CLINICAL TRIAL REPORT FOR THE 24-WEEK SHORT-TERM TREATMENT PERIOD PLUS THE 28-WEEK LONG-TERM EXTENSION 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 2)

This report summarizes data collected during the entire 52 weeks study period.
The results of the 24-week initial main study are provided in the clinical trial report for the 24-week short-term treatment period (version 1.1, dated 11 Jan 2017).

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 1.0, 21 March 2017
Sponsor:	Uppsala University
24-week Double-Blind Main Study:	
First Subject Enrolled (date):	08 Dec 2014
Last Subject Completed (date):	31 Aug 2015
Optional 28-week Open-Label Extension Study:	
First Subject Enrolled (date):	04 Jun 2015
Last Subject Completed (date):	14 Mar 2016
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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 2)

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:

Jan E 2017-04-18

Prof Jan Eriksson, MD, PhD — Date

Biostatistician:

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Nils Adriansson, BSc, PCG Clinical Services AB — Date

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Rose-Marie Lindgren, MSc, Med Lic, PCG Clinical Services AB — Date

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, Uppsala, Sweden and
Section for Diabetes and Endocrinology at the Uppsala University Hospital, SE-751 85 Uppsala, Sweden

Publication (reference):
Lundkvist et al. Dapagliflozin once-daily and exenatide once-weekly dual therapy: A 24-week randomized, placebo-controlled, phase II study examining effects on body weight and prediabetes in obese adults without diabetes. Diabetes, Obesity and Metabolism (2017 Jan; 19[1]:49-60).

Studied period (years):	**Phase of development:**
<u>24-week double-blind main study:</u> (date of first screening visit): 08 Dec 2014 (date of last completed): 31 Aug 2015 **<u>28-week open-label extension study:</u>** (date of first subject enrolled): 04 Jun 2015 (date of last completed): 14 Mar 2016	IIa

Objectives:

<u>Primary Objective</u>
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.

<u>Secondary Objective</u>
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.

<u>Exploratory objectives</u>

- 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 a 28-week open-label treatment period with dapagliflozin 10 mg once daily and exenatide 2 mg once weekly following 24 weeks blinded treatment with dapagliflozin 10 mg once daily and exenatide 2 mg once weekly to maintain or enhance body weight reduction in obese subjects.
- To assess the efficacy of a 28-week open-label treatment period with dapagliflozin 10 mg once daily and exenatide 2 mg once weekly following 24 weeks blinded treatment with placebo on body weight reduction in obese subjects
- 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 DNA for future exploratory research of genes/genetic variation that is related to obesity or to treatment response to dapagliflozin in combination with exenatide.

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 24-week main 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, abdominal 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 trial report describes the efficacy and safety results obtained during the 24-week double-blind main study period and the 28-week open-label extension study period.

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 subjects (planned and analysed):

24-week double-blind main study:	**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 (PPAS):	**22**	**20**	**42**
No. analysed for safety:			
Safety analysis set:	**25**	**25**	**50**
No. completed:	**23**	**20**	**43**

Number of subjects (planned and analysed):

28-week open-label study:	**24 weeks Test drug/ 28 weeks Test drug**	**24 weeks Placebo/ 28 weeks Test drug**	**Total**
No. planned:	15-20	15-20	30-40
No. eligible and treated (Extension-FAS)**:**	**21**	**17**	**38**
Females/Males:	13/8	11/6	24/14
Mean age (range):	53 years (20-69)	50 years (23-68)	52 years (20-69)
Mean body weight at baseline (week 0):	106.4 kg	102.9 kg	104.7 kg
Mean body weight at 24 weeks:	102.2 kg	102.2 kg	102.2 kg
No. analysed for efficacy:			
Extension-FAS:	**21**	**17**	**38**
Extension-PPAS:	**15**	**15**	**30**
Full FAS	**25**	**24**	**49**
No. analysed for safety:			
Extension safety analysis set:	**21**	**17**	**38**
No. completed:	**16**	**17**	**33**

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 products, dose and mode of administration, batch numbers:

Dapagliflozin, 10 mg tablet, administered orally once daily.
Batch numbers: 3035126/3035127 (main study); 4J82440 (extension study).

Exenatide, 2 mg, administered as once weekly subcutaneous injection.
Batch numbers: 3035170/3035171 (main study); 14J018 (extension study).

Duration of treatment:

24 weeks (for subjects participating in 24-week double-blind main study only)
52 weeks (for subjects participating in 24-week double-blind main study and 28-week optional open-label extension study)

Reference therapies, dose and mode of administration, batch numbers:

Corresponding dapagliflozin 10 mg placebo tablet, administered orally once daily (during the 24-week double-blind period).
Batch numbers: 3035126, 3035127.

Corresponding exenatide, 2 mg placebo, administered as once weekly subcutaneous injection (during the 24-week double-blind period).
Batch numbers: 3035170, 3035171

No reference therapy was administered during the 28-week open-label extension 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, 24, 38 and 52.
- Whole body magnetic resonance imaging (MRI) scans (optional) were performed for assessment of the percentage liver fat, abdominal visceral fat, abdominal subcutaneous fat, total fat volume and total lean tissue at randomization and weeks 24 and 52. Total body fat (%) was also assessed by bioimpedance at randomization and weeks 12, 24, 38 and 52.
- 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, 24 and 52.

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.
Only subjects who received active treatment with dapagliflozin and exenatide during the initial 24-week treatment period underwent the 3h-OGTT and ingested a glucose solution at the week 52 visit.

- The proportion of subject with impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) was calculated at baseline, weeks 24 and 52 and shift from baseline and week 24.
- Estimated glomerular filtration rate (eGFR) was assessed at screening and weeks 12, 24 and 52.

Note: 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. The results of insulin sensitivity, insulin secretion analyses and UGE measured during the 3h-OGTT are presented in the clinical trial report for the 24-week short-term treatment period (version 1.1, dated 11 Jan 2017).

Safety

- Clinical laboratory tests (clinical chemistry, haematology) were performed at screening and weeks 12, 24 and 52. Urinalysis was performed at screening.
- Creatinine clearance was assessed at screening and weeks 12, 24 and 52.
- Vital signs were assessed at screening, randomization and weeks 4, 8, 12, 24, 38 and 52.
- Incidence and type of adverse events (AEs) and serious adverse events (SAEs). AE reporting started at screening and continued throughout the entire treatment period until week 24 or up to week 52 for subjects participating in the extension study. 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 weeks 24 and 52, just prior to start of the 3h-OGTT, and an additional blood sample was collected during the 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 this clinical trial report and in the clinical trial report for the 24-week short-term treatment period (version 1.1, dated 11 Jan 2017).
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

Subjects participating in the 24-week double-blind main study were classified into the following 3 analysis sets prior to breaking the blind:

- The **full analysis set (FAS [main study])**: 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 (main study).
- The **per-protocol analysis set (PPAS [main study])**: a subset of the FAS (main study), 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 (main study)**: all randomized subjects who received at least one dose of study medication and who provided any safety records.

Subjects participating in the 28-week open-label extension study were classified into the following analysis sets:

- The **extension-FAS** included all enrolled subjects who received at least one dose of study medication during the 28-week extended open–label treatment period, and who had a non-missing Visit 8 value and at least one post-Visit 8

value for at least one efficacy variable during the extension period.

- The **extension-PPAS,** a subset of the extension-FAS, included all subjects who had sufficiently complied with the protocol, e.g. no major protocol deviations, had available data at 52 weeks for the primary variable and had been compliant to IP (at least 22 weeks of IP treatment during the extension period and 80% to 120% of intended IPs).
- The **extension safety analysis set** included all enrolled in the 28-week open-label extension study who received at least one dose of study medication and who provided any safety records.

In addition:

- The **full-FAS** population included all subjects in the FAS (main study) population earlier defined irrespective of continuation status to the extension.

Subject and baseline data

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

Efficacy analyses

All efficacy analyses were performed on FAS, extension-FAS, full-FAS, PPAS and extension-PPAS.

Primary efficacy variable

The primary efficacy variable was change in body weight (kg) from baseline to 24 weeks. The treatment effect was tested (FAS and PPAS) 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.
Within-group analyses of the change in body weight (kg) from baseline to 24 weeks, from 24 weeks to 52 weeks and from baseline to 52 weeks, were performed on the extension-FAS and extension-PPAS, using the same analysis methods as above.

Secondary efficacy variable

The secondary efficacy variable was percentage change in body weight (%) from baseline to 24 weeks and was analysed for the FAS (main study) and PPAS (main study) with the same method as the primary variable.
Within-group analyses of the change in body weight (%) from baseline to 24 weeks, from 24 weeks to 52 weeks and from baseline to 52 weeks, were performed on the extension-FAS and extension-PPAS, using the same analysis methods as the primary efficacy variable.

