.57 (0.65)
Median	1.37	1.43
Q1, Q3	1.02, 1.78	1.10, 2.02
Min, Max	0.5, 3.2	0.5, 3.0
Week 12		
n/nmiss	22/0	20/0
Mean (SD)	1.21 (0.44)	1.56 (0.72)
Median	1.19	1.45
Q1, Q3	0.86, 1.42	0.98, 2.02
Min, Max	0.6, 2.5	0.6, 3.3
Week 24		
n/nmiss	21/1	20/0
Mean (SD)	1.32 (0.57)	1.53 (0.71)
Median	1.16	1.43
Q1, Q3	0.99, 1.58	0.92, 1.97
Min, Max	0.5, 2.5	0.6, 3.1
Number of subjects included in analysis	22	20
Adjusted mean change (95% CI)	-0.129 (-0.323, 0.066)	-0.001 (-0.201, 0.198)
Difference (95% CI)	-0.127 (-0.404, 0.150)	
p-value	0.3581	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
A mixed model for repeated measures (MMRM) adjusted for treatment, week, treatment*week, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Screening = week -2-(-1)

14.2.2.8 Vital Signs

Table 174 Mixed model for repeated measures of change from baseline in Systolic blood pressure (mmHg). Per-protocol analysis set

Systolic blood pressure (mmHg)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Week -2(-1)		
n/nmiss	22/0	20/0
Mean (SD)	135.93 (18.22)	137.03 (15.50)
Median	133.50	135.75
Q1, Q3	121.50, 145.00	122.00, 148.75
Min, Max	108.0, 171.0	114.0, 167.5
Week 0 (Baseline)		
n/nmiss	22/0	20/0
Mean (SD)	133.45 (12.94)	137.28 (14.62)
Median	133.00	136.25
Q1, Q3	122.50, 144.50	127.75, 149.00
Min, Max	114.0, 162.5	112.5, 161.0
Week 4		
n/nmiss	22/0	20/0
Mean (SD)	129.30 (16.48)	137.78 (17.41)
Median	130.00	135.50
Q1, Q3	117.00, 143.50	126.00, 142.00
Min, Max	102.5, 159.0	115.0, 190.0
Adjusted mean change (95% CI)	-4.54 (-10.26, 1.18)	1.35 (-4.63, 7.32)
Difference (95% CI)	-5.89 (-14.14, 2.36)	
p-value	0.1568	
Week 8		
n/nmiss	22/0	20/0
Mean (SD)	123.98 (13.83)	133.58 (13.89)
Median	124.00	131.75
Q1, Q3	114.00, 131.50	122.50, 143.75
Min, Max	100.0, 150.0	112.5, 163.0
Adjusted mean change (95% CI)	-9.86 (-13.68, -6.04)	-2.85 (-6.82, 1.12)
Difference (95% CI)	-7.01 (-12.48, -1.53)	
p-value	0.0136	
Week 12		
n/nmiss	22/0	20/0
Mean (SD)	125.11 (15.81)	132.23 (12.57)
Median	124.25	132.50
Q1, Q3	110.00, 133.50	127.25, 141.75
Min, Max	105.0, 167.0	100.0, 155.0
Adjusted mean change (95% CI)	-8.72 (-13.33, -4.12)	-4.20 (-9.00, 0.60)
Difference (95% CI)	-4.52 (-11.15, 2.10)	
p-value	0.1755	
Week 24		
n/nmiss	22/0	20/0

Systolic blood pressure (mmHg)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Mean (SD)	124.41 (11.12)	133.33 (12.86)
Median	122.25	133.50
Q1, Q3	117.00, 133.00	125.25, 142.50
Min, Max	97.0, 142.5	111.0, 156.5
Adjusted mean change (95% CI)	-9.43 (-13.77, -5.09)	-3.10 (-7.62, 1.42)
Difference (95% CI)	-6.33 (-12.56, -0.09)	
p-value	0.0470	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
A mixed model for repeated measures (MMRM) adjusted for treatment, week, treatment*week, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.
Source: G:\StudData\Uppsala University\Dapalost\BIS\SASprog\DDP\BIS\Tables\Exploratory - Extended MMRM.sas

Table 175 Mixed model for repeated measures of change from baseline in Diastolic blood pressure (mmHg) at week 24. Full analysis set

Diastolic blood pressure (mmHg)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Week -2-(-1)		
n/nmiss	25/0	24/0
Mean (SD)	80.00 (11.19)	78.56 (9.86)
Median	82.50	79.00
Q1, Q3	70.00, 90.00	70.00, 86.00
Min, Max	53.5, 94.5	60.0, 95.0
Week 0 (Baseline)		
n/nmiss	25/0	24/0
Mean (SD)	75.80 (10.62)	77.04 (12.60)
Median	75.50	76.50
Q1, Q3	70.50, 81.00	68.75, 89.50
Min, Max	45.0, 95.5	55.0, 97.5
Week 4		
n/nmiss	25/0	24/0
Mean (SD)	73.20 (9.32)	75.27 (13.15)
Median	75.00	76.25
Q1, Q3	66.00, 80.00	66.50, 80.00
Min, Max	54.0, 89.0	52.0, 110.0
Week 8		
n/nmiss	24/1	23/1
Mean (SD)	73.21 (10.51)	78.48 (11.49)
Median	75.50	79.00
Q1, Q3	64.50, 80.50	75.00, 83.00
Min, Max	55.0, 93.5	52.0, 96.5
Week 12		
n/nmiss	23/2	21/3
Mean (SD)	76.65 (11.55)	76.60 (8.51)
Median	79.00	76.00
Q1, Q3	70.00, 87.00	73.00, 81.00
Min, Max	55.0, 96.0	56.0, 91.0
Week 24		
n/nmiss	23/2	20/4

Diastolic blood pressure (mmHg)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Mean (SD)	78.00 (10.56)	80.90 (10.62)
Median	78.00	79.00
Q1, Q3	70.00, 83.00	73.25, 88.50
Min, Max	57.0, 97.0	66.0, 107.0
Number of subjects included in analysis	25	24
Adjusted mean change (95% CI)	1.79 (-2.72, 6.30)	2.27 (-2.55, 7.10)
Difference (95% CI)	-0.48 (-7.06, 6.10)	
p-value	0.8827	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
A mixed model for repeated measures (MMRM) adjusted for treatment, week, treatment*week, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.

Table 176 Mixed model for repeated measures of change from baseline in Diastolic blood pressure (mmHg) at week 24. Per-protocol analysis set

Diastolic blood pressure (mmHg)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Week -2-(-1)		
n/nmiss	22/0	20/0
Mean (SD)	78.43 (11.01)	78.13 (10.21)
Median	80.75	78.50
Q1, Q3	69.50, 86.00	70.00, 86.00
Min, Max	53.5, 94.5	60.0, 95.0
Week 0 (Baseline)		
n/nmiss	22/0	20/0
Mean (SD)	74.89 (10.10)	79.33 (12.18)
Median	75.25	77.25
Q1, Q3	70.50, 80.50	71.50, 90.50
Min, Max	45.0, 95.5	55.0, 97.5
Week 4		
n/nmiss	22/0	20/0
Mean (SD)	72.27 (9.50)	77.13 (13.48)
Median	74.50	78.00
Q1, Q3	64.00, 80.00	71.25, 81.00
Min, Max	54.0, 89.0	52.0, 110.0
Week 8		
n/nmiss	22/0	20/0
Mean (SD)	72.02 (9.92)	79.83 (11.66)
Median	73.75	79.75
Q1, Q3	64.00, 80.00	77.75, 86.75
Min, Max	55.0, 91.0	52.0, 96.5
Week 12		
n/nmiss	22/0	20/0
Mean (SD)	76.55 (11.81)	76.88 (8.63)
Median	77.50	76.25
Q1, Q3	70.00, 87.00	74.00, 82.25
Min, Max	55.0, 96.0	56.0, 91.0
Week 24		
n/nmiss	22/0	20/0
Mean (SD)	77.86 (10.79)	80.90 (10.62)
Median	78.00	79.00
Q1, Q3	70.00, 83.00	73.25, 88.50
Min, Max	57.0, 97.0	66.0, 107.0
Number of subjects included in analysis	22	20
Adjusted mean change (95% CI)	1.58 (-3.10, 6.26)	2.63 (-2.28, 7.53)
Difference (95% CI)	-1.05 (-7.82, 5.72)	
p-value	0.7553	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
A mixed model for repeated measures (MMRM) adjusted for treatment, week, treatment*week, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.

Table 177 Mixed model for repeated measures of change in Pulse (beats/min) from baseline to week 24. Full analysis set

Pulse (BEATS/MIN)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Week -2-(-1)		
n/nmiss	25/0	24/0
Mean (SD)	64.16 (7.94)	63.75 (7.25)
Median	64.00	62.00
Q1, Q3	60.00, 70.00	59.00, 66.00
Min, Max	50.0, 80.0	52.0, 84.0
Week 0 (Baseline)		
n/nmiss	25/0	24/0
Mean (SD)	67.80 (9.52)	66.96 (9.21)
Median	68.00	64.00
Q1, Q3	62.00, 72.00	60.00, 70.00
Min, Max	52.0, 88.0	52.0, 94.0
Week 4		
n/nmiss	25/0	24/0
Mean (SD)	71.12 (8.53)	67.50 (8.59)
Median	70.00	66.00
Q1, Q3	64.00, 78.00	60.00, 71.00
Min, Max	58.0, 92.0	56.0, 86.0
Week 8		
n/nmiss	24/1	23/1
Mean (SD)	70.46 (9.83)	69.04 (9.95)
Median	68.00	70.00
Q1, Q3	63.00, 78.00	62.00, 78.00
Min, Max	55.0, 96.0	48.0, 84.0
Week 12		
n/nmiss	23/2	21/3
Mean (SD)	66.87 (7.86)	63.62 (8.32)
Median	66.00	62.00
Q1, Q3	62.00, 72.00	58.00, 68.00
Min, Max	52.0, 88.0	50.0, 78.0
Week 24		
n/nmiss	23/2	20/4
Mean (SD)	69.52 (9.97)	66.40 (9.68)
Median	66.00	64.00
Q1, Q3	62.00, 74.00	60.00, 70.00
Min, Max	52.0, 100.0	54.0, 86.0
Number of subjects included in analysis	25	24
Adjusted mean change (95% CI)	2.6 (-0.1, 5.3)	0.4 (-2.5, 3.3)
Difference (95% CI)	2.1 (-1.8, 6.1)	

Pulse (BEATS/MIN)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
p-value	0.2812	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
A mixed model for repeated measures (MMRM) adjusted for treatment, week, treatment*week, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.