Exploratory efficacy variables

Body fat composition/MRI data: For MRI data, i.e., liver fat percentage, liver volume, total liver fat, abdominal 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.
Within-group analyses of changes in liver fat, total liver fat, abdominal visceral adipose tissue, abdominal subcutaneous adipose tissue, total adipose tissue and total lean tissue from baseline to 24 weeks, from 24 weeks to 52 weeks and from baseline to 52 weeks, were performed on the extension-FAS and extension-PPAS. The ANCOVA model adjusted for gender, visit and baseline value was used to test a null hypothesis of no difference within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
Within-group analyses of the change in body fat percentage from baseline to 24 weeks, from 24 weeks to 52 weeks and from baseline to 52 weeks, were performed on the extension-FAS and extension-PPAS, using the same analysis methods as the primary efficacy variable.

OGTT variables: 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 (FAS and PPAS): glucose, glucagon (at 24 weeks only), 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.
Within-group analyses of changes in glucose at 120 minutes during OGTT from baseline to 24 weeks, from 24 weeks to 52 weeks and from baseline to 52 weeks, were performed on the extension-FAS and extension-PPAS. The ANCOVA model adjusted for gender, visit and baseline value was used to test a null hypothesis of no difference within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.
Descriptive statistics of plasma glucose, glucagon (at 24 weeks only), FFA, insulin, C-peptide and ketones in blood (all fasting) were presented by treatment group including mean change from baseline and corresponding 95% confidence

interval for the extension-FAS and extension-PPAS.

AUC: For the laboratory variables glucose, glycerol, FFA and insulin, the area under the curve (AUC) was calculated (FAS and PPAS). 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.
Within-group analyses of changes in glucose AUC_{0-2h} and insulin AUC from baseline to 24 weeks, from 24 weeks to 52 weeks and from baseline to 52 weeks, were performed on the extension-FAS and extension-PPAS. The ANCOVA model adjusted for gender, visit and baseline value was used to test a null hypothesis of no difference within treatment groups against a two-sided alternative hypothesis at the 5% level of significance

IFG and IGT: 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 (FAS and PPAS). The difference in proportions between the treatment groups was tested using a Cochran-Mantel-Haenszel test (FAS and PPAS). 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.
The difference in proportions of subjects with IFG and IGT at screening, week 24 and week 52 within the Dapa+Exe/Dapa+Exe group was tested on the extension-FAS and extension-PPAS using a paired McNemar test.

Laboratory efficacy variables: 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 (FAS and PPAS).
Within-group analyses of changes in HbA1c, FPG and fasting insulin from baseline to 24 weeks, from 24 weeks to 52 weeks and from baseline to 52 weeks, were performed on the extension-FAS and extension-PPAS, using the same analysis methods as the primary efficacy variable.
Descriptive statistics of TC, LDL-C, HDL-C and TG (all fasting) were presented by treatment group including mean change from baseline and corresponding 95% confidence interval for the extension-FAS and extension-PPAS.

Vital signs and other anthropometric measurements: Vital signs, waist circumference, WHR and BMI were analysed for FAS (main study) and PPAS (main study) with the same method as the primary efficacy variable.
Within-group analyses of changes in systolic blood pressure, diastolic blood pressure, pulse, waist circumference, WHR and BMI from baseline to 24 weeks, from 24 weeks to 52 weeks and from baseline to 52 weeks, were performed on the extension-FAS and extension-PPAS, using the same analysis methods as the primary efficacy variable

Estimated glomerular filtration rate: Estimated glomerular filtration rate (eGFR) based on MDRD was analysed (FAS and PPAS) with the same method as the primary efficacy variable.
Descriptive statistics are presented for all efficacy variables alongside the statistical analyses.

Note: The results of the following variables (analysed after the 24 weeks main study period) are presented in the clinical trial report for the 24-week short-term treatment period (version 1.1, dated 11 Jan 2017):
-The proportion of subjects with at least 10% and 5% reduction in weight at 24 weeks
-Mean change in body weight (kg) and percentage change in body weight (Exploratory)
-QUICKI index, Revised QUICKI index, weighted Matsuda index adjusted for UGE and Insulinogenic index.
-UGE: (descriptive statistics of eGFR only in this report)
-Exploratory model building

Safety Evaluation
Safety data are presented descriptively using the safety analysis set (for initial 24-week double-blind main study) and the extension safety analysis set (for 28-week open-label extension study). The safety parameters included clinical chemistry, haematology, vital signs, creatinine clearance, eGFR (extension safety analysis set only) 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
No sample size calculations were performed for the 28-week open-label extension study as all subjects participating in the 24-week double-blind study were offered to participate (if eligible) in the extension part.

EFFICACY RESULTS
In this report, mainly the results of the efficacy analyses of the extension-FAS and extension-PPAS populations are presented. Detailed results of the FAS (main study) and PPAS (main study) analyses are provided in the clinical trial report for the 24-week short-term treatment period (version 1.1, dated 11 Jan 2017).

Primary Efficacy Variable

Mean Change in Body Weight (kg)

- **Extension-FAS and extension-PPAS:** A statistically significant reduction in mean body weight (kg) of 4.3 kg (p<0.0001) between baseline (week 0) and week 24 was observed within the group that had been on active treatment with dapagliflozin and exenatide for 24 weeks in the main study (Dapa+Exe/Dapa+Exe group) but not within the group that had been on placebo (Placebo/Dapa+Exe group). Similar results were obtained for the extension-PPAS.
  During the following 28-week open label extension study period, no further statistically significant weight reduction was observed within the Dapa+Exe/Dapa+Exe group whereas a statistically significant reduction in mean body weight by 4.8 kg (p<0.0001) was evident within the Placebo/Dapa+Exe group. Similar results were obtained for the extension-PPAS.
  Overall, from baseline (week 0) to week 52, there was a statistically significant reduction in body weight, within both groups (p=0.0013, Dapa+Exe/Dapa+Exe group; p=0.0023, Placebo/Dapa+Exe group). The adjusted mean change from baseline to week 52 was 5.3 kg in the group who received active treatment for 52 weeks and -5.4 kg in the group who received placebo for 24 weeks and active treatment for 28 weeks. The main weight reduction was observed during the first 12 weeks or 14 weeks of treatment with dapagliflozin/exenatide in both groups. Similar results were obtained for the extension-PPAS.

- **Full FAS:** When data from all subjects were included in the analyses, irrespective of continuation in the extension part of the study, corresponding statistically significant reductions in mean body weight (kg) were observed between baseline (week 0) and week 24 within the Dapa+Exe/Dapa+Exe group (4.5 kg, p<0.0001, full FAS), between week 24 and week 52 within the placebo group (3.8 kg, p=0.0006, full FAS) and between baseline and week 52 within both groups (-5.7 kg, p=0.0003, Dapa+Exe/Dapa+Exe group [full FAS]; -4.2 kg, p=0.0088, Placebo/Dapa+Exe group [full FAS]).

Secondary Efficacy Variable

Percentage Change in Body Weight

- **Extension-FAS and extension-PPAS:** A statistically significant reduction in mean body weight of 4.3% based on percentage change between baseline (week 0) and week 24 was observed within the Dapa+Exe/Dapa+Exe group (p<0.0001), but not within the Placebo/Dapa+Exe group.
  During the following 28-week open label extension study period, a statistically significant reduction in mean body weight of 4.7% was observed within the Placebo/Dapa+Exe group (p<0.0001). No further statistically significant decrease was observed within the Dapa+Exe/Dapa+Exe group.
  Overall, from baseline (week 0) to week 52, there was a statistically significant reduction in mean body weight (%) within both groups (p=0.0007, Dapa+Exe/Dapa+Exe group; p=0.0023, Placebo/Dapa+Exe group). The adjusted mean percentage change was -5.3% and -5.2% in the respective groups.

- **Full-FAS:** Corresponding statistically significant reductions in mean body weight (%) were observed between baseline (week 0) and week 24 within the Dapa+Exe/Dapa+Exe group (-4.5%, p<0.0001, full FAS), between week 24 and week 52 within the placebo group (-3.8%, p=0.0002, full FAS) and between baseline (week 0) and week 52 within both groups (-5.7%, p=0.0002, Dapa+Exe/Dapa+Exe group [full FAS]; -4.1%, p=0.0064, Placebo/Dapa+Exe group [full FAS]).

Exploratory Variables (Extension-FAS and extension-PPAS)

Body fat composition

- Statistically significant differences within the group that received dapagliflozin/exenatide for 24 +28 weeks were observed in total adipose tissue (from baseline to week 24: -3.9 L, p=0.0008; from baseline to week 52: -5.1 L, p=0.0149), in abdominal visceral adipose tissue (from baseline to week 24: -0.39 L, p=0.0167), in abdominal subcutaneous adipose tissue (from baseline to week 24: -1.3 L, p=0.0008; from baseline to week 52: -1.6 L, p=0.0053), in total lean tissue (from baseline to week 24: -0.93 L, p=0.0111; from baseline to week 52: -1.3 L, p=0.0051) and in total liver fat (from week 24 to week 52: -0.043 L, p=0.0265).