Table 178 Mixed model for repeated measures of change from baseline in Pulse (beats/min) at week 24. Per-protocol analysis set

Pulse (BEATS/MIN)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Week -2-(-1)		
n/nmiss	22/0	20/0
Mean (SD)	63.45 (8.10)	62.70 (4.35)
Median	62.00	62.00
Q1, Q3	60.00, 70.00	59.00, 66.00
Min, Max	50.0, 80.0	56.0, 73.0
Week 0 (Baseline)		
n/nmiss	22/0	20/0
Mean (SD)	67.77 (10.10)	66.15 (8.91)
Median	67.00	64.00
Q1, Q3	60.00, 74.00	60.00, 70.00
Min, Max	52.0, 88.0	52.0, 94.0
Week 4		
n/nmiss	22/0	20/0
Mean (SD)	71.09 (8.85)	66.70 (8.52)
Median	69.00	66.00
Q1, Q3	64.00, 78.00	60.00, 70.00
Min, Max	58.0, 92.0	56.0, 86.0
Week 8		
n/nmiss	22/0	20/0
Mean (SD)	70.59 (10.05)	68.40 (10.34)
Median	68.00	66.50
Q1, Q3	64.00, 80.00	61.00, 78.00
Min, Max	55.0, 96.0	48.0, 84.0
Week 12		
n/nmiss	22/0	20/0
Mean (SD)	66.45 (7.78)	63.40 (8.47)
Median	66.00	62.00
Q1, Q3	62.00, 70.00	58.00, 69.00
Min, Max	52.0, 88.0	50.0, 78.0
Week 24		
n/nmiss	22/0	20/0
Mean (SD)	69.41 (10.19)	66.40 (9.68)
Median	66.00	64.00
Q1, Q3	62.00, 74.00	60.00, 70.00
Min, Max	52.0, 100.0	54.0, 86.0
Number of subjects included in analysis	22	20
Adjusted mean change (95% CI)	2.4 (-0.4, 5.3)	0.3 (-2.7, 3.2)
Difference (95% CI)	2.2 (-1.9, 6.2)	
p-value	0.2931	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
A mixed model for repeated measures (MMRM) adjusted for treatment, week, treatment*week, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.

14.2.2.9 Other Anthropometric Measurements

14.2.2.9.1 Waist Circumference

Table 179 Mixed model for repeated measures of change from baseline to week 24 in Waist circumference (cm). Full analysis set

Waist circumference (cm)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Week -2-(-1)		
n/nmiss	25/0	24/0
Mean (SD)	117.28 (10.85)	114.23 (13.03)
Median	117.50	111.50
Q1, Q3	111.50, 124.00	105.00, 119.75
Min, Max	94.5, 149.0	94.0, 143.0
Week 0 (Baseline)		
n/nmiss	25/0	24/0
Mean (SD)	117.56 (11.34)	114.35 (12.55)
Median	117.00	109.25
Q1, Q3	110.00, 125.00	107.00, 120.25
Min, Max	93.5, 148.5	94.0, 143.0
Week 4		
n/nmiss	25/0	24/0
Mean (SD)	115.98 (10.22)	112.96 (12.03)
Median	115.00	110.00
Q1, Q3	109.50, 121.00	104.25, 117.00
Min, Max	96.0, 143.0	98.5, 141.5
Week 8		
n/nmiss	24/1	23/1
Mean (SD)	116.13 (10.87)	114.65 (12.18)
Median	115.00	111.00
Q1, Q3	108.00, 122.50	105.00, 121.00
Min, Max	95.0, 147.5	101.0, 144.0
Week 12		
n/nmiss	23/2	21/3
Mean (SD)	113.37 (11.13)	112.60 (13.25)
Median	113.00	109.50
Q1, Q3	105.00, 120.00	104.00, 116.50
Min, Max	91.5, 145.0	96.5, 144.0
Week 24		
n/nmiss	23/2	20/4
Mean (SD)	111.54 (12.02)	113.00 (14.70)
Median	112.00	111.25
Q1, Q3	102.00, 120.00	101.25, 120.50
Min, Max	88.0, 143.0	94.0, 144.0
Number of subjects included in analysis	25	24
Adjusted mean change (95% CI)	-5.32 (-7.49, -3.14)	-2.55 (-4.84, -0.25)
Difference (95% CI)	-2.77 (-5.91, 0.37)	
p-value	0.0827	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
A mixed model for repeated measures (MMRM) adjusted for treatment, week, treatment*week, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.

Table 180 Mixed model for repeated measures of change from baseline to week 24 in Waist circumference (cm). Per-protocol analysis set

Waist circumference (cm)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Week -2-(-1)		
n/nmiss	22/0	20/0
Mean (SD)	116.59 (10.93)	115.13 (14.11)
Median	117.50	113.50
Q1, Q3	111.50, 122.00	104.00, 121.25
Min, Max	94.5, 149.0	94.0, 143.0
Week 0 (Baseline)		
n/nmiss	22/0	20/0
Mean (SD)	116.86 (11.36)	115.43 (13.49)
Median	116.00	110.75
Q1, Q3	110.00, 125.00	107.00, 121.00
Min, Max	93.5, 148.5	94.0, 143.0
Week 4		
n/nmiss	22/0	20/0
Mean (SD)	115.32 (10.51)	113.88 (12.96)
Median	114.50	111.25
Q1, Q3	108.50, 121.00	103.25, 120.00
Min, Max	96.0, 143.0	98.5, 141.5
Week 8		
n/nmiss	22/0	20/0
Mean (SD)	115.18 (10.84)	115.80 (12.65)
Median	113.50	113.50
Q1, Q3	107.50, 121.50	106.25, 121.50
Min, Max	95.0, 147.5	101.0, 144.0
Week 12		
n/nmiss	22/0	20/0
Mean (SD)	112.95 (11.21)	112.75 (13.57)
Median	112.75	109.50
Q1, Q3	105.00, 120.00	103.00, 118.75
Min, Max	91.5, 145.0	96.5, 144.0
Week 24		
n/nmiss	22/0	20/0
Mean (SD)	111.07 (12.08)	113.00 (14.70)
Median	111.50	111.25
Q1, Q3	102.00, 119.00	101.25, 120.50
Min, Max	88.0, 143.0	94.0, 144.0
Number of subjects included in analysis	22	20
Adjusted mean change (95% CI)	-5.36 (-7.63, -3.09)	-2.30 (-4.66, 0.06)
Difference (95% CI)	-3.06 (-6.31, 0.19)	
p-value	0.0643	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
A mixed model for repeated measures (MMRM) adjusted for treatment, week, treatment*week, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.

14.2.2.9.2 Waist-hip Ratio

Table 181 Mixed model for repeated measures of change in Waist-hip ratio from baseline to week 24. Full analysis set

Waist-hip ratio	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Week -2-(-1)		
n/nmiss	25/0	24/0
Mean (SD)	0.97 (0.10)	0.97 (0.11)
Median	0.96	0.98
Q1, Q3	0.91, 1.04	0.87, 1.05
Min, Max	0.8, 1.2	0.8, 1.2
Week 0 (Baseline)		
n/nmiss	25/0	24/0
Mean (SD)	0.97 (0.10)	0.97 (0.09)
Median	0.97	0.99
Q1, Q3	0.89, 1.03	0.90, 1.03
Min, Max	0.8, 1.1	0.8, 1.2
Week 4		
n/nmiss	25/0	24/0
Mean (SD)	0.97 (0.10)	0.97 (0.10)
Median	0.96	0.98
Q1, Q3	0.90, 1.03	0.89, 1.02
Min, Max	0.8, 1.1	0.8, 1.2
Week 8		
n/nmiss	24/1	23/1
Mean (SD)	0.97 (0.09)	0.97 (0.09)
Median	0.96	0.98
Q1, Q3	0.93, 1.05	0.91, 1.03
Min, Max	0.8, 1.1	0.8, 1.1
Week 12		
n/nmiss	23/2	21/3
Mean (SD)	0.96 (0.08)	0.96 (0.10)
Median	0.95	0.95
Q1, Q3	0.90, 1.00	0.88, 1.04
Min, Max	0.8, 1.1	0.8, 1.1
Week 24		
n/nmiss	23/2	20/4
Mean (SD)	0.95 (0.11)	0.96 (0.12)
Median	0.96	1.00
Q1, Q3	0.86, 1.02	0.83, 1.05
Min, Max	0.8, 1.2	0.8, 1.1
Number of subjects included in analysis	25	24
Adjusted mean change (95% CI)	-0.018 (-0.037, 0.000)	-0.013 (-0.033, 0.007)
Difference (95% CI)	-0.005 (-0.033, 0.022)	
p-value	0.7104	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
A mixed model for repeated measures (MMRM) adjusted for treatment, week, treatment*week, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.

Table 182 Mixed model for repeated measures of change from baseline to week 24 in Waist-hip ratio. Per-protocol analysis set

Waist-hip ratio	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Week -2-(-1)		
n/nmiss	22/0	20/0
Mean (SD)	0.97 (0.09)	0.97 (0.12)
Median	0.96	0.99
Q1, Q3	0.91, 1.03	0.87, 1.06
Min, Max	0.8, 1.2	0.8, 1.2
Week 0 (Baseline)		
n/nmiss	22/0	20/0
Mean (SD)	0.96 (0.09)	0.97 (0.10)
Median	0.97	1.00
Q1, Q3	0.89, 1.03	0.89, 1.04
Min, Max	0.8, 1.1	0.8, 1.2
Week 4		
n/nmiss	22/0	20/0
Mean (SD)	0.96 (0.10)	0.97 (0.11)
Median	0.96	0.98
Q1, Q3	0.90, 1.02	0.89, 1.04
Min, Max	0.8, 1.1	0.8, 1.2
Week 8		
n/nmiss	22/0	20/0
Mean (SD)	0.96 (0.09)	0.97 (0.09)
Median	0.95	0.98
Q1, Q3	0.92, 1.04	0.92, 1.04
Min, Max	0.8, 1.1	0.8, 1.1
Week 12		
n/nmiss	22/0	20/0
Mean (SD)	0.95 (0.08)	0.96 (0.10)
Median	0.95	0.95
Q1, Q3	0.90, 1.00	0.88, 1.05
Min, Max	0.8, 1.1	0.8, 1.1
Week 24		
n/nmiss	22/0	20/0
Mean (SD)	0.94 (0.11)	0.96 (0.12)
Median	0.96	1.00
Q1, Q3	0.86, 1.00	0.83, 1.05
Min, Max	0.8, 1.2	0.8, 1.1
Number of subjects included in analysis	22	20
Adjusted mean change (95% CI)	-0.017 (-0.036, 0.003)	-0.012 (-0.032, 0.009)
Difference (95% CI)	-0.005 (-0.033, 0.023)	
p-value	0.7129	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
A mixed model for repeated measures (MMRM) adjusted for treatment, week, treatment*week, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.