Haemoglobin A1c

- Statistically significant reductions of HbA1c levels were observed within the Dapa+Exe/Dapa+Exe group (from baseline to week 24: -3.9 mmol/L, p<0.0001; from baseline to week 52: -3.1 mmol/L, p<0.0001) and within Placebo/Dapa+Exe group (from baseline to week 24: -1.6 mmol/L, p=0.0041; from week 24 to week 52: -1.4 mmol/L, p=0.0038; from baseline to week 52: -3.1 mmol/L, p<0.0001).

Glucose

- Statistically significant reductions of glucose (FPG) levels were observed within Dapa+Exe/Dapa+Exe group (from baseline to week 24: -0.42 mmol/L, p<0.0001; from baseline to week 52: -0.31 mmol/L, p=0.0006) and within

Placebo/Dapa+Exe group (from week 24 to week 52: -0.27 mmol/L, p=0.0046; from baseline to week 52: -0.29 mmol/L, p=0.0012).
Statistically significant reductions of 120 minutes post-challenge plasma glucose levels were observed within Dapa+Exe/Dapa+Exe group (from baseline to week 24: -218.0 mmol/L x 180 min, p=0.0002; from baseline to week 52: -2.2 mmol/L, p<0.0001). Also, statistically significant reductions in mean AUC0-3h for plasma glucose were observed (from baseline to week 24: -1.8 mmol/L, p=0.0002; from baseline to week 52: -248.7 mmol/L x 180 min, p<0.0001).

Impaired fasting plasma glucose and impaired glucose tolerance

- The proportion of subject with IFG (FPG ≥5.6 mmol/L) was significantly lower within the Dapa+Exe/Dapa+Exe group between baseline (screening) and week 24 (p=0.0082). Between baseline (screening) and week 24, 33.3% of the subjects shifted from raised to normal IFG status and at week 52, 35.3% shifted from raised to normal.
There were statistically significant reductions observed in the proportion of subjects with IGT (post-challenge plasma glucose ≥7.8 mmol/L at Time 120 minutes during the 3h-OGTT) within the Dapa+Exe/Dapa+Exe group, between baseline (screening) and week 24 (p=0.0196) and week 52 (p=0.0253), respectively. A proportion of 38.1% shifted from raised to normal IGT status between baseline (screening) and week 24, 33.3% between baseline (screening) and week 52, and 6.7% shifted from raised to normal IGT status between 24 weeks and 52 weeks.
There were statistically significant differences in the proportion of subjects with IFG and/or IGT observed in the Dapa+Exe/Dapa+Exe group compared to the Placebo/Dapa+Exe group, between baseline (screening) and week 24 (p=0.0031, Cochran–Mantel–Haenszel test). The proportion of subjects with raised status was lower in the Dapa+Exe/Dapa+Exe group (33.3%) than in the Placebo/Dapa+Exe group (82.4%) at week 24 and also at week 52 (28.6% vs 52.9%).
Within the Dapa+Exe/Dapa+Exe group, there was a statistically significant reduction in the proportion of subjects with IFG and/or IGT between baseline (screening) and week 24 (p=0.0047, McNemar's test) and between baseline (screening) to week 52 (p=0.0143, McNemar's test).

Insulin secretion and insulin sensitivity

- A statistically significant reduction in mean fasting insulin was observed within the Dapa+Exe/Dapa+Exe group between week 24 and week 52 (p=0.0006), but not within the Placebo/Dapa+Exe group. The adjusted mean change in fasting insulin was -4.9 mU/L and 1.1 mU/L in the respective group. No statistically significant changes in mean AUC0-3h for insulin were observed within the Dapa+Exe/Dapa+Exe group at any of the time points.

Other variables

- No apparent differences between the treatment groups, or relevant changes in mean values from screening to week 12, week 24 or week 52 (where applicable) (descriptive statistics only), were observed for any of the variables (plasma glucose, glucagon [at 24 weeks only], insulin, C-peptide and ketones).

Blood lipid profile

- No apparent differences between the treatment groups, or relevant changes in mean values from screening to week 12, week 24 or week 52 (descriptive statistics only), were observed for any of the blood lipid profile variables (TC, LDL-C, HDL-C and TG).

Vital signs

- **Extension-FAS and PPAS (main study + extension study):** Statistically significant reductions in mean systolic blood pressure were observed within Dapa+Exe/Dapa+Exe group (from baseline to week 24: -8.8 mmHg, p=0.0004; from baseline to week 52: -13.0 mmHg, p<0.0001) and within the Placebo/Dapa+Exe group (from baseline to week 52: -8.6 mmHg, p=0.0045). Also, significant increases in mean pulse were observed within the Placebo/Dapa+Exe group (between week 24 and week 52: 5.9 bets/min, p=0.0096; from baseline to week 52: 5.6 beats/min, p=0.0107).

Other anthropometric measurements

- Statistically significant reductions in waist circumference were observed within the Dapa+Exe/Dapa+Exe group (from baseline to week 24: -5.3 cm, p<0.0001; from baseline to week 52: -7.3 cm, p<0.0001) and within the Placebo/Dapa+Exe group (from week 24 to week 52: -4.8 cm, p=0.0020; from baseline to week 52: -7.2 cm, p=0.0003).
Statistically significant reductions in waist-hip ratio were observed within the Dapa+Exe/Dapa+Exe group (from baseline to week 52: -0.03, p=0.0049) and within the Placebo/Dapa+Exe group (from baseline to week 52: -0.03, p=0.0140)
Statistically significant reductions in BMI were observed within the Dapa+Exe/Dapa+Exe group (from baseline to week 24: -1.4 kg/m^2, p<0.0001; from baseline to week 52: -1.7 kg/m^2, p=0.0014) and within the Placebo/Dapa+Exe group (from week 24 to week 52: -1.6 kg/m^2, p<0.0001; from baseline to week 52: -1.8 kg/m^2,

p=0.0026).

SAFETY RESULTS:
In this report, mainly the results of the safety analyses in the 28-week open-label extension study (extension safety analysis set population) are presented. Detailed results of the safety analysis set analyses are provided in the clinical trial report for the 24-week short-term treatment period (version 1.1, dated 11 Jan 2017).

- No new safety concerns based on clinical laboratory tests, creatinine clearance, vital signs and AEs/SAEs, were identified for the combined treatment with dapagliflozin (10 mg once daily) and exenatide (2 mg weekly injections), in obese non-diabetic subjects, during the initial 24 weeks of treatment or during the continuing 28 weeks extended treatment.

Extent of exposure

- During the 24-week double-blind main study period, the mean duration of exposure and treatment compliance was largely similar in both groups, however during the 28-week extension period, there was a difference of approximately 18 days in mean duration of exposure between the groups: 25.4 vs 28.0 weeks for exenatide and 178 vs 196 days for dapagliflozin. This was due to the lower drop-out rate in the Placebo/Dapa+Exe group.

Clinical laboratory evaluation

- There were no major changes in mean laboratory values or no apparent differences between treatment groups observed during the entire 52-week study. A numerical decrease in the creatinine clearance rate (-7.4 mL/min) between baseline and week 24, was observed in the Dapa+Exe/Dapa+Exe group, however not in the Placebo/Dapa+Exe group (0.8 mL/min). Between baseline and week 52, the mean change was -4.2 mL/min and -7.7 mL/min in the respective group. As body weight is included as one of the variables in the formula for calculation of creatinine clearance, the reduced creatinine clearance observed in both groups, after exposure to dapagliflozin/exenatide, is likely to in part be attributable to the reduced mean body weight.

Summary of adverse events

- All 38 subjects that participated in the extension study (extension safety analysis set), reported AEs and in both groups, the main part of AEs were reported during the initial 24-week main study period; 238 AEs, whereof 147 AEs reported by 21 subjects (100.0%) in the Dapa+Exe/Dapa+Exe group and 91 AEs reported by 17 subjects (100.0%) in the Placebo/Dapa+Exe group.
  Between week 24 and week 52, a total of 103 AEs were reported; 61 AEs reported by 17 subjects (81.0%) in the Dapa+Exe/Dapa+Exe group and 42 AEs reported by 16 subjects (94.1%) in the Placebo/Dapa+Exe group).

Adverse events by severity and relationship to investigational product

- Between baseline and week 24, the majority of the reported AEs were of mild intensity (74.8% of reported AEs in the Dapa+Exe/Dapa+Exe group and 74.7% in the Placebo/Dapa+Exe group), 24.5% vs 24.2% of reported AEs in the respective group were of moderate intensity and 1 AE in each group was assessed as severe.
  Most AEs were assessed as possibly related to treatment (60.5% vs 59.3%). Five of reported AEs (3.4%) in the Dapa+Exe/Dapa+Exe group and 2 AEs (2.2%) in the Placebo/Dapa+Exe group, were assessed as related to the IP (all of mild intensity).
  Also between week 24 and week 52, the majority of the reported AEs were mild (63.9% vs 83.3%), while 31.1% vs 14.3% were of moderate intensity and 4 AEs were severe. The majority was assessed as possibly related to the IP in both groups (63.9% vs 66.6%). No AE reported during this period was assessed as related to the IP.

Withdrawals due to adverse events

- Four subjects (all in the Dapa+Exe/Dapa+Exe group) were withdrawn from the study during the 28-week open-label extension period due to the occurrence of AEs (1 subject due to eye allergy and 1 subject due to dizziness, fatigue and nausea) or SAEs (1 subject due to gastrointestinal haemorrhage and adenocarcinoma of colon and 1 subject due to angioedema). In addition, 1 subject (Dapa+Exe/Dapa+Exe group) reported SAE injury, during the initial 24-week study period, however completed the entire 52-week study.

Adverse events by system organ class and preferred term

- The most common SOCs, reported by >50% of subjects in any group, during entire 52-week study, were: general disorders and administration site conditions (76.2% vs 76.5% of all subjects in the Dapa+Exe/Dapa+Exe and Placebo/Dapa+Exe groups, respectively), gastrointestinal disorders (71.4% vs 76.5%) and infections and infestations (61.9% vs 52.9%).
  The most common PTs reported in the Dapa+Exe/Dapa+Exe group were nausea (42.9% vs 23.5% in Placebo/Dapa+Exe group), nasopharyngitis (38.1% vs 17.6%), dizziness (33.3% vs 17.6%) and decreased appetite (33.3% vs 11.8%).
  The most common PTs reported in the Placebo/Dapa+Exe group were pollakiuria (64.7% [23.8% in

Dapa+Exe/Dapa+Exe group]), injection site mass (35.3% [28.6%]) and fatigue (35.3% [28.6%]).

Adverse events of special interest

- 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 entire study and there was no major difference in reporting frequency between treatment groups.
- During the entire study period, gastrointestinal AEs of special interest with regard to the mode of action of exenatide treatment were reported by a smaller proportion of subjects in the Dapa+Exe/Dapa+Exe group than in the Placebo/Dapa+Exe group: 61.9% vs 76.5% of all subjects in the two groups respectively. Most AEs reported in the Placebo/Dapa+Exe group were reported during the 24-week main study, i.e. the subjects were on placebo treatment. The most common gastrointestinal symptoms were nausea, upper abdominal pain and diarrhoea.
- Injection site-related AEs were similarly reported in both groups: 42.8% vs 41.2% of all subjects in the Dapa+Exe/Dapa+Exe and Placebo/Dapa+Exe groups, respectively. All reactions, except one, were reported during the 24-week main study. The most common injection site-related AEs were injection site mass, injection site pruritus and injection site erythema.

OVERALL CONCLUSIONS:

EFFICACY

- Combined treatment with dapagliflozin (10 mg once daily) and exenatide (2 mg weekly injections) in obese, non-diabetic subjects resulted in a statistically significant weight loss of approximately 5.3 kg over 52 weeks. The weight reduction was most prominent during the first 12 to 14 weeks after start of treatment and was largely accounted for by a loss of adipose tissue.
  In addition to the weight-reducing effect, the combined dapagliflozin/exenatide treatment significantly lowered plasma levels of HbA1c and FPG with no clear signs of hypoglycaemia.
- In response to a glucose challenge, both post-challenge plasma glucose levels and $AUC_{0\ 3h}$ as well as the fasting glucose were significantly reduced following 24 and 52 weeks treatment with dapagliflozin and exenatide. Fasting insulin was significantly reduced between 24 and 52 weeks in the group that was on active treatment for 24 +28 weeks.
- Combined treatment with dapagliflozin and exenatide led to a statistically significant reduction of mean systolic blood pressure of 13.0 mmHg over 52 weeks.

SAFETY

- No major safety issues were identified for the combined treatment with dapagliflozin (10 mg once daily) and exenatide (2 mg weekly injections) in obese, non-diabetic, subjects during 52 weeks of treatment, based on clinical laboratory tests, creatinine clearance, vital signs and AEs/SAEs.
- The AE reporting did not reveal any sign of new safety or tolerability issues 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 subjects were given the combination of dapagliflozin and exenatide.

3. TABLE OF CONTENTS

3.1 LIST OF TABLES

3.2 LIST OF FIGURES

Notice to the Reader

In this report, mainly the results of the analyses of the extension-FAS, extension-PPAS and extension-safety analysis set are presented.

Detailed results for the FAS, PPAS and safety analysis set are provided in the clinical trial report for the 24-week short-term treatment period (version 1.1, dated 11 Jan 2017).

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
Bioimpedance	Bioelectrical impedance analysis
BMI	Body mass index
CK	Creatine kinase
CRF	Case report form
CRO	Contract research organisation
CRP	C-reactive protein
CSP	Clinical study protocol
DPP	Dipeptidyl peptidase
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
FAS	Full analysis set
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
HLT	High level term
iAUC	Incremental area under the curve
ICH	International Conference on Harmonisation
ICF	Informed consent form
IEC	Independent ethics committee
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
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
MMRM	Mixed model for repeated measures
MRI	Magnetic resonance imaging
NA	Not applicable

Abbreviation or special term	Explanation
od	Once daily
OGTT	Oral glucose tolerance test
3h-OGTT	3 hour oral glucose tolerance test
2h-PG	2 hour plasma glucose
PCG	PCG Clinical Services AB
PPAS	Per-protocol analysis set
PPG	Post-challenge glucose
PT	Preferred term
QUICKI	Quantitative insulin sensitivity check index
RA	Regulatory authorities
SAE	Serious adverse event
SAP	Statistical analysis plan
SDV	Source data verification
SGLT	Sodium-glucose cotransporter
SOC	System organ class
SD	Standard deviation
SUSAR	Suspected unexpected serious adverse reaction
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 one 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 (ICF) prior to receiving open-label study treatment. Copies of the subject information and ICFs used for the initial 24-week double-blind main study and for the 28-week open-label extension 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 vitae for all important participants in the study is provided in Appendix 16.1.4.

Table 1 Key Study Personnel

Role	Name, affiliation	Address
Sponsor and Principal Investigator:	Prof Jan Eriksson, MD, PhD	Department of Medical Sciences Uppsala University Hospital SE-751 85 Uppsala, Sweden Phone: +46 (0)18 611 44 19 Mobile: +46 (0)73 868 11 33 E-mail: jan.eriksson@medsci.uu.se
Co-investigator:	Per Lundkvist, MD	Department of Medical Sciences, Clinical Diabetology and Metabolism Akademiska sjukhuset Entrance 40, 5tr Uppsala University SE-751 85 Uppsala, Sweden
Study nurses:	Caroline Moberg Lovisa Nordlinder Monica Gelotte Tanya Pütger Carola Almström	
Project Managers:	Daniel Seisdedos, MSc (from 13 Oct 2015) Daniel Bjermo, MSc (08 Sep 2014 to 13 Oct 2015) Caroline Engvall, PhD (11 Aug 2014 to 08 Oct 2014)	PCG Clinical Services AB Kungsängsvägen 19 SE-753 23 Uppsala, Sweden Phone: +46-(0)18 430 31 00
Monitors:	Erik Sjöström, MSc (from 01 Mar 2016) Pernilla Andresen, MSc (until 14 Oct 2015)	
Clinical Data Manager:	Pontus Larsson, MSc	
Biostatistician:	Nils Adriansson, BSc	
Medical Writer:	Rose-Marie Lindgren, MSc, MedLic	
Central Laboratory:	Clinical Chemistry Laboratory	Akademiska sjukhuset SE-751 85 Uppsala, Sweden
Electronic case report form (eCRF)/Viedoc™ provider		PCG Solutions AB Dragarbrunnsgatan 46 SE-753 20 Uppsala, Sweden Phone: +46 (0)18 430 3100
Magnetic resonance imaging (MRI) provider:	Eva Hägglund	Antaros Medical BioVenture Hub Pepparedsleden 1 SE-431 83 Mölndal, Sweden Phone: +46 (0)70 3237318

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 co-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), post-challenge 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 abdominal subcutaneous and abdominal 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 an 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 may partly be prevented and possibly lead to additive or synergistic 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 was to demonstrate maintained, or additional, weight reduction by active treatment up to 12 months. The results obtained after the initial 24-week double-blind main study were in detail reported in the clinical trial report for the 24-week short-term treatment period (version 1.1, dated 11 Jan 2017),

provided in Appendix 16.5) and also published.[10] This report describes the results obtained during the entire 52-week study 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 a 28-week open-label treatment period with dapagliflozin 10 mg once daily and exenatide 2 mg once weekly following 24 weeks blinded treatment with dapagliflozin 10 mg once daily and exenatide 2 mg once weekly to maintain or enhance body weight reduction in obese subjects.
- To assess the efficacy of a 28-week open-label treatment period with dapagliflozin 10 mg once daily and exenatide 2 mg once weekly following 24 weeks blinded treatment with placebo on body weight reduction in obese subjects
- 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 DNA for future exploratory research of genes/genetic variation that is related to obesity or to treatment response to dapagliflozin in combination with exenatide.

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 ICF 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.