14.2.2.9.3 Body Mass Index

Table 183 Mixed model for repeated measures of change in Body mass index (BMI) (kg/m²) from baseline to week 24. Full analysis set

Body mass index (BMI) (kg/m2)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Week -2-(-1)		
n/nmiss	25/0	24/0
Mean (SD)	35.94 (2.92)	34.95 (3.59)
Median	36.13	33.94
Q1, Q3	33.83, 37.89	33.08, 35.87
Min, Max	30.9, 44.2	30.7, 44.7
Week 0 (Baseline)		
n/nmiss	25/0	24/0
Mean (SD)	35.82 (2.88)	34.98 (3.69)
Median	36.13	33.92
Q1, Q3	33.74, 37.55	32.98, 35.95
Min, Max	30.9, 44.1	30.6, 44.8
Week 4		
n/nmiss	25/0	24/0
Mean (SD)	35.51 (3.05)	34.77 (3.62)
Median	35.79	33.88
Q1, Q3	32.99, 37.31	32.48, 35.36
Min, Max	29.8, 43.5	30.6, 44.6
Week 8		
n/nmiss	24/1	23/1
Mean (SD)	35.26 (3.15)	34.86 (3.68)
Median	35.76	34.11
Q1, Q3	32.71, 37.03	32.43, 35.78
Min, Max	28.9, 42.8	30.6, 45.0
Week 12		
n/nmiss	23/2	21/3
Mean (SD)	34.59 (3.50)	35.06 (3.98)
Median	35.22	34.02
Q1, Q3	31.29, 36.80	32.47, 35.78
Min, Max	27.6, 42.6	30.3, 45.2
Week 24		
n/nmiss	23/2	20/4
Mean (SD)	34.40 (4.01)	35.31 (4.05)
Median	35.05	34.14
Q1, Q3	30.82, 36.60	32.47, 37.50
Min, Max	26.1, 43.8	31.2, 45.3
Number of subjects included in analysis	25	24
Adjusted mean change (95% CI)	-1.501 (-2.043, -0.958)	-0.092 (-0.660, 0.475)
Difference (95% CI)	-1.408 (-2.192, -0.624)	
p-value	0.0008	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
A mixed model for repeated measures (MMRM) adjusted for treatment, week, treatment*week, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.

Table 184 Mixed model for repeated measures of change from baseline to week 24 in Body mass index (kg/m²). Per-protocol analysis set

Body mass index (BMI) (kg/m2)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Week -2-(-1)		
n/nmiss	22/0	20/0
Mean (SD)	35.94 (2.96)	35.44 (3.68)
Median	36.07	34.15
Q1, Q3	33.83, 37.89	33.37, 36.94
Min, Max	30.9, 44.2	31.0, 44.7
Week 0 (Baseline)		
n/nmiss	22/0	20/0
Mean (SD)	35.76 (2.94)	35.50 (3.78)
Median	35.81	34.20
Q1, Q3	33.74, 37.55	33.28, 36.84
Min, Max	30.9, 44.1	30.8, 44.8
Week 4		
n/nmiss	22/0	20/0
Mean (SD)	35.51 (3.14)	35.22 (3.76)
Median	35.56	34.17
Q1, Q3	32.99, 37.32	32.80, 36.75
Min, Max	29.8, 43.5	30.6, 44.6
Week 8		
n/nmiss	22/0	20/0
Mean (SD)	35.14 (3.26)	35.26 (3.76)
Median	35.43	34.27
Q1, Q3	32.41, 37.19	33.01, 36.41
Min, Max	28.9, 42.8	30.6, 45.0
Week 12		
n/nmiss	22/0	20/0
Mean (SD)	34.54 (3.58)	35.25 (3.98)
Median	35.22	34.03
Q1, Q3	31.29, 36.80	32.73, 36.68
Min, Max	27.6, 42.6	30.3, 45.2
Week 24		
n/nmiss	22/0	20/0
Mean (SD)	34.30 (4.07)	35.31 (4.05)
Median	34.98	34.14
Q1, Q3	30.82, 36.56	32.47, 37.50
Min, Max	26.1, 43.8	31.2, 45.3
Number of subjects included in analysis	22	20
Adjusted mean change (95% CI)	-1.458 (-2.028, -0.889)	-0.187 (-0.783, 0.409)
Difference (95% CI)	-1.271 (-2.093, -0.450)	
p-value	0.0034	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
A mixed model for repeated measures (MMRM) adjusted for treatment, week, treatment*week, gender and baseline value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.

14.2.2.10 Urinary Glucose Excretion

Table 185 U-glucose (mmol/L). Per-protocol analysis set

Glucose (mmol/L)	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Week 24		
n/nmiss	22/0	20/0
Mean (SD)	188.67 (109.74)	0.95 (2.05)
Median	166.00	0.30
Q1, Q3	112.00, 311.00	0.20, 0.65
Min, Max	45.8, 387.0	0.1, 9.4

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.

14.2.2.11 Estimated Glomerular Filtration Rate

Table 186 Mixed model for repeated measures of change from screening in estimated glomerular filtration rate (mL/min) at week 24. Full analysis set

eGFR	Dapagliflozin/ Exenatide (N=25)	Placebo (N=24)
Screening		
n/nmiss	25/0	22/2
Mean (SD)	84.99 (17.34)	84.59 (12.13)
Median	83.33	80.69
Q1, Q3	68.98, 96.95	75.53, 95.62
Min, Max	60.8, 127.0	64.3, 108.6
Week 12		
n/nmiss	23/2	21/3
Mean (SD)	85.67 (21.23)	89.25 (17.55)
Median	81.25	86.68
Q1, Q3	68.71, 98.89	78.25, 94.83
Min, Max	54.8, 133.2	66.3, 145.3
Week 24		
n/nmiss	23/2	20/4
Mean (SD)	82.05 (16.43)	88.78 (16.22)
Median	77.61	86.34
Q1, Q3	70.16, 96.57	78.98, 98.14
Min, Max	54.6, 118.3	66.3, 125.6
Number of subjects included in analysis	25	24
Adjusted mean change (95% CI)	-1.968 (-6.522, 2.587)	2.469 (-2.651, 7.588)
Difference (95% CI)	-4.436 (-11.219, 2.346)	
p-value	0.1930	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
A mixed model for repeated measures (MMRM) adjusted for treatment, week, treatment*week, gender and screening value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.

Table 187 Mixed model for repeated measures of change from screening in estimated glomerular filtration rate (mL/min) at week 24. Per-protocol analysis set

eGFR	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Screening		
n/nmiss	22/0	18/2
Mean (SD)	84.18 (17.47)	85.34 (12.57)
Median	81.84	81.53
Q1, Q3	68.56, 96.95	76.86, 95.62
Min, Max	60.8, 127.0	64.3, 108.6
Week 12		
n/nmiss	22/0	20/0
Mean (SD)	86.32 (21.50)	89.83 (17.80)
Median	83.07	87.40
Q1, Q3	68.71, 98.89	79.34, 97.53
Min, Max	54.8, 133.2	66.3, 145.3
Week 24		
n/nmiss	22/0	20/0
Mean (SD)	82.65 (16.56)	88.78 (16.22)
Median	79.33	86.34
Q1, Q3	70.29, 96.57	78.98, 98.14
Min, Max	54.6, 118.3	66.3, 125.6
Number of subjects included in analysis	22	20
Adjusted mean change (95% CI)	-1.750 (-6.501, 3.000)	2.563 (-2.656, 7.783)
Difference (95% CI)	-4.313 (-11.284, 2.658)	
p-value	0.2172	

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
A mixed model for repeated measures (MMRM) adjusted for treatment, week, treatment*week, gender and screening value was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
CI = Confidence interval.

14.2.2.12 Model Building for Identification of Potential Covariates

Table 188 Analysis of covariance of change from baseline to week 24 in Body weight (kg). Per-protocol analysis set

Weight	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Number of subjects included in analysis	22	20
Adjusted mean change (95% CI)	-4.35 (-5.94, -2.76)	-0.54 (-2.20, 1.13)
Difference (95% CI)	-3.81 (-6.11, -1.51)	
p-value	0.0018	

CI = Confidence interval.
An analysis of covariance (ANCOVA) model adjusted for treatment and baseline BMI was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 189 Analysis of covariance of change from baseline to week 24 in Body weight (kg). Per-protocol analysis set

Effect	Levels	Reference	Estimate	Standard error	t-value	p-value
Treatment	Dapagliflozin/ Exenatide	No	-3.81	1.14	-3.35	0.0018
	Placebo	Yes				
Baseline BMI		No	0.45	0.17	2.63	0.0122

Estimates based on an analysis of covariance (ANCOVA) model.

Table 190 Analysis of covariance of percentage change from baseline to week 24 in Body weight (kg). Per-protocol analysis set

Weight	Dapagliflozin/ Exenatide (N=22)	Placebo (N=20)
Number of subjects included in analysis	22	20
Adjusted mean change (95% CI)	-4.38 (-5.91, -2.84)	-0.54 (-2.15, 1.07)
Difference (95% CI)	-3.84 (-6.07, -1.62)	
p-value	0.0012	

CI = Confidence interval.
An analysis of covariance (ANCOVA) model adjusted for treatment and baseline BMI was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 191 Analysis of covariance of percentage change from baseline to week 24 in Body weight (kg). Per-protocol analysis set

Effect	Levels	Reference	Estimate	Standard error	t-value	p-value
Treatment	Dapagliflozin/ Exenatide	No	-3.84	1.1	-3.49	0.0012
	Placebo	Yes				
Baseline BMI		No	0.47	0.17	2.83	0.0072

Estimates based on an analysis of covariance (ANCOVA) model.

14.3 SAFETY DATA

14.3.1 Safety Laboratory Variables

Table 192 B-Haemoglobin (g/L). Safety analysis set

B-Haemoglobin (Hb) (g/L)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=25)
Week -2-(-1)		
n/nmiss	25/0	25/0
Mean (SD)	140.16 (15.93)	143.88 (12.49)
Median	141.00	140.00
Q1, Q3	134.00, 152.00	136.00, 153.00
Min, Max	108.0, 164.0	123.0, 166.0
Week 12		
n/nmiss	23/2	22/3
Mean (SD)	147.09 (16.85)	145.14 (13.14)
Median	151.00	144.00
Q1, Q3	136.00, 160.00	135.00, 153.00
Min, Max	104.0, 168.0	123.0, 175.0
Change from screening to week 12		
n/nmiss	23/2	22/3
Mean (SD)	6.96 (9.98)	1.27 (5.36)
Median	7.00	0.50
Q1, Q3	2.00, 12.00	-1.00, 3.00
Min, Max	-9.0, 38.0	-8.0, 11.0
Week 24		
n/nmiss	23/2	21/4
Mean (SD)	143.57 (16.41)	142.00 (13.81)
Median	145.00	142.00
Q1, Q3	132.00, 156.00	134.00, 151.00
Min, Max	104.0, 167.0	116.0, 174.0
Change from screening to week 24		
n/nmiss	23/2	21/4
Mean (SD)	3.43 (12.29)	-1.81 (7.55)
Median	2.00	-3.00
Q1, Q3	-4.00, 7.00	-7.00, 3.00
Min, Max	-11.0, 39.0	-14.0, 14.0

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
Week -2-(1-) = screening (baseline)

Table 193 Creatinine (µmol/L). Safety analysis set

Creatinine (umol/L)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=25)
Week -2-(-1)		
n/nmiss	25/0	23/2
Mean (SD)	73.32 (14.53)	73.04 (11.55)
Median	73.00	70.00
Q1, Q3	63.00, 83.00	66.00, 85.00
Min, Max	49.0, 106.0	54.0, 94.0
Week 12		
n/nmiss	23/2	22/3
Mean (SD)	73.70 (17.02)	70.55 (12.91)
Median	72.00	68.50
Q1, Q3	64.00, 82.00	62.00, 76.00
Min, Max	44.0, 116.0	52.0, 101.0
Change from screening to week 12		
n/nmiss	23/2	20/5
Mean (SD)	-0.17 (6.71)	-2.15 (6.16)
Median	-1.00	-2.00
Q1, Q3	-6.00, 5.00	-6.50, 0.50
Min, Max	-11.0, 14.0	-15.0, 13.0
Week 24		
n/nmiss	23/2	21/4
Mean (SD)	75.48 (15.68)	71.71 (13.72)
Median	74.00	72.00
Q1, Q3	67.00, 87.00	61.00, 80.00
Min, Max	48.0, 111.0	50.0, 101.0
Change from screening to week 24		
n/nmiss	23/2	19/6
Mean (SD)	1.61 (7.58)	-1.21 (5.95)
Median	1.00	-1.00
Q1, Q3	-4.00, 6.00	-6.00, 3.00
Min, Max	-13.0, 17.0	-11.0, 12.0

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
Week -2-(1-) = screening (baseline)

Table 194 Total bilirubin (µmol/L). Safety analysis set

Total bilirubin (umol/L)		Dapagliflozin/ Exenatide (N=25)	Placebo (N=25)
	Week -2-(-1)		
n/nmiss		25/0	25/0
Mean (SD)		12.36 (5.62)	10.92 (3.43)
Median		10.00	11.00
Q1, Q3		9.00, 16.00	8.00, 14.00
Min, Max		6.5, 31.0	5.9, 16.0
	Week 12		
n/nmiss		23/2	21/4
Mean (SD)		12.39 (6.88)	12.29 (4.54)
Median		10.00	12.00
Q1, Q3		8.60, 12.00	9.20, 14.00
Min, Max		6.2, 34.0	5.6, 24.0
	Change from screening to week 12		
n/nmiss		23/2	21/4
Mean (SD)		0.16 (4.28)	1.12 (4.74)
Median		0.00	0.00
Q1, Q3		-1.50, 1.00	-3.00, 4.30
Min, Max		-8.0, 14.0	-6.1, 10.4
	Week 24		
n/nmiss		23/2	21/4
Mean (SD)		12.04 (5.85)	11.42 (3.93)
Median		10.00	11.00
Q1, Q3		8.20, 14.00	9.40, 13.00
Min, Max		5.5, 27.0	5.1, 18.0
	Change from screening to week 24		
n/nmiss		23/2	21/4
Mean (SD)		-0.18 (3.26)	0.53 (3.17)
Median		-0.80	0.90
Q1, Q3		-2.80, 2.00	-1.60, 2.40
Min, Max		-6.0, 7.0	-5.5, 6.0

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
Week -2-(1-) = screening (baseline)

Table 195 Alkaline phosphatase (µkat/L). Safety analysis set

Alkaline phosphatise (ALP) (ukat/L)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=25)
Week -2-(-1)		
n/nmiss	24/1	25/0
Mean (SD)	1.22 (0.27)	1.09 (0.26)
Median	1.20	1.10
Q1, Q3	1.05, 1.40	0.94, 1.30
Min, Max	0.8, 1.8	0.6, 1.7
Week 12		
n/nmiss	23/2	20/5
Mean (SD)	1.25 (0.28)	1.11 (0.25)
Median	1.30	1.10
Q1, Q3	1.00, 1.50	0.91, 1.30
Min, Max	0.7, 1.9	0.6, 1.6
Change from screening to week 12		
n/nmiss	22/3	20/5
Mean (SD)	-0.02 (0.19)	0.02 (0.11)
Median	0.00	0.04
Q1, Q3	-0.10, 0.10	-0.08, 0.10
Min, Max	-0.7, 0.2	-0.2, 0.2
Week 24		
n/nmiss	20/5	19/6
Mean (SD)	1.17 (0.22)	1.09 (0.26)
Median	1.20	1.10
Q1, Q3	0.99, 1.35	0.89, 1.30
Min, Max	0.8, 1.6	0.6, 1.6
Change from screening to week 24		
n/nmiss	19/6	19/6
Mean (SD)	-0.10 (0.17)	-0.04 (0.09)
Median	-0.10	-0.01
Q1, Q3	-0.20, 0.09	-0.10, 0.00
Min, Max	-0.5, 0.1	-0.2, 0.1

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
Week -2-(1-) = screening (baseline)

Table 196 Aspartate transaminase (µkat/L). Safety analysis set

Aspartate transaminase (AST) (ukat/L)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=25)
Week -2-(-1)		
n/nmiss	25/0	24/1
Mean (SD)	0.54 (0.19)	0.53 (0.15)
Median	0.51	0.50
Q1, Q3	0.41, 0.63	0.41, 0.62
Min, Max	0.3, 1.2	0.3, 0.9
Week 12		
n/nmiss	23/2	22/3
Mean (SD)	0.50 (0.15)	0.50 (0.13)
Median	0.46	0.50
Q1, Q3	0.41, 0.54	0.40, 0.61
Min, Max	0.3, 0.9	0.3, 0.8
Change from screening to week 12		
n/nmiss	23/2	21/4
Mean (SD)	-0.03 (0.11)	-0.03 (0.15)
Median	-0.03	-0.04
Q1, Q3	-0.09, 0.02	-0.09, 0.01
Min, Max	-0.3, 0.2	-0.5, 0.3
Week 24		
n/nmiss	23/2	21/4
Mean (SD)	0.48 (0.15)	0.46 (0.10)
Median	0.43	0.44
Q1, Q3	0.37, 0.55	0.38, 0.54
Min, Max	0.3, 1.0	0.3, 0.7
Change from screening to week 24		
n/nmiss	23/2	20/5
Mean (SD)	-0.06 (0.14)	-0.09 (0.13)
Median	-0.06	-0.06
Q1, Q3	-0.13, -0.01	-0.16, -0.03
Min, Max	-0.3, 0.3	-0.5, 0.2

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
Week -2-(1-) = screening (baseline)

Table 197 Alanine transaminase (µkat/L). Safety analysis set

Alanine transaminase (ALT) (ukat/L)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=25)
Week -2-(-1)		
n/nmiss	25/0	24/1
Mean (SD)	0.63 (0.38)	0.67 (0.43)
Median	0.58	0.54
Q1, Q3	0.35, 0.67	0.37, 0.90
Min, Max	0.2, 1.6	0.2, 2.0
Week 12		
n/nmiss	23/2	22/3
Mean (SD)	0.64 (0.43)	0.67 (0.29)
Median	0.54	0.57
Q1, Q3	0.35, 0.77	0.48, 0.97
Min, Max	0.2, 2.1	0.3, 1.2
Change from screening to week 12		
n/nmiss	23/2	21/4
Mean (SD)	0.02 (0.26)	-0.04 (0.38)
Median	-0.01	-0.01
Q1, Q3	-0.10, 0.07	-0.09, 0.10
Min, Max	-0.3, 0.9	-1.4, 0.6
Week 24		
n/nmiss	23/2	21/4
Mean (SD)	0.57 (0.32)	0.60 (0.31)
Median	0.55	0.52
Q1, Q3	0.30, 0.72	0.36, 0.88
Min, Max	0.2, 1.6	0.2, 1.2
Change from screening to week 24		
n/nmiss	23/2	20/5
Mean (SD)	-0.05 (0.24)	-0.13 (0.38)
Median	-0.04	-0.07
Q1, Q3	-0.15, 0.04	-0.21, 0.03
Min, Max	-0.5, 0.6	-1.6, 0.4

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
Week -2-(1-) = screening (baseline)

Table 198 Albumin (g/L). Safety analysis set

Albumin (g/L)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=25)
Week -2-(-1)		
n/nmiss	24/1	25/0
Mean (SD)	37.63 (2.18)	38.40 (2.48)
Median	37.00	38.00
Q1, Q3	36.00, 38.50	37.00, 40.00
Min, Max	33.0, 42.0	34.0, 43.0
Week 12		
n/nmiss	23/2	22/3
Mean (SD)	38.43 (3.01)	39.50 (2.86)
Median	38.00	40.00
Q1, Q3	37.00, 42.00	37.00, 41.00
Min, Max	33.0, 43.0	34.0, 44.0
Change from screening to week 12		
n/nmiss	22/3	22/3
Mean (SD)	0.82 (2.08)	1.05 (2.19)
Median	1.00	1.00
Q1, Q3	1.00, 2.00	0.00, 3.00
Min, Max	-5.0, 5.0	-3.0, 5.0
Week 24		
n/nmiss	23/2	21/4
Mean (SD)	37.70 (2.95)	38.43 (2.36)
Median	38.00	39.00
Q1, Q3	35.00, 40.00	37.00, 40.00
Min, Max	32.0, 43.0	34.0, 44.0
Change from screening to week 24		
n/nmiss	22/3	21/4
Mean (SD)	0.18 (2.04)	-0.05 (1.72)
Median	0.00	-1.00
Q1, Q3	-1.00, 1.00	-1.00, 1.00
Min, Max	-4.0, 5.0	-3.0, 4.0

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
Week -2-(1-) = screening (baseline)

Table 199 Potassium (mmol/L). Safety analysis set

Potassium (mmol/L)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=25)
Week -2-(-1)		
n/nmiss	25/0	25/0
Mean (SD)	3.76 (0.30)	3.68 (0.25)
Median	3.70	3.60
Q1, Q3	3.60, 3.90	3.60, 3.90
Min, Max	3.0, 4.4	3.1, 4.3
Week 12		
n/nmiss	23/2	22/3
Mean (SD)	3.95 (0.28)	3.88 (0.23)
Median	4.00	3.90
Q1, Q3	3.80, 4.20	3.80, 4.00
Min, Max	3.1, 4.3	3.4, 4.3
Change from screening to week 12		
n/nmiss	23/2	22/3
Mean (SD)	0.18 (0.29)	0.21 (0.22)
Median	0.10	0.20
Q1, Q3	0.00, 0.40	0.00, 0.30
Min, Max	-0.3, 0.6	-0.2, 0.7
Week 24		
n/nmiss	23/2	21/4
Mean (SD)	3.74 (0.30)	3.78 (0.23)
Median	3.80	3.70
Q1, Q3	3.50, 4.00	3.70, 3.90
Min, Max	3.1, 4.3	3.3, 4.2
Change from screening to week 24		
n/nmiss	23/2	21/4
Mean (SD)	-0.03 (0.21)	0.12 (0.16)
Median	0.00	0.10
Q1, Q3	-0.20, 0.10	0.00, 0.20
Min, Max	-0.4, 0.2	-0.3, 0.4

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
Week -2-(1-) = screening (baseline)

Table 200 Total calcium (mmol/L). Safety analysis set

Total calcium (mmol/L)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=25)
Week -2-(-1)		
n/nmiss	25/0	25/0
Mean (SD)	2.29 (0.08)	2.31 (0.09)
Median	2.29	2.29
Q1, Q3	2.22, 2.34	2.24, 2.36
Min, Max	2.1, 2.4	2.1, 2.5
Week 12		
n/nmiss	22/3	22/3
Mean (SD)	2.30 (0.07)	2.35 (0.07)
Median	2.30	2.35
Q1, Q3	2.26, 2.33	2.29, 2.39
Min, Max	2.2, 2.5	2.2, 2.5
Change from screening to week 12		
n/nmiss	22/3	22/3
Mean (SD)	0.02 (0.08)	0.04 (0.10)
Median	0.04	0.05
Q1, Q3	-0.06, 0.09	-0.04, 0.11
Min, Max	-0.1, 0.2	-0.2, 0.2
Week 24		
n/nmiss	23/2	21/4
Mean (SD)	2.34 (0.06)	2.38 (0.08)
Median	2.33	2.37
Q1, Q3	2.29, 2.39	2.32, 2.42
Min, Max	2.2, 2.5	2.2, 2.6
Change from screening to week 24		
n/nmiss	23/2	21/4
Mean (SD)	0.05 (0.07)	0.08 (0.07)
Median	0.06	0.09
Q1, Q3	-0.01, 0.12	0.06, 0.11
Min, Max	-0.1, 0.2	-0.1, 0.2