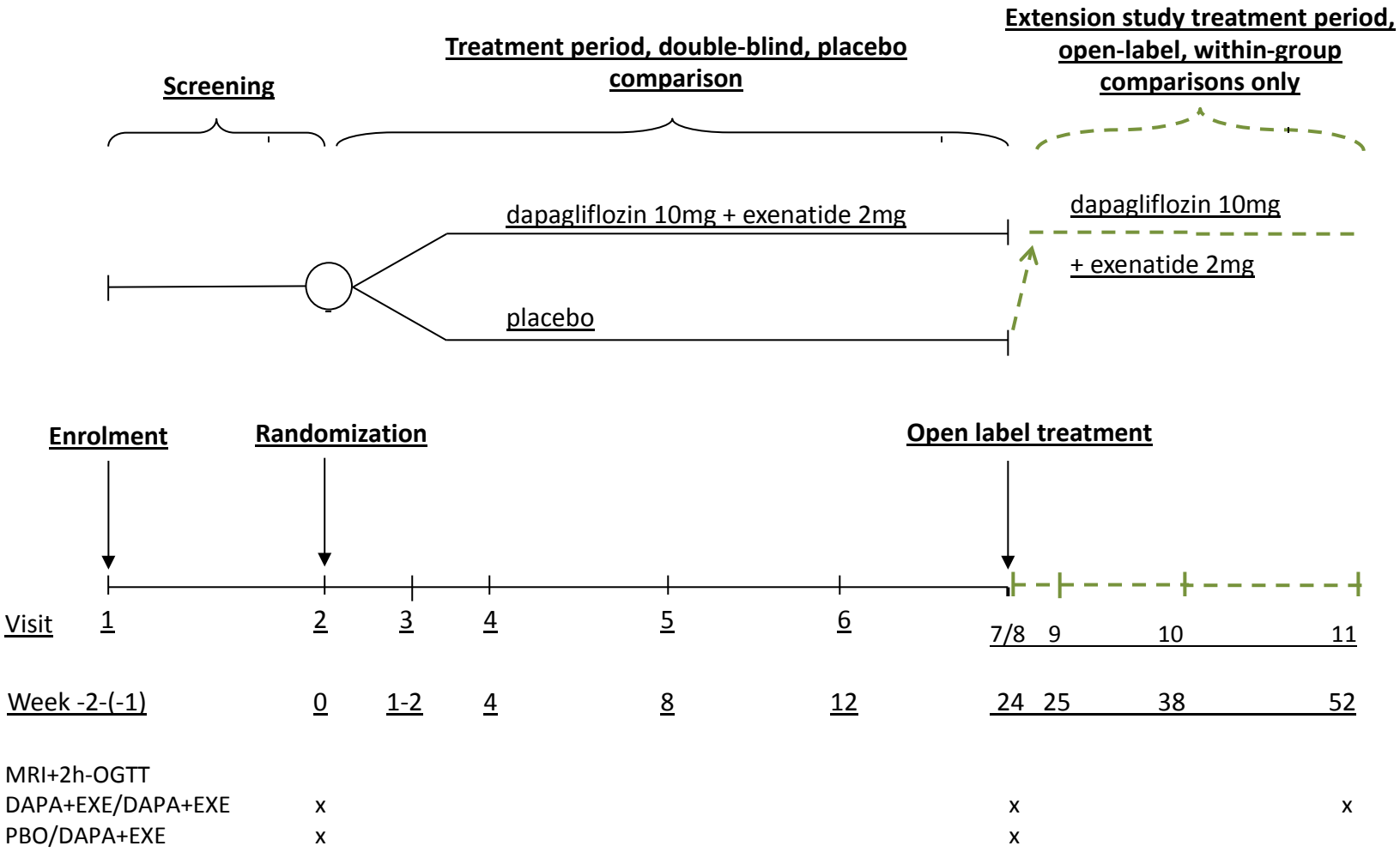
An administrative interim analysis, blinded to the study team and Principal Investigator, was planned after all subjects had conducted 12 weeks of treatment. A copy of the database at 12 weeks was stored.

A full database lock was conducted on 5 Oct 2015 after all subjects had completed 24 weeks of blinded treatment and a second full database lock was conducted on 4 May 2016 after all subjects participating in the 28-week extension study had completed the study at week 52.

Data collected during the initial 24-week double-blind study period was presented in detail in the clinical trial report for the 24-week short-term treatment period (version 1.1, dated 11 Jan 2017), provided in Appendix 16.5. This report describes the results obtained during the entire 52-week study period.

For further details on the study procedures, refer to Table 6 and 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, non-diabetic 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 non-diabetic 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, abdominal visceral adipose tissue and liver fat) together with measures of glucose, insulin and glucagon (at 24 weeks only) 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, Visit 7/8 and Visit 11, 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 and Visit 11
- 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 Visit 2, Visit 7/8 and Visit 11. 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 were 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 (AE): 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 to be asked about the reason(s) and the presence of any AE. 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

Table 2 Treatment, initial 24-week double-blind main study period

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

Table 3 Treatment, 28-week open-label extension study period

Treatment in double-blind 24-week study	Treatment in open-label 28-week study	Dose	Dose	Route of administration
Dapagliflozin 10mg + Exenatide 2mg	Dapagliflozin Exenatide	10 mg 2 mg	Once daily Once weekly	Oral administration of tablet Subcutaneous injection
Matching placebo	Dapagliflozin Exenatide	10 mg 2 mg	Once daily Once weekly	Oral administration of tablet Subcutaneous injection

9.4.2 Identity of Investigational Products

The identity of the IPs is summarized in Table 4 and Table 5. 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.

Being an open-label study, commercially available IP were to be used during the 28-week extension study. The IP was to be requisitioned from the hospital pharmacy and stored at the clinic.

Table 4 Investigational products in the 24-week double-blind main study (Week 1 to 24)

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

Table 5 Investigational products in the 28-week open-label extension study (Week 25 to 52)

Investigational products for open-label treatment	Dosage form and strength	Batch numbers	Manufacturer
Dapagliflozin (FORXIGA®)	Biconvex, diamond shape, yellow tablets size 11 x 8 mm, 10 mg	4J82440	AstraZeneca
Exenatide (BYDUREON™) once-weekly suspension	2.0 mg injection	14J018	AstraZeneca

9.4.3 Method of Assigning Patients to Treatment Groups

During the 24-weeks double-blind treatment period, eligible subjects were randomized to 1 of 2 treatment arms, active treatment (dapagliflozin and exenatide) or matching placebo, in a 1:1 ratio. Random assignment to study treatment was done in balanced blocks and was stratified by gender.

All subjects that were eligible for participation in the 28-weeks open-label extension study, received active treatment (dapagliflozin and exenatide.

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, contract research organisation [CRO] personnel and AstraZeneca collaborators) remained blinded during the initial 24-week double-blind main study, 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 for 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 (see 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 electronic case report form (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. Subjects 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 eCRF. 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 6.

Table 6 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, 24, 38 and 52 (Table 6). 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, 24 and 52 (Table 6, Section 9.5.1). All efficacy laboratory variables are summarized in Table 7.

A 3 hour oral glucose tolerance test (3h-OGTT) was performed at screening and weeks 24 and 52 (only for subjects that received active treatment with dapagliflozin and exenatide during the initial 24-week treatment period). 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, and urine volume during OGTT) were performed at the study site, Department of Medical Sciences, Clinical Diabetology and Metabolism at Akademiska sjukhuset, Uppsala, Sweden.

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

Table 7 Efficacy laboratory variables

Visit	1	2	3	4	5	6	7/8	11
Study week	**-2-(-1)**	**0**	**1-2**	**4**	**8**	**12**	**24**	**52**
HbA1c	X					X	X	X
FPG	X	(X[a])				X	X	X
IFG	X						X	X
IGT	X						X	X[b]
Insulin	X					X	X	X
C-peptide	X					X	X	X
Glucagon	X					X	X	
Glycerol	X					X	X	X
3h-OGTT	X						X	X[b]
TC	X					X	X	X
LDL-C	X					X	X	X
HDL-C	X					X	X	X
TG	X					X	X	X
FFA	X					X	X	X
Ketones in blood	X					X	X	X
eGFR	X					X	X	X
Exploratory analysis	X						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.
[b] Was only performed for subjects in the Dapa+Exe/Dapa+Exe group.

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, 24, 38 and 52 (Table 6).

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

The MRI was performed at randomization (week 0) and weeks 24 and 52 (only for subjects that received active treatment with dapagliflozin and exenatide during the initial 24-week treatment period) to assess liver fat and body composition (Table 6, Section 9.5.1). 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 the CSP, 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)
- Total liver fat (%): Liver volumes measured to investigate the total liver fat content: total liver fat (l) = liver fat (%) * liver volume.
- Total adipose tissue: assessed from the whole body MRI scans.
- Abdominal subcutaneous adipose tissue and abdominal 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 (L).

In addition, total body fat (%) was assessed at randomization and weeks 12, 24, 38 and 52 using bioelectrical impedance analysis (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 8.

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.