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
Week -2-(1-) = screening (baseline)

Table 201 Sodium (mmol/L). Safety analysis set

Sodium (mmol/L)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=25)
Week -2-(-1)		
n/nmiss	24/1	25/0
Mean (SD)	141.96 (1.60)	142.72 (1.34)
Median	142.00	143.00
Q1, Q3	141.00, 143.00	142.00, 144.00
Min, Max	139.0, 146.0	140.0, 145.0
Week 12		
n/nmiss	23/2	22/3
Mean (SD)	141.09 (2.09)	142.09 (1.06)
Median	141.00	142.00
Q1, Q3	140.00, 142.00	141.00, 143.00
Min, Max	137.0, 147.0	140.0, 144.0
Change from screening to week 12		
n/nmiss	22/3	22/3
Mean (SD)	-0.91 (1.87)	-0.64 (1.26)
Median	-1.00	0.00
Q1, Q3	-2.00, 0.00	-2.00, 0.00
Min, Max	-5.0, 3.0	-3.0, 2.0
Week 24		
n/nmiss	23/2	21/4
Mean (SD)	141.78 (1.59)	142.14 (1.56)
Median	142.00	142.00
Q1, Q3	141.00, 142.00	142.00, 143.00
Min, Max	139.0, 147.0	138.0, 144.0
Change from screening to week 24		
n/nmiss	22/3	21/4
Mean (SD)	-0.23 (1.34)	-0.62 (1.56)
Median	0.00	-1.00
Q1, Q3	-1.00, 1.00	-2.00, 0.00
Min, Max	-3.0, 2.0	-3.0, 3.0

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
Week -2-(1-) = screening (baseline)

Table 202 Creatine kinase (µkat/L). Safety analysis set

Creatine kinase (CK) (ukat/L)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=25)
Week -2-(-1)		
n/nmiss	25/0	24/1
Mean (SD)	2.21 (1.43)	2.13 (1.15)
Median	1.80	1.95
Q1, Q3	1.50, 2.20	1.20, 3.10
Min, Max	0.7, 6.2	0.5, 4.3
Week 12		
n/nmiss	23/2	22/3
Mean (SD)	2.22 (2.10)	2.06 (1.02)
Median	1.60	1.80
Q1, Q3	1.30, 2.60	1.40, 2.50
Min, Max	0.7, 10.9	0.5, 4.0
Change from screening to week 12		
n/nmiss	23/2	21/4
Mean (SD)	0.14 (1.89)	-0.11 (0.77)
Median	0.10	0.00
Q1, Q3	-0.50, 0.30	-0.30, 0.30
Min, Max	-3.6, 7.2	-2.1, 1.3
Week 24		
n/nmiss	23/2	21/4
Mean (SD)	2.24 (2.06)	1.84 (0.79)
Median	1.70	1.50
Q1, Q3	1.30, 2.00	1.20, 2.50
Min, Max	0.6, 8.5	0.9, 3.5
Change from screening to week 24		
n/nmiss	23/2	20/5
Mean (SD)	0.16 (2.26)	-0.41 (0.68)
Median	0.10	-0.25
Q1, Q3	-0.80, 0.30	-0.95, 0.00
Min, Max	-4.6, 7.6	-1.5, 1.0

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
Week -2-(1-) = screening (baseline)

Table 203 C-reactive protein (mg/L). Safety analysis set

C-reactive protein (mg/L)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=25)
Week -2-(-1)		
n/nmiss	25/0	24/1
Mean (SD)	3.36 (2.51)	3.37 (2.65)
Median	2.60	2.40
Q1, Q3	1.60, 4.10	1.45, 5.15
Min, Max	0.5, 9.7	0.6, 9.2
Week 12		
n/nmiss	18/7	21/4
Mean (SD)	9.54 (19.52)	3.36 (2.32)
Median	2.00	2.20
Q1, Q3	1.30, 10.00	1.60, 4.80
Min, Max	0.6, 84.0	0.6, 8.5
Change from screening to week 12		
n/nmiss	18/7	20/5
Mean (SD)	6.07 (19.33)	-0.05 (2.33)
Median	0.06	0.03
Q1, Q3	-1.00, 3.80	-0.95, 0.48
Min, Max	-2.2, 81.8	-5.0, 5.4
Week 24		
n/nmiss	22/3	21/4
Mean (SD)	3.38 (2.84)	2.58 (2.07)
Median	2.95	2.20
Q1, Q3	1.40, 4.20	1.20, 3.20
Min, Max	0.3, 13.0	0.7, 10.0
Change from screening to week 24		
n/nmiss	22/3	20/5
Mean (SD)	0.09 (2.17)	-0.81 (2.25)
Median	0.15	0.04
Q1, Q3	-0.60, 1.60	-0.65, 0.64
Min, Max	-5.2, 3.9	-6.2, 1.2

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
Week -2-(1-) = screening (baseline)

Table 204 Creatinine clearance (mL/min). Safety analysis set

Creatinine clearance (mL/min)	Dapagliflozin/ Exenatide (N=25)	Placebo (N=25)
Week -2-(-1)		
n/nmiss	25/0	23/2
Mean (SD)	145.97 (42.95)	145.88 (41.12)
Median	141.49	132.52
Q1, Q3	109.81, 186.18	121.02, 173.99
Min, Max	89.9, 212.0	82.3, 236.8
Week 12		
n/nmiss	23/2	22/3
Mean (SD)	141.61 (51.49)	153.30 (51.21)
Median	128.29	139.72
Q1, Q3	95.43, 180.07	121.29, 170.42
Min, Max	73.7, 245.7	86.4, 315.2
Change from screening to week 12		
n/nmiss	23/2	20/5
Mean (SD)	-2.23 (17.52)	3.68 (20.54)
Median	-3.90	2.21
Q1, Q3	-15.76, 4.86	-6.78, 9.62
Min, Max	-26.2, 56.4	-24.8, 78.4
Week 24		
n/nmiss	23/2	21/4
Mean (SD)	135.42 (46.75)	154.01 (44.56)
Median	117.86	147.39
Q1, Q3	98.71, 175.30	121.29, 160.74
Min, Max	70.8, 228.7	99.0, 278.7
Change from screening to week 24		
n/nmiss	23/2	19/6
Mean (SD)	-8.43 (18.64)	1.41 (17.08)
Median	-7.38	1.44
Q1, Q3	-17.37, 0.32	-7.76, 11.29
Min, Max	-46.4, 39.4	-33.0, 41.9

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
Week -2-(1-) = screening (baseline)

14.3.2 Displays of Adverse Events

14.3.2.1 Adverse events by SOC and PT

Table 205 Adverse events. Safety analysis set

	Dapagliflozin/ Exenatide (N=25)		Placebo (N=25)	
System organ class/Preferred term	**n (%)**	**m**	**n (%)**	**m**
Infections and infestations	11 (44.0%)	15	9 (36.0%)	12
Ear infection	1 (4.0%)	1	0	0
Enterobiasis	0	0	1 (4.0%)	1
Gastroenteritis	0	0	1 (4.0%)	1
Influenza	0	0	2 (8.0%)	2
Localised infection	1 (4.0%)	1	0	0
Nasopharyngitis	9 (36.0%)	9	4 (16.0%)	4
Oral herpes	0	0	1 (4.0%)	1
Pneumonia	1 (4.0%)	1	1 (4.0%)	1
Pyelonephritis acute	1 (4.0%)	1	0	0
Sinusitis	0	0	1 (4.0%)	1
Urinary tract infection	0	0	1 (4.0%)	1
Urinary tract infection fungal	1 (4.0%)	1	0	0
Vaginal infection	1 (4.0%)	1	0	0
Blood and lymphatic system disorders	1 (4.0%)	1	0	0
Anaemia	1 (4.0%)	1	0	0
Metabolism and nutrition disorders	10 (40.0%)	11	5 (20.0%)	5
Decreased appetite	8 (32.0%)	8	3 (12.0%)	3
Diabetes mellitus	0	0	1 (4.0%)	1
Hyperlipidaemia	0	0	1 (4.0%)	1
Hypokalaemia	1 (4.0%)	1	0	0
Increased appetite	1 (4.0%)	1	0	0
Vitamin B12 deficiency	1 (4.0%)	1	0	0
Psychiatric disorders	1 (4.0%)	2	2 (8.0%)	2
Anger	1 (4.0%)	1	0	0
Nervousness	1 (4.0%)	1	0	0
Restlessness	0	0	1 (4.0%)	1

System organ class/Preferred term	Dapagliflozin/ Exenatide (N=25) n (%)	m	Placebo (N=25) n (%)	m
Sleep disorder	0	0	1 (4.0%)	1
Nervous system disorders	12 (48.0%)	21	6 (24.0%)	12
Dizziness	5 (20.0%)	5	3 (12.0%)	4
Head discomfort	1 (4.0%)	1	1 (4.0%)	1
Headache	8 (32.0%)	12	4 (16.0%)	4
Hypoaesthesia	1 (4.0%)	1	0	0
Migraine	0	0	1 (4.0%)	1
Tremor	2 (8.0%)	2	2 (8.0%)	2
Cardiac disorders	1 (4.0%)	1	1 (4.0%)	1
Arrhythmia	1 (4.0%)	1	0	0
Palpitations	0	0	1 (4.0%)	1
Vascular disorders	2 (8.0%)	2	5 (20.0%)	5
Flushing	0	0	1 (4.0%)	1
Hypertension	1 (4.0%)	1	2 (8.0%)	2
Hypotension	0	0	1 (4.0%)	1
Varicose vein	1 (4.0%)	1	0	0
Vasculitis	0	0	1 (4.0%)	1
Respiratory, thoracic and mediastinal disorders	4 (16.0%)	6	4 (16.0%)	4
Cough	1 (4.0%)	1	1 (4.0%)	1
Dyspnoea	1 (4.0%)	1	1 (4.0%)	1
Oropharyngeal pain	3 (12.0%)	4	0	0
Pharyngeal disorder	0	0	1 (4.0%)	1
Rhinitis allergic	0	0	1 (4.0%)	1
Gastrointestinal disorders	18 (72.0%)	37	13 (52.0%)	15
Abdominal discomfort	1 (4.0%)	1	0	0
Abdominal distension	3 (12.0%)	3	2 (8.0%)	2
Abdominal pain	1 (4.0%)	1	0	0
Abdominal pain upper	3 (12.0%)	4	2 (8.0%)	2
Constipation	2 (8.0%)	2	1 (4.0%)	1
Diarrhoea	3 (12.0%)	3	3 (12.0%)	3
Dry mouth	1 (4.0%)	1	0	0
Dyspepsia	2 (8.0%)	2	0	0
Frequent bowel movements	0	0	1 (4.0%)	1

System organ class/Preferred term	Dapagliflozin/ Exenatide (N=25) n (%)	m	Placebo (N=25) n (%)	m
Gastritis	1 (4.0%)	1	0	0
Gastrooesophageal reflux disease	3 (12.0%)	3	1 (4.0%)	1
Lip dry	1 (4.0%)	1	0	0
Lip swelling	1 (4.0%)	1	0	0
Nausea	7 (28.0%)	8	3 (12.0%)	3
Oesophagitis	1 (4.0%)	1	0	0
Oral pain	1 (4.0%)	1	0	0
Toothache	0	0	1 (4.0%)	1
Vomiting	3 (12.0%)	4	1 (4.0%)	1
Hepatobiliary disorders	2 (8.0%)	2	0	0
Cholelithiasis	1 (4.0%)	1	0	0
Hyperbilirubinaemia	1 (4.0%)	1	0	0
Skin and subcutaneous tissue disorders	7 (28.0%)	9	3 (12.0%)	3
Blister	1 (4.0%)	1	0	0
Cold sweat	3 (12.0%)	3	0	0
Erythema	1 (4.0%)	1	0	0
Hyperhidrosis	3 (12.0%)	3	1 (4.0%)	1
Rash	0	0	1 (4.0%)	1
Rash pruritic	1 (4.0%)	1	0	0
Skin ulcer	0	0	1 (4.0%)	1
Musculoskeletal and connective tissue disorders	11 (44.0%)	15	5 (20.0%)	9
Arthralgia	3 (12.0%)	3	3 (12.0%)	3
Back pain	4 (16.0%)	4	2 (8.0%)	3
Joint swelling	2 (8.0%)	3	0	0
Muscle spasms	0	0	1 (4.0%)	1
Myalgia	1 (4.0%)	2	0	0
Osteitis	0	0	1 (4.0%)	1
Pain in extremity	2 (8.0%)	2	0	0
Spinal column stenosis	0	0	1 (4.0%)	1
Tendon pain	1 (4.0%)	1	0	0
Renal and urinary disorders	5 (20.0%)	5	6 (24.0%)	6
Pollakiuria	5 (20.0%)	5	5 (20.0%)	5
Urinary incontinence	0	0	1 (4.0%)	1

System organ class/Preferred term	Dapagliflozin/ Exenatide (N=25) n (%)	m	Placebo (N=25) n (%)	m
Congenital, familial and genetic disorders	1 (4.0%)	1	0	0
Polycystic liver disease	1 (4.0%)	1	0	0
General disorders and administration site conditions	16 (64.0%)	36	17 (68.0%)	30
Asthenia	2 (8.0%)	2	0	0
Chest pain	1 (4.0%)	1	1 (4.0%)	1
Early satiety	1 (4.0%)	1	1 (4.0%)	1
Fatigue	3 (12.0%)	3	6 (24.0%)	6
Feeling hot	1 (4.0%)	1	2 (8.0%)	2
Hunger	1 (4.0%)	1	3 (12.0%)	3
Inflammation	1 (4.0%)	2	0	0
Injection site cyst	1 (4.0%)	1	0	0
Injection site erythema	3 (12.0%)	3	1 (4.0%)	1
Injection site mass	7 (28.0%)	7	5 (20.0%)	5
Injection site nodule	2 (8.0%)	2	1 (4.0%)	1
Injection site pain	1 (4.0%)	1	0	0
Injection site pruritus	7 (28.0%)	7	2 (8.0%)	2
Injection site rash	0	0	1 (4.0%)	1
Injection site swelling	0	0	2 (8.0%)	2
Malaise	0	0	1 (4.0%)	1
Peripheral swelling	0	0	1 (4.0%)	1
Pyrexia	2 (8.0%)	2	1 (4.0%)	1
Thirst	2 (8.0%)	2	2 (8.0%)	2
Investigations	0	0	3 (12.0%)	3
Blood ketone body increased	0	0	1 (4.0%)	1
Blood pressure increased	0	0	1 (4.0%)	1
General physical condition abnormal	0	0	1 (4.0%)	1
Injury, poisoning and procedural complications	2 (8.0%)	3	3 (12.0%)	4
Injury	1 (4.0%)	1	0	0
Ligament sprain	1 (4.0%)	1	1 (4.0%)	2
Post concussion syndrome	1 (4.0%)	1	0	0
Upper limb fracture	0	0	1 (4.0%)	1
Wound	0	0	1 (4.0%)	1
Surgical and medical procedures	1 (4.0%)	1	2 (8.0%)	2
Meniscus operation	0	0	1 (4.0%)	1

System organ class/Preferred term	Dapagliflozin/ Exenatide (N=25) n (%)	m	Placebo (N=25) n (%)	m
Shoulder operation	1 (4.0%)	1	0	0
Spinal laminectomy	0	0	1 (4.0%)	1

Adverse events are coded according to MedDRA version 18.0E.
n is the number of subjects, m is the number of events
Percentages are based on the number of subjects in the Safety analysis set

14.3.2.2 Adverse Events by Severity. Safety analysis set, Dapagliflozin/ Exenatide

Table 206 Adverse events by severity. Safety analysis set, Dapagliflozin/ Exenatide

	MILD		MODERATE		SEVERE	
System organ class/Preferred term	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**
Infections and infestations	9 (36.0%)	11	3 (12.0%)	4	0	0
Ear infection	0	0	1 (4.0%)	1	0	0
Localised infection	1 (4.0%)	1	0	0	0	0
Nasopharyngitis	8 (32.0%)	8	1 (4.0%)	1	0	0
Pneumonia	1 (4.0%)	1	0	0	0	0
Pyelonephritis acute	0	0	1 (4.0%)	1	0	0
Urinary tract infection fungal	1 (4.0%)	1	0	0	0	0
Vaginal infection	0	0	1 (4.0%)	1	0	0
Blood and lymphatic system disorders	0	0	1 (4.0%)	1	0	0
Anaemia	0	0	1 (4.0%)	1	0	0
Metabolism and nutrition disorders	10 (40.0%)	11	0	0	0	0
Decreased appetite	8 (32.0%)	8	0	0	0	0
Hypokalaemia	1 (4.0%)	1	0	0	0	0
Increased appetite	1 (4.0%)	1	0	0	0	0
Vitamin B12 deficiency	1 (4.0%)	1	0	0	0	0
Psychiatric disorders	1 (4.0%)	2	0	0	0	0
Anger	1 (4.0%)	1	0	0	0	0
Nervousness	1 (4.0%)	1	0	0	0	0
Nervous system disorders	11 (44.0%)	19	2 (8.0%)	2	0	0
Dizziness	5 (20.0%)	5	0	0	0	0
Head discomfort	1 (4.0%)	1	0	0	0	0
Headache	7 (28.0%)	10	2 (8.0%)	2	0	0
Hypoaesthesia	1 (4.0%)	1	0	0	0	0
Tremor	2 (8.0%)	2	0	0	0	0
Cardiac disorders	0	0	1 (4.0%)	1	0	0
Arrhythmia	0	0	1 (4.0%)	1	0	0
Vascular disorders	1 (4.0%)	1	1 (4.0%)	1	0	0
Hypertension	1 (4.0%)	1	0	0	0	0

System organ class/Preferred term	MILD n (%)	MILD m	MODERATE n (%)	MODERATE m	SEVERE n (%)	SEVERE m
Varicose vein	0	0	1 (4.0%)	1	0	0
Respiratory, thoracic and mediastinal disorders	4 (16.0%)	4	1 (4.0%)	2	0	0
Cough	0	0	1 (4.0%)	1	0	0
Dyspnoea	1 (4.0%)	1	0	0	0	0
Oropharyngeal pain	3 (12.0%)	3	1 (4.0%)	1	0	0
Gastrointestinal disorders	15 (60.0%)	27	7 (28.0%)	10	0	0
Abdominal discomfort	1 (4.0%)	1	0	0	0	0
Abdominal distension	3 (12.0%)	3	0	0	0	0
Abdominal pain	0	0	1 (4.0%)	1	0	0
Abdominal pain upper	1 (4.0%)	1	3 (12.0%)	3	0	0
Constipation	2 (8.0%)	2	0	0	0	0
Diarrhoea	1 (4.0%)	1	2 (8.0%)	2	0	0
Dry mouth	1 (4.0%)	1	0	0	0	0
Dyspepsia	2 (8.0%)	2	0	0	0	0
Gastritis	1 (4.0%)	1	0	0	0	0
Gastrooesophageal reflux disease	3 (12.0%)	3	0	0	0	0
Lip dry	1 (4.0%)	1	0	0	0	0
Lip swelling	0	0	1 (4.0%)	1	0	0
Nausea	5 (20.0%)	6	2 (8.0%)	2	0	0
Oesophagitis	1 (4.0%)	1	0	0	0	0
Oral pain	0	0	1 (4.0%)	1	0	0
Vomiting	3 (12.0%)	4	0	0	0	0
Hepatobiliary disorders	2 (8.0%)	2	0	0	0	0
Cholelithiasis	1 (4.0%)	1	0	0	0	0
Hyperbilirubinaemia	1 (4.0%)	1	0	0	0	0
Skin and subcutaneous tissue disorders	4 (16.0%)	5	3 (12.0%)	4	0	0
Blister	0	0	1 (4.0%)	1	0	0
Cold sweat	2 (8.0%)	2	1 (4.0%)	1	0	0
Erythema	0	0	1 (4.0%)	1	0	0
Hyperhidrosis	3 (12.0%)	3	0	0	0	0
Rash pruritic	0	0	1 (4.0%)	1	0	0
Musculoskeletal and connective tissue disorders	6 (24.0%)	7	5 (20.0%)	8	0	0
Arthralgia	1 (4.0%)	1	2 (8.0%)	2	0	0
Back pain	3 (12.0%)	3	1 (4.0%)	1	0	0

System organ class/Preferred term	MILD n (%)	MILD m	MODERATE n (%)	MODERATE m	SEVERE n (%)	SEVERE m
Joint swelling	0	0	2 (8.0%)	3	0	0
Myalgia	1 (4.0%)	2	0	0	0	0
Pain in extremity	1 (4.0%)	1	1 (4.0%)	1	0	0
Tendon pain	0	0	1 (4.0%)	1	0	0
Renal and urinary disorders	5 (20.0%)	5	0	0	0	0
Pollakiuria	5 (20.0%)	5	0	0	0	0
Congenital, familial and genetic disorders	1 (4.0%)	1	0	0	0	0
Polycystic liver disease	1 (4.0%)	1	0	0	0	0
General disorders and administration site conditions	15 (60.0%)	30	3 (12.0%)	6	0	0
Asthenia	2 (8.0%)	2	0	0	0	0
Chest pain	1 (4.0%)	1	0	0	0	0
Early satiety	1 (4.0%)	1	0	0	0	0
Fatigue	3 (12.0%)	3	0	0	0	0
Feeling hot	1 (4.0%)	1	0	0	0	0
Hunger	1 (4.0%)	1	0	0	0	0
Inflammation	0	0	1 (4.0%)	2	0	0
Injection site cyst	1 (4.0%)	1	0	0	0	0
Injection site erythema	2 (8.0%)	2	1 (4.0%)	1	0	0
Injection site mass	6 (24.0%)	6	1 (4.0%)	1	0	0
Injection site nodule	2 (8.0%)	2	0	0	0	0
Injection site pain	1 (4.0%)	1	0	0	0	0
Injection site pruritus	6 (24.0%)	6	1 (4.0%)	1	0	0
Pyrexia	1 (4.0%)	1	1 (4.0%)	1	0	0
Thirst	2 (8.0%)	2	0	0	0	0
Injury, poisoning and procedural complications	0	0	2 (8.0%)	2	1 (4.0%)	1
Injury	0	0	0	0	1 (4.0%)	1
Ligament sprain	0	0	1 (4.0%)	1	0	0
Post concussion syndrome	0	0	1 (4.0%)	1	0	0
Surgical and medical procedures	0	0	1 (4.0%)	1	0	0
Shoulder operation	0	0	1 (4.0%)	1	0	0