Blood sampling procedure during OGTT at week 52: Fasting blood samples (Time 0 minutes samples) were taken from all subjects, including samples for: haematology, clinical chemistry, glucose, HbA1c, insulin, glycerol, ketones, C-peptide, FFA, TC, TG, HDL-C, LDL-C and exploratory analysis. The haematology and clinical chemistry variables are listed in Table 8.

No further blood samples were taken from subjects from the initial placebo group. Only subjects having received active treatment with dapagliflozin and exenatide during the initial 24-week treatment period were to undergo OGTT and ingest a glucose solution at the week 52 visit (same procedure as described above for screening and week 24 visits).

Urine sampling procedure during OGTT at screening, week 24 and week 52. The urine produced during OGTT was to be collected for measurement of urinary glucose excretion (UGE). 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 weeks 24 and 52 and shift from baseline and week 24 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 Estimated Glomerular Filtration Rate

Calculation of the median change from screening to weeks 12, 24 and 52 in estimated glomerular filtration rate (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 and urinalysis were collected at the time points indicated in Table 6. The laboratory safety variables measured are presented in Table 8.

Table 8 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 phosphatase (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 sitting 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, 24, 38 and 52 (Table 6, Section 9.5.1).

9.5.4.3 Other Safety Variable; Creatinine Clearance

Creatinine clearance was assessed at screening, weeks 12, 24 and 52 and calculated using the method of Cockcroft-Gault:

Males:

$$\text{Creatinine clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age [years]})}{\text{serum creatinine (µmol/L)}} \times 1.23$$

Females:

$$\text{Creatinine clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age [years]})}{\text{serum creatinine (µmol/L)}} \times 1.04$$

9.5.4.4 Adverse Events

AE 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 and sweating).

AEs 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 Sections 6.3 and 6.4 in the CSP (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, week 24 and week 52, 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 will be 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 (PCG). 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, Uppsala, Sweden.

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.

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 investigators 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, 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, Uppsala, Sweden.

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

9.6.4 Data Management

Data management was performed by PCG 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.

A first full database lock was conducted on 05 Oct 2015 after all subjects had completed 24 weeks of blinded treatment and a second full database lock was conducted on 04 May 2016 when all subjects participating in the 28-week extension study had 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 10) and Section 9.8.3 (Post-hoc analyses). The original SAP (dated 02 Oct 2015) and the final amended version (dated 13 May 2016) are provided in 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.

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 (SD), 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

In the 24-week double-blind main study, 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.

Before the database lock for the 28-week open-label extension study part, the extension-FAS, extension-PPAS and extension safety analysis sets were defined, for subjects who participated in the 28-week open-label extension study period, see Section 9.8.2 (Changes to the planned analyses). The efficacy analyses, as defined in the amended SAP, were performed on both the extension-FAS and extension-PPAS and the safety analyses were performed on the extension safety analysis set.

After the database lock for the 28-week extension study, the full-FAS analysis set was defined, see Section 9.8.2 (Changes to the planned analyses) and the clean file protocol amendment (dated 12 Oct 2016). All efficacy analyses performed on the extension-FAS and extension-PPAS were also performed on the full-FAS.

See the below sections for definitions of the respective analysis data sets.

9.7.2.1 Full Analysis Sets

The FAS (main study) 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.

The extension-FAS included all enrolled subjects who received at least one dose of study medication during the 28-week open-label extension study period, and who had a non-missing Visit 8 value and at least one post-Visit 8 value for at least one efficacy variable during the extension period. In case of severe noncompliance with the protocol a subject could be excluded from the full analysis set.

The full-FAS population included all subjects in the FAS (main study) population earlier defined irrespective of continuation status to the extension.

9.7.2.2 Per-Protocol Analysis Sets

The PPAS – being a subset of the full analysis set – included all subjects who had 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 (main study) 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.

The extension-PPAS included all subjects who had taken IPs during at least 22 weeks during the 28-week open-label extension study period and 80% to 120% of intended IPs, and who had no major protocol deviations which might affect the study outcome significantly.

Thus, the extension-PPAS is a subset of the extension-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 52 weeks for the primary variable
3. Subjects had been compliant; a duration of at least 22 weeks of IP treatment and 80% to 120% of intended IPs

9.7.2.3 Safety Analysis Sets

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.

The extension safety analysis set included all subjects enrolled in the 28-week open-label extension study who received at least one dose of study medication and who provided any safety records.

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 were summarized by treatment group and in total, for the 24-week double-blind main study and the 28-week open-label extension study, respectively (see Section 9.8.2, Changes to the planned analyses). 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, for the 24-week double-blind main study and the 28-week open-label extension study, respectively (see Section 9.8.2, Changes to the planned analyses).

9.7.5 Body Weight and Other Anthropometric Measures

Height, body weight, BMI, waist circumference and hip circumference were summarized as appropriate depending on the data type by treatment group for each visit and in total for each the safety analysis set, the FAS (main study) and the extension safety analysis set.

Body weight (kg) over the 24-week period was also presented in a line chart (FAS [main study] and PPAS [main study]). Spaghetti charts for body weight over the 24-week treatment period were presented for the FAS (main study) and the PPAS (main study).

9.7.6 Waist-Hip Ratio (WHR)

Summary statistics were presented by treatment group for each visit. Line charts were presented by treatment group from baseline to week 24 (FAS [main study] and PPAS [main study]).

9.7.7 Compliance

Treatment compliance (number of injections and number of tablets received relative to planned) were summarized by treatment groups, for the 24-week double-blind main study and the 28-week open-label extension study (baseline to 24 weeks and 24 to 52 weeks), respectively (see Section 9.8.2, Changes to the planned analyses).

9.7.8 Medical History and Concurrent Diseases

Medical history, including surgical and medical procedures and concurrent diseases were

summarized by treatment groups, for the 24-week double-blind main study part and the 28-week open-label extension study part, respectively (see Section 9.8.2, Changes to the planned analyses).

Obesity history, including time since started, maximum weight and weight 3 and 12 months ago, were summarized by treatment, for the 24-week double-blind main study part.

Medical and surgical history and concurrent diseases were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 18.0 by PCG 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

Prior and concomitant medications were summarized by treatment groups, for the 24-week double-blind main study part and the 28-week open-label extension study part (baseline to 24 weeks, baseline to 52 weeks and 24 to 52 weeks), respectively (see Section 9.8.2, Changes to the planned analyses).

Medications were coded using the AstraZeneca Drug Dictionary version 14.2 by PCG (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 were presented for the safety analysis set and the extension 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 a mixed model for repeated measures (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.

Within-group analyses of the change in body weight (kg) from baseline to 24 weeks, from 24 weeks to 52 weeks and from baseline to 52 weeks, were performed on the extension-FAS, extension-PPAS, using the same analysis methods as above (see Section 9.8.2, Changes to the planned analyses).

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.

Within-group analyses of the change in body weight (%) from baseline to 24 weeks, from 24 weeks to 52 weeks and from baseline to 52 weeks, were performed on the extension-FAS, extension-PPAS using the same analysis methods as the primary efficacy variable (see Section 9.8.2, Changes to the planned analyses).

9.7.10.3 Exploratory Efficacy Variables

9.7.10.3.1 MRI Variables

For MRI data, i.e. liver fat percentage, liver volume, total liver fat, abdominal 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 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.

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

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

Within-group analyses of changes in liver fat (%), total liver fat (L), abdominal visceral adipose tissue (L), abdominal subcutaneous adipose tissue (L), total adipose tissue (L) and total lean tissue (L) from baseline to 24 weeks, from 24 weeks to 52 weeks and from baseline to 52 weeks, were performed on the extension-FAS and extension-PPAS. The ANCOVA model adjusted for gender, visit and baseline value was used to test a null hypothesis of no difference within treatment groups against a two-sided alternative hypothesis at the 5% level of significance (data from baseline to 24 weeks and from 24 weeks to 52 weeks). Baseline to 52 weeks data were analysed with the same analysis methods as the primary efficacy variable (MMRM) (see Section 9.8.2, Changes to the planned analyses).

Within-group analyses of the change in body fat (%) from baseline to 24 weeks, from 24 weeks to 52 weeks and from baseline to 52 weeks, were performed on the extension-FAS and extension-PPAS, using the same analysis methods as the primary efficacy variable (see Section 9.8.2, Changes to the planned analyses).

9.7.10.3.2 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 (FAS [main study] and PPAS [main study]): 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.

Within-group analyses of changes in glucose (mmol/L) at 120 minutes during OGTT from baseline to 24 weeks, from 24 weeks to 52 weeks and from baseline to 52 weeks, were performed on the

extension-FAS and extension-PPAS. The ANCOVA model adjusted for gender, visit and baseline value was used to test a null hypothesis of no difference within treatment groups against a two-sided alternative hypothesis at the 5% level of significance (data from baseline to 24 weeks and from 24 weeks to 52 weeks). Baseline to 52 weeks data were analysed with the same analysis methods as the primary efficacy variable (MMRM) (see Section 9.8.2, Changes to the planned analyses).

In addition, descriptive statistics of plasma glucose (mmol/L), insulin (mU/L), C-peptide (nmol/L) and ketones in blood (all fasting) were presented by treatment group including mean change from baseline and corresponding 95% confidence interval for the extension-FAS and extension-PPAS (see Section 9.8.2, Changes to the planned analyses).

9.7.10.3.3 Area under the Curve (Post-hoc Analysis)

For the laboratory variables glucose, glycerol, FFAs and insulin the area under the curve (AUC) was calculated (FAS and PPAS). 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 (FAS and PPAS). The iAUC was calculated using the trapezium (trapezoidal) rule and corresponds to the net incremental area under curve.

Within-group analyses of changes in glucose $AUC_{0\text{-}3h}$ and insulin AUC from baseline to 24 weeks, from 24 weeks to 52 weeks and from baseline to 52 weeks, were performed on the extension-FAS and extension-PPAS. The ANCOVA model adjusted for gender, visit and baseline value was used to test a null hypothesis of no difference within treatment groups against a two-sided alternative hypothesis at the 5% level of significance (data from baseline to 24 weeks and from 24 weeks to 52 weeks). Baseline to 52 weeks data were analysed with the same analysis methods as the primary efficacy variable (see Section 9.8.2, Changes to the planned analyses).

9.7.10.3.4 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.

The difference in proportions of subjects with IFG and IGT at screening, week 24 and week 52 within the Dapa+Exe/Dapa+Exe group (Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg) was tested on the extension-FAS and extension-PPAS using a paired McNemar test (see Section 9.8.2, Changes to the planned analyses).

9.7.10.3.5 Laboratory Efficacy Variables

Laboratory efficacy variables include TC, LDL-C, HDL-C, TG, HbA1c and fasting plasma glucose (FPG). These variables were analysed with the same method as the primary efficacy variable.

Within-group analyses of changes in HbA1c (mmol/mol), FPG (mmol/L) and fasting insulin (mU/L)

from baseline to 24 weeks, from 24 weeks to 52 weeks and from baseline to 52 weeks, were performed on the extension-FAS and extension-PPAS. The ANCOVA model adjusted for gender, visit and baseline value was used to test a null hypothesis of no difference within treatment groups against a two-sided alternative hypothesis at the 5% level of significance (data from 24 weeks to 52 weeks). Data from baseline to 24 weeks and baseline to 52 weeks were analysed with the same analysis methods as the primary efficacy variable (MMRM) (see Section 9.8.2, Changes to the planned analyses).

In addition, descriptive statistics of TC (mmol/L), LDL-C (mmol/L), HDL-C (mmol/L) and TG (mmol/L) (all fasting) were presented by treatment group including mean change from baseline and corresponding 95% confidence interval for the extension-FAS and extension-PPAS (see Section 9.8.2, Changes to the planned analyses).

9.7.10.3.6 Vital Signs and Anthropometric Efficacy Variables

Vital signs (systolic blood pressure [mmHg], diastolic blood pressure [mmHg], pulse [beats/min]), waist circumference, WHR and BMI were analysed with the same method as the primary efficacy variable.

Within-group analyses of changes in systolic blood pressure (mmHg), diastolic blood pressure (mmHg), pulse (beats/min), waist circumference (cm), WHR and BMI from baseline to 24 weeks, from 24 weeks to 52 weeks and from baseline to 52 weeks, were performed on the extension-FAS and extension-PPAS, using the same analysis methods as the primary efficacy variable (see Section 9.8.2, Changes to the planned analyses).

9.7.10.3.7 Estimated Glomerular Filtration Rate (Post-hoc Analysis)

The eGFR based on Modification of Diet in Renal Disease (MDRD)[11] was analysed for the FAS (main study) and PPAS (main study) 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).

See Section 9.7.11.3 for description of eGFR analysis in 28-week open-label extension study.

9.7.10.3.8 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.

9.7.10.4 Efficacy Variables Full FAS Population

The statistical analyses on all variables for the full-FAS population were analysed with the same analysis methods as the primary efficacy variable (Section 9.7.10.1). Custom hypotheses tests for the difference between visits were made within treatment groups. See Section 9.8.2, Changes to the planned analyses.

9.7.11 Safety Evaluation

The analysis of safety was based on the safety analysis set and the extension safety analysis set,

respectively. Safety data obtained from randomization at Visit 2 (Week 0) to the final Study Completion Visit at Visit 7/8 (Week 24) and Visit 11 (Week 52) were evaluated and variables were summarized descriptively for the 24-week double-blind study period and for the 28-week open-label extension study period (from baseline to 24 weeks, from 24 weeks to 52 weeks and from baseline to 52 weeks), respectively (see Section 9.8.2, Changes to the planned analyses).

9.7.11.1 Extent of Exposure

Duration of exposure to exenatide injections (weekly) and dapagliflozin tablets (once daily) was summarised by treatment.

9.7.11.2 Laboratory Safety

Chemistry, haematology and urinalysis were 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 and Estimated Glomerular Filtration Rate

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.

Descriptive statistics of creatinine clearance (µkat/L) is presented by treatment group including mean change from baseline and corresponding 95% confidence interval for the extension safety analysis set (see Section 9.8.2, Changes to the planned analyses).

In addition, descriptive statistics of eGFR (mL/min/1.73m^2) is presented by treatment group including mean change from baseline and corresponding 95% confidence interval for the extension safety analysis set (see Section 9.8.2, Changes to the planned analyses).

9.7.11.4 Adverse Events

AEs were coded by SOC and PT according to MedDRA version 18.0 by PCG. 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 an 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.

No sample size calculations were performed for the 28-week open-label extension study as all subjects participating in the 24-week double-blind study were offered to participate (if eligible) in the

extension part. The number of subjects willing to enter the 28-week extension study was estimated to be between 30 to 40 subjects.

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 are presented with one decimal and a percentage sign. Confidence interval bounds are presented with the same number of decimals as the corresponding point estimate, and p-values are 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 one substantial amendment to the original CSP (dated 27 Oct 2014). The details of the amendment are specified in Table 9 (page 65).

The changes to the original CSP were not implemented until regulatory and ethical approvals had been received. 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.

9.8.2 Changes to the Planned Analyses

Amendments to the original SAP (dated 02 Oct 2015) were made after code-breaking and database-lock. The final version of the SAP (dated 13 May 2016) is provided in Appendix 16.1.9.

A summary of changes to the planned analyses of the 24-week double-blind main study, with reason for change included, is presented in Table 10 (page 66).

For the open-label 28-week extension study, the CSP specified descriptive statistics only, however, a selected number of variables were analysed (see details in the summary of changes to the planned analyses, Table 11, page 66).

In addition, a clean file protocol amendment was issued 12 Oct 2016, after the second database lock, to define and describe a new analysis population (full-FAS) and the analyses to be performed. This change was done to strengthen findings from the analyses in the extension part of the trial (see details in Table 11, page 66).

Another clean file protocol amendment was issued 01 Dec 2016 due to the discovery of a malfunction in the medical coding system (built in WHO-DD dictionary) in the e-CRF/Viedoc™, resulting in updated coding of prior and concomitant medications (see details in Table 11, page 66).

9.8.3 Post-hoc Analyses

A list of additional efficacy variables added to the original SAP (dated 02 Oct 2015) after code-breaking are presented in Table 12 (page 69). The final version of the SAP (dated 13 May 2016) is provided in Appendix 16.1.9.

Table 9 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.

Table 10 Summary of changes to planned analyses – 24-week double-blind main study

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

Table 11 Summary of changes to planned analyses – 28-week open-label extension study

Scope	Change			Reason for change	Responsible
Efficacy analysis	**Treatment in double-blind 24-week study**	**Treatment in open-label 28-week study**	**Treatment labels in analysis covering the 52-week period**	Definition of treatment groups in the extension study.	Sponsor/ Biostatistician
	Dapagliflozin 10mg + Exenatide 2mg	Dapagliflozin 10mg + Exenatide 2mg	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg		
	Placebo	Dapagliflozin 10mg + Exenatide 2mg	Placebo/Dapa 10mg+Exe 2mg		
Efficacy analysis	The extension full analysis set (extension-FAS) included all enrolled subjects who received at least one dose of study medication during the 28-week extended open-label treatment period, and who had a non-missing Visit 8 value and at least one post-Visit 8 value for at least one efficacy variable during the extension period. In case of severe noncompliance with the protocol a subject may be excluded from the full analysis set. The extension per-protocol analysis set (extension-PPAS) – being a subset of the full analysis set – included all subjects who had taken IPs during at least 22 weeks during the extension period and 80% - 120% of intended IPs, and who had no major protocol deviations which may affect the study outcome significantly. Thus, the extension-PPAS is a subset of the extension-FAS and consists of patients who also have fulfilled the following: 1. have sufficiently complied with the protocol, e.g. no major protocol deviations,			Definition of analysis data sets (extension-FAS and extension-PPAS) for the subjects that had participated in the optional 28-week open-label extension study.	Sponsor