Adverse events are coded according to MedDRA version 18.0E.
n is the number of subjects, m is the number of events
Percentages are based on the number of subjects in the Safety analysis set

14.3.2.3 Adverse Events by Severity. Safety analysis set, Placebo

Table 207 Adverse events by severity. Safety analysis set, Placebo

	MILD		MODERATE		SEVERE	
System organ class/Preferred term	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**
Infections and infestations	5 (20.0%)	8	4 (16.0%)	4	0	0
Enterobiasis	1 (4.0%)	1	0	0	0	0
Gastroenteritis	0	0	1 (4.0%)	1	0	0
Influenza	0	0	2 (8.0%)	2	0	0
Nasopharyngitis	4 (16.0%)	4	0	0	0	0
Oral herpes	1 (4.0%)	1	0	0	0	0
Pneumonia	0	0	1 (4.0%)	1	0	0
Sinusitis	1 (4.0%)	1	0	0	0	0
Urinary tract infection	1 (4.0%)	1	0	0	0	0
Metabolism and nutrition disorders	4 (16.0%)	4	1 (4.0%)	1	0	0
Decreased appetite	3 (12.0%)	3	0	0	0	0
Diabetes mellitus	0	0	1 (4.0%)	1	0	0
Hyperlipidaemia	1 (4.0%)	1	0	0	0	0
Psychiatric disorders	2 (8.0%)	2	0	0	0	0
Restlessness	1 (4.0%)	1	0	0	0	0
Sleep disorder	1 (4.0%)	1	0	0	0	0
Nervous system disorders	5 (20.0%)	10	2 (8.0%)	2	0	0
Dizziness	3 (12.0%)	4	0	0	0	0
Head discomfort	1 (4.0%)	1	0	0	0	0
Headache	3 (12.0%)	3	1 (4.0%)	1	0	0
Migraine	0	0	1 (4.0%)	1	0	0
Tremor	2 (8.0%)	2	0	0	0	0
Cardiac disorders	0	0	1 (4.0%)	1	0	0
Palpitations	0	0	1 (4.0%)	1	0	0
Vascular disorders	4 (16.0%)	4	1 (4.0%)	1	0	0
Flushing	1 (4.0%)	1	0	0	0	0
Hypertension	2 (8.0%)	2	0	0	0	0
Hypotension	1 (4.0%)	1	0	0	0	0
Vasculitis	0	0	1 (4.0%)	1	0	0

System organ class/Preferred term	MILD n (%)	MILD m	MODERATE n (%)	MODERATE m	SEVERE n (%)	SEVERE m
Respiratory, thoracic and mediastinal disorders	2 (8.0%)	2	1 (4.0%)	1	1 (4.0%)	1
Cough	0	0	1 (4.0%)	1	0	0
Dyspnoea	0	0	0	0	1 (4.0%)	1
Pharyngeal disorder	1 (4.0%)	1	0	0	0	0
Rhinitis allergic	1 (4.0%)	1	0	0	0	0
Gastrointestinal disorders	13 (52.0%)	14	1 (4.0%)	1	0	0
Abdominal distension	2 (8.0%)	2	0	0	0	0
Abdominal pain upper	2 (8.0%)	2	0	0	0	0
Constipation	1 (4.0%)	1	0	0	0	0
Diarrhoea	3 (12.0%)	3	0	0	0	0
Frequent bowel movements	1 (4.0%)	1	0	0	0	0
Gastrooesophageal reflux disease	1 (4.0%)	1	0	0	0	0
Nausea	3 (12.0%)	3	0	0	0	0
Toothache	1 (4.0%)	1	0	0	0	0
Vomiting	0	0	1 (4.0%)	1	0	0
Skin and subcutaneous tissue disorders	2 (8.0%)	2	1 (4.0%)	1	0	0
Hyperhidrosis	1 (4.0%)	1	0	0	0	0
Rash	1 (4.0%)	1	0	0	0	0
Skin ulcer	0	0	1 (4.0%)	1	0	0
Musculoskeletal and connective tissue disorders	2 (8.0%)	3	4 (16.0%)	6	0	0
Arthralgia	0	0	3 (12.0%)	3	0	0
Back pain	1 (4.0%)	2	1 (4.0%)	1	0	0
Muscle spasms	0	0	1 (4.0%)	1	0	0
Osteitis	1 (4.0%)	1	0	0	0	0
Spinal column stenosis	0	0	1 (4.0%)	1	0	0
Renal and urinary disorders	6 (24.0%)	6	0	0	0	0
Pollakiuria	5 (20.0%)	5	0	0	0	0
Urinary incontinence	1 (4.0%)	1	0	0	0	0
General disorders and administration site conditions	16 (64.0%)	25	4 (16.0%)	4	1 (4.0%)	1
Chest pain	0	0	1 (4.0%)	1	0	0
Early satiety	1 (4.0%)	1	0	0	0	0
Fatigue	5 (20.0%)	5	0	0	1 (4.0%)	1
Feeling hot	2 (8.0%)	2	0	0	0	0

	MILD		MODERATE		SEVERE	
System organ class/Preferred term	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**
Hunger	3 (12.0%)	3	0	0	0	0
Injection site erythema	1 (4.0%)	1	0	0	0	0
Injection site mass	3 (12.0%)	3	2 (8.0%)	2	0	0
Injection site nodule	1 (4.0%)	1	0	0	0	0
Injection site pruritus	2 (8.0%)	2	0	0	0	0
Injection site rash	1 (4.0%)	1	0	0	0	0
Injection site swelling	2 (8.0%)	2	0	0	0	0
Malaise	1 (4.0%)	1	0	0	0	0
Peripheral swelling	1 (4.0%)	1	0	0	0	0
Pyrexia	0	0	1 (4.0%)	1	0	0
Thirst	2 (8.0%)	2	0	0	0	0
Investigations	1 (4.0%)	1	2 (8.0%)	2	0	0
Blood ketone body increased	0	0	1 (4.0%)	1	0	0
Blood pressure increased	0	0	1 (4.0%)	1	0	0
General physical condition abnormal	1 (4.0%)	1	0	0	0	0
Injury, poisoning and procedural complications	0	0	3 (12.0%)	4	0	0
Ligament sprain	0	0	1 (4.0%)	2	0	0
Upper limb fracture	0	0	1 (4.0%)	1	0	0
Wound	0	0	1 (4.0%)	1	0	0
Surgical and medical procedures	0	0	1 (4.0%)	1	1 (4.0%)	1
Meniscus operation	0	0	0	0	1 (4.0%)	1
Spinal laminectomy	0	0	1 (4.0%)	1	0	0

Adverse events are coded according to MedDRA version 18.0E.
n is the number of subjects, m is the number of events
Percentages are based on the number of subjects in the Safety analysis set

14.3.2.4 Adverse events by Relation to IP. Safety analysis set

Table 208 Adverse events by relation to IP. Safety analysis set

	Dapagliflozin/ Exenatide (N=25)				Placebo (N=25)			
	Not Related		Related		Not Related		Related	
System organ class/Preferred term	n (%)	m	n (%)	m	n (%)	m	n (%)	m
Infections and infestations	10 (40.0%)	13	2 (8.0%)	2	9 (36.0%)	11	1 (4.0%)	1
Ear infection	1 (4.0%)	1	0	0	0	0	0	0
Enterobiasis	0	0	0	0	1 (4.0%)	1	0	0
Gastroenteritis	0	0	0	0	1 (4.0%)	1	0	0
Influenza	0	0	0	0	2 (8.0%)	2	0	0
Localised infection	1 (4.0%)	1	0	0	0	0	0	0
Nasopharyngitis	9 (36.0%)	9	0	0	4 (16.0%)	4	0	0
Oral herpes	0	0	0	0	1 (4.0%)	1	0	0
Pneumonia	1 (4.0%)	1	0	0	1 (4.0%)	1	0	0
Pyelonephritis acute	1 (4.0%)	1	0	0	0	0	0	0
Sinusitis	0	0	0	0	1 (4.0%)	1	0	0
Urinary tract infection	0	0	0	0	0	0	1 (4.0%)	1
Urinary tract infection fungal	0	0	1 (4.0%)	1	0	0	0	0
Vaginal infection	0	0	1 (4.0%)	1	0	0	0	0
Blood and lymphatic system disorders	1 (4.0%)	1	0	0	0	0	0	0
Anaemia	1 (4.0%)	1	0	0	0	0	0	0
Metabolism and nutrition disorders	1 (4.0%)	2	9 (36.0%)	9	1 (4.0%)	1	4 (16.0%)	4
Decreased appetite	0	0	8 (32.0%)	8	0	0	3 (12.0%)	3
Diabetes mellitus	0	0	0	0	1 (4.0%)	1	0	0
Hyperlipidaemia	0	0	0	0	0	0	1 (4.0%)	1
Hypokalaemia	1 (4.0%)	1	0	0	0	0	0	0
Increased appetite	0	0	1 (4.0%)	1	0	0	0	0
Vitamin B12 deficiency	1 (4.0%)	1	0	0	0	0	0	0
Psychiatric disorders	0	0	1 (4.0%)	2	1 (4.0%)	1	1 (4.0%)	1
Anger	0	0	1 (4.0%)	1	0	0	0	0
Nervousness	0	0	1 (4.0%)	1	0	0	0	0
Restlessness	0	0	0	0	0	0	1 (4.0%)	1
Sleep disorder	0	0	0	0	1 (4.0%)	1	0	0

	Dapagliflozin/ Exenatide (N=25)				Placebo (N=25)			
	Not Related		Related		Not Related		Related	
System organ class/Preferred term	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**
Nervous system disorders	4 (16.0%)	5	10 (40.0%)	16	1 (4.0%)	1	6 (24.0%)	11
Dizziness	0	0	5 (20.0%)	5	0	0	3 (12.0%)	4
Head discomfort	1 (4.0%)	1	0	0	0	0	1 (4.0%)	1
Headache	3 (12.0%)	3	6 (24.0%)	9	0	0	4 (16.0%)	4
Hypoaesthesia	1 (4.0%)	1	0	0	0	0	0	0
Migraine	0	0	0	0	1 (4.0%)	1	0	0
Tremor	0	0	2 (8.0%)	2	0	0	2 (8.0%)	2
Cardiac disorders	1 (4.0%)	1	0	0	1 (4.0%)	1	0	0
Arrhythmia	1 (4.0%)	1	0	0	0	0	0	0
Palpitations	0	0	0	0	1 (4.0%)	1	0	0
Vascular disorders	2 (8.0%)	2	0	0	3 (12.0%)	3	2 (8.0%)	2
Flushing	0	0	0	0	1 (4.0%)	1	0	0
Hypertension	1 (4.0%)	1	0	0	2 (8.0%)	2	0	0
Hypotension	0	0	0	0	0	0	1 (4.0%)	1
Varicose vein	1 (4.0%)	1	0	0	0	0	0	0
Vasculitis	0	0	0	0	0	0	1 (4.0%)	1
Respiratory, thoracic and mediastinal disorders	4 (16.0%)	6	0	0	4 (16.0%)	4	0	0
Cough	1 (4.0%)	1	0	0	1 (4.0%)	1	0	0
Dyspnoea	1 (4.0%)	1	0	0	1 (4.0%)	1	0	0
Oropharyngeal pain	3 (12.0%)	4	0	0	0	0	0	0
Pharyngeal disorder	0	0	0	0	1 (4.0%)	1	0	0
Rhinitis allergic	0	0	0	0	1 (4.0%)	1	0	0
Gastrointestinal disorders	3 (12.0%)	3	17 (68.0%)	34	4 (16.0%)	4	10 (40.0%)	11
Abdominal discomfort	0	0	1 (4.0%)	1	0	0	0	0
Abdominal distension	0	0	3 (12.0%)	3	0	0	2 (8.0%)	2
Abdominal pain	0	0	1 (4.0%)	1	0	0	0	0
Abdominal pain upper	0	0	3 (12.0%)	4	0	0	2 (8.0%)	2
Constipation	0	0	2 (8.0%)	2	0	0	1 (4.0%)	1
Diarrhoea	0	0	3 (12.0%)	3	0	0	3 (12.0%)	3
Dry mouth	0	0	1 (4.0%)	1	0	0	0	0
Dyspepsia	0	0	2 (8.0%)	2	0	0	0	0
Frequent bowel movements	0	0	0	0	0	0	1 (4.0%)	1
Gastritis	0	0	1 (4.0%)	1	0	0	0	0

	Dapagliflozin/ Exenatide (N=25)				Placebo (N=25)			
	Not Related		Related		Not Related		Related	
System organ class/Preferred term	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**
Gastrooesophageal reflux disease	1 (4.0%)	1	2 (8.0%)	2	1 (4.0%)	1	0	0
Lip dry	0	0	1 (4.0%)	1	0	0	0	0
Lip swelling	0	0	1 (4.0%)	1	0	0	0	0
Nausea	2 (8.0%)	2	5 (20.0%)	6	1 (4.0%)	1	2 (8.0%)	2
Oesophagitis	0	0	1 (4.0%)	1	0	0	0	0
Oral pain	0	0	1 (4.0%)	1	0	0	0	0
Toothache	0	0	0	0	1 (4.0%)	1	0	0
Vomiting	0	0	3 (12.0%)	4	1 (4.0%)	1	0	0
Hepatobiliary disorders	2 (8.0%)	2	0	0	0	0	0	0
Cholelithiasis	1 (4.0%)	1	0	0	0	0	0	0
Hyperbilirubinaemia	1 (4.0%)	1	0	0	0	0	0	0
Skin and subcutaneous tissue disorders	1 (4.0%)	1	6 (24.0%)	8	1 (4.0%)	1	2 (8.0%)	2
Blister	0	0	1 (4.0%)	1	0	0	0	0
Cold sweat	0	0	3 (12.0%)	3	0	0	0	0
Erythema	0	0	1 (4.0%)	1	0	0	0	0
Hyperhidrosis	1 (4.0%)	1	2 (8.0%)	2	0	0	1 (4.0%)	1
Rash	0	0	0	0	1 (4.0%)	1	0	0
Rash pruritic	0	0	1 (4.0%)	1	0	0	0	0
Skin ulcer	0	0	0	0	0	0	1 (4.0%)	1
Musculoskeletal and connective tissue disorders	8 (32.0%)	10	4 (16.0%)	5	3 (12.0%)	4	3 (12.0%)	5
Arthralgia	2 (8.0%)	2	1 (4.0%)	1	2 (8.0%)	2	1 (4.0%)	1
Back pain	2 (8.0%)	2	2 (8.0%)	2	0	0	2 (8.0%)	3
Joint swelling	1 (4.0%)	1	1 (4.0%)	2	0	0	0	0
Muscle spasms	0	0	0	0	0	0	1 (4.0%)	1
Myalgia	1 (4.0%)	2	0	0	0	0	0	0
Osteitis	0	0	0	0	1 (4.0%)	1	0	0
Pain in extremity	2 (8.0%)	2	0	0	0	0	0	0
Spinal column stenosis	0	0	0	0	1 (4.0%)	1	0	0
Tendon pain	1 (4.0%)	1	0	0	0	0	0	0
Renal and urinary disorders	0	0	5 (20.0%)	5	1 (4.0%)	1	5 (20.0%)	5
Pollakiuria	0	0	5 (20.0%)	5	0	0	5 (20.0%)	5
Urinary incontinence	0	0	0	0	1 (4.0%)	1	0	0

	Dapagliflozin/ Exenatide (N=25)				Placebo (N=25)			
	Not Related		Related		Not Related		Related	
System organ class/Preferred term	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**
Congenital, familial and genetic disorders	1 (4.0%)	1	0	0	0	0	0	0
Polycystic liver disease	1 (4.0%)	1	0	0	0	0	0	0
General disorders and administration site conditions	5 (20.0%)	6	14 (56.0%)	30	4 (16.0%)	4	16 (64.0%)	26
Asthenia	1 (4.0%)	1	1 (4.0%)	1	0	0	0	0
Chest pain	1 (4.0%)	1	0	0	1 (4.0%)	1	0	0
Early satiety	0	0	1 (4.0%)	1	0	0	1 (4.0%)	1
Fatigue	1 (4.0%)	1	2 (8.0%)	2	1 (4.0%)	1	5 (20.0%)	5
Feeling hot	0	0	1 (4.0%)	1	0	0	2 (8.0%)	2
Hunger	0	0	1 (4.0%)	1	1 (4.0%)	1	2 (8.0%)	2
Inflammation	1 (4.0%)	1	1 (4.0%)	1	0	0	0	0
Injection site cyst	0	0	1 (4.0%)	1	0	0	0	0
Injection site erythema	0	0	3 (12.0%)	3	0	0	1 (4.0%)	1
Injection site mass	0	0	7 (28.0%)	7	0	0	5 (20.0%)	5
Injection site nodule	0	0	2 (8.0%)	2	0	0	1 (4.0%)	1
Injection site pain	0	0	1 (4.0%)	1	0	0	0	0
Injection site pruritus	0	0	7 (28.0%)	7	0	0	2 (8.0%)	2
Injection site rash	0	0	0	0	0	0	1 (4.0%)	1
Injection site swelling	0	0	0	0	0	0	2 (8.0%)	2
Malaise	0	0	0	0	0	0	1 (4.0%)	1
Peripheral swelling	0	0	0	0	0	0	1 (4.0%)	1
Pyrexia	2 (8.0%)	2	0	0	1 (4.0%)	1	0	0
Thirst	0	0	2 (8.0%)	2	0	0	2 (8.0%)	2
Investigations	0	0	0	0	1 (4.0%)	1	2 (8.0%)	2
Blood ketone body increased	0	0	0	0	0	0	1 (4.0%)	1
Blood pressure increased	0	0	0	0	1 (4.0%)	1	0	0
General physical condition abnormal	0	0	0	0	0	0	1 (4.0%)	1
Injury, poisoning and procedural complications	2 (8.0%)	3	0	0	3 (12.0%)	4	0	0
Injury	1 (4.0%)	1	0	0	0	0	0	0
Ligament sprain	1 (4.0%)	1	0	0	1 (4.0%)	2	0	0
Post concussion syndrome	1 (4.0%)	1	0	0	0	0	0	0
Upper limb fracture	0	0	0	0	1 (4.0%)	1	0	0
Wound	0	0	0	0	1 (4.0%)	1	0	0
Surgical and medical procedures	1 (4.0%)	1	0	0	2 (8.0%)	2	0	0

	Dapagliflozin/ Exenatide (N=25)				Placebo (N=25)			
	Not Related		Related		Not Related		Related	
System organ class/Preferred term	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**
Meniscus operation	0	0	0	0	1 (4.0%)	1	0	0
Shoulder operation	1 (4.0%)	1	0	0	0	0	0	0
Spinal laminectomy	0	0	0	0	1 (4.0%)	1	0	0

Adverse events are coded according to MedDRA version 18.0E.
n is the number of subjects, m is the number of events.
R=related, NR=not related.
Percentages are based on the number of subjects in the Safety analysis set.

14.3.3 Listings of Deaths, Other Serious and Significant Adverse Events

Individual AE listings are provided in Appendix 16.2.7.

14.3.4 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events

Not applicable.

15. REFERENCE LIST

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16. APPENDICES

16.1 TRIAL INFORMATION

16.1.1 Protocol and Protocol Amendments

16.1.2 Sample of Case Report Form (Unique Pages Only)

16.1.3 List of IECs or IRBs (Plus the Name of the Committee Chair if Required by the Regulatory Authority) - Representative Written Information for Patient and Sample Consent Forms

16.1.4 List and Description of Investigators and Other Important Participants in the Trial, Including Brief (1 page) CVs or Equivalent Summaries of Training and Experience Relevant to the Performance of the Clinical Trial

16.1.5 Signatures of Principal or Coordinating Investigator(s) or Sponsor's Responsible Medical Officer, Depending on the Regulatory Authority's Requirement (Not applicable)

16.1.6 Listing of Patients Receiving Test Drug(s)/ Investigational Product(s) From Specific Batches, where More than One Batch was Used *(*Not applicable)

16.1.7 Randomization Scheme and Codes (Patient Identification and Treatment Assigned) (Not applicable)

16.1.8 Audit Certificates (Not available)

16.1.9 Documentation of Statistical Methods

16.1.10 Documentation of Inter-Laboratory Standardisation Methods and Quality Assurance Procedures if Used

16.1.11 Publications Based on the Trial (Not available)

16.1.12 Important Publications Referenced in the Report (Not applicable)

16.2 PATIENT DATA LISTINGS

16.2.1 Discontinued Patients

16.2.2 Protocol Deviations

16.2.3 Patients Excluded From the Efficacy Analysis

16.2.4 Demographic Data

16.2.5 Compliance and/or Drug Concentration Data (If Available)

16.2.6 Individual Efficacy Response Data

16.2.7 Adverse Event Listings (Each Patient)

16.2.8 Listing of Individual Laboratory Measurements by Patient, when Required by Regulatory Authorities.

16.3 CASE REPORT FORMS

16.3.1 CRFs of Deaths, Other Serious Adverse Events and Withdrawals for AE

16.3.2 Other CRFs Submitted (Not applicable)

16.4 INDIVIDUAL PATIENT DATA LISTINGS (US ARCHIVAL LISTINGS) (Not applicable)