Scope	Change	Reason for change	Responsible
	2. have available data at 52 weeks for the primary variable and 3. have been compliant; a duration of at least 22 weeks of IP treatment and 80% - 120% of intended IPs		
Efficacy analysis	Within-group analyses of change from baseline (Week 2, Week 0 where applicable) was performed using the analysis methods specified in efficacy evaluation section of the Statistical analysis plan, for the following time periods: • Week 0 to Week 24; • Week 24 to Week 52; • Week 0 to Week 52. The following variables were analysed: • Change from baseline in: body weight; body fat (%); waist circumference; waist/hip ratio; systolic blood pressure; diastolic blood pressure; pulse; HbA1c; fasting plasma glucose and fasting insulin • Percentage change from baseline in body weight In addition, for the treatment group Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg the following were analysed: • Impaired fasting glucose (IFG); • Impaired glucose tolerance (IGT); • Change from baseline in: glucose area under curve; insulin area under curve; glucose incremental area under curve; insulin incremental area under curve; glucose at 120 minutes during the OGTT; liver fat (%);total liver fat; abdominal visceral adipose fat; abdominal subcutaneous adipose fat; total adipose tissue and total lean tissue For the variables which were analysed descriptive statistics were also presented. In addition, descriptive statistics were presented by treatment group including mean change from baseline and corresponding 95% confidence interval for the following variables: • Glucose; Insulin; C-peptide; Total cholesterol; Low-density lipoprotein cholesterol; High-density lipoprotein cholesterol; Triglycerides and Ketones in blood.	The protocol specified descriptive statistics only for the 28-week open-label extension study, however a selected number of variables were analysed for within-group change from baseline.	Sponsor

Scope	Change	Reason for change	Responsible
Safety analysis	Disposition and demographic overview were presented for the same time periods as the efficacy variables.	The protocol specified descriptive statistics only for the extension study, however a selected number of safety variables were analysed.	Sponsor
Efficacy analysis (Clean file amendment 12 Oct 2016)	Full FAS population included all patients in the FAS population earlier defined for the main study irrespective of continuation status to the extension.	A new analysis population (Full FAS) was defined and described. The rationale behind the addition of the new analysis population was to strengthen findings from the PPAS and FAS analyses in the extension part of the trial. The extension study population might be biased towards subjects being more compliant with study protocol and dietary restrictions which in turn affects study results. Furthermore, subjects without treatment effect are believed to have prematurely terminated the study in greater extent than subjects having the opposite response after entering the trial.	Sponsor
Efficacy analysis (Clean file amendment 12 Oct 2016)	The Full FAS population was to be submitted to the same analyses as the FAS and PPAS populations in the extension study. Meaning that analyses for which data were not collected according to protocol during the extension, e.g. MRI, were to be omitted for subjects previously treated with placebo in the main study.	Description of the analyses to be performed on the new analysis population (Full FAS).	Sponsor
Analysis of prior and concomitant medications (Clean file amendment 01 Dec 2016)	A total of 26 incorrectly coded prior and concomitant medications were updated with correct coding in an external file. The correct coding were incorporated into the datasets and the old, incorrect data, were overwritten. The database in Viedoc™ was not be updated. The tables and listing of prior and concomitant medications were updated.	A total of 26 coded values for concomitant medications were indivertibly changed due to a malfunction in the e-CRF/Viedoc™ in built WHO-DD coding module. Viedoc™ selected the last ATC pathway in the uploaded dictionary even though the medical coder had selected another path in the coding module. All coded medications for which there could be more than one ATC-path were identified and listed using Viedoc™ functionality. The list was exported and checked by a medical coder to identify faulty codes and the coding was updated.	Data management

Table 12 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 for both the 24-week double-blind main study part (Visit 1 to Visit 7) and the 28-week open-label extension study part (Visit 8 to Visit 11) is presented in Section 10.1. Visit 7 of the 24-week double-blind main part corresponds to Visit 8 of the 28-week open-label part. Reasons for premature withdrawal are discussed in Section 10.1.1.

Summary tables pertaining to this section are presented in Section 14.1. Individual data listings for the extension populations are provided in Appendix 16.2.1 to Appendix 16.2.3.

Additional summary tables and individual data listings for the 24-week double-blind main study are provided in the clinical trial report for the 24-week short-term treatment period (version 1.1, dated 11 Jan 2017), in Appendix 16.5.

10.1 DISPOSITION OF SUBJECTS

An overview of the subject flow in the study (main part and extension part) is presented in Figure 2 and summary tables are provided in Section 14.1.1 (Table 84, Table 85 and Table 86).

Both study parts were conducted at a single site in Sweden. A total of 61 subjects were screened and 50 subjects were randomized in the initial 24-week double-blind main study (Figure 2 and Table 84, Section 14.1.1). Eligible subjects were randomized to 1 of 2 treatment arms, active treatment with dapagliflozin/exenatide or matching placebo, in a 1:1 ratio.

Eleven subjects were screening failures and were never randomized in the main 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 (2 subjects withdrew consent, 1 had planned surgery). There were no non-eligible subjects randomized in the study and all randomized subjects received study medication.

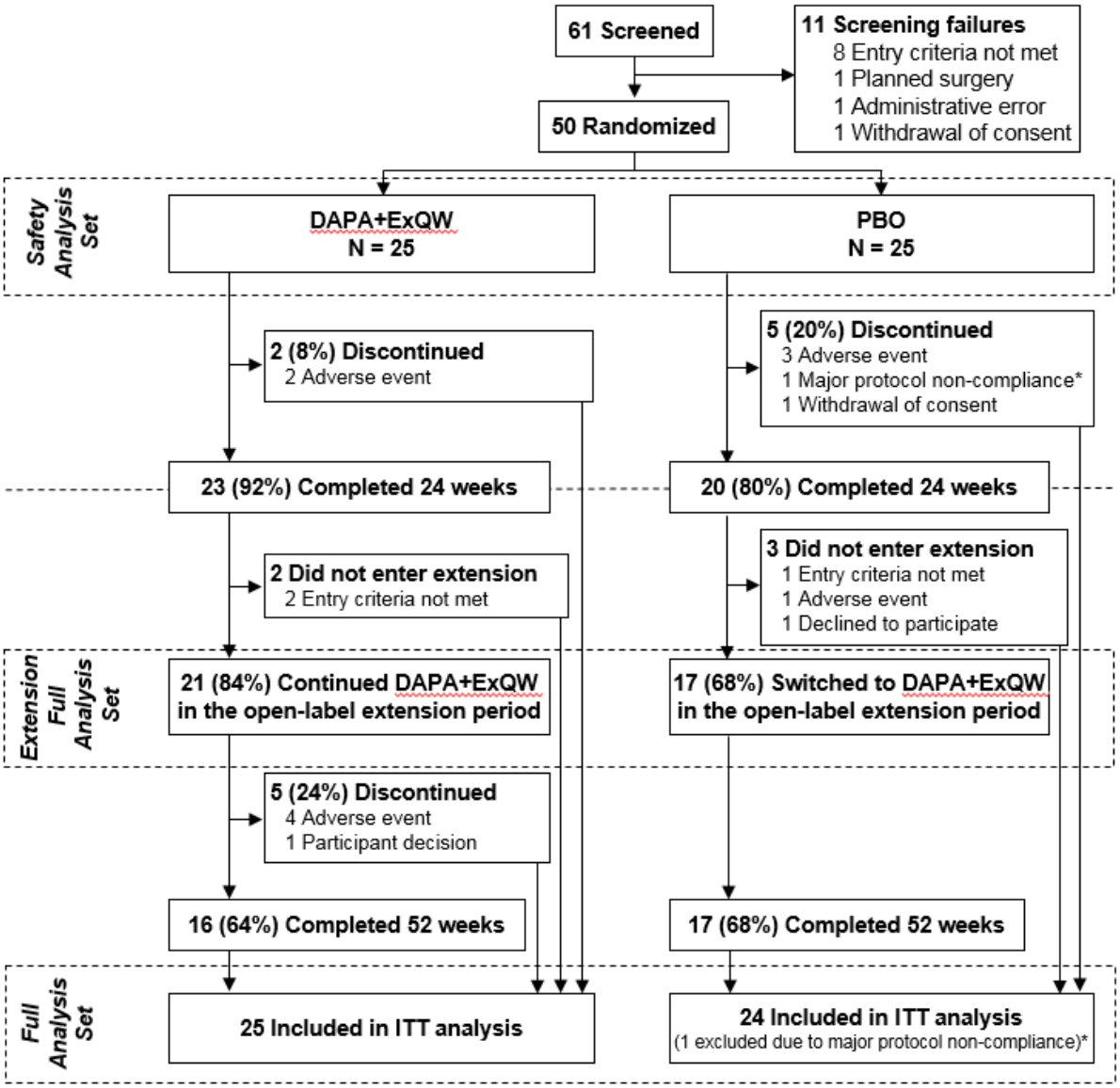
In the 24-week double-blind main study, the first subject was screened on 8 Dec 2014, the first subject was dosed 19 Dec 2014 and the last subject completed the last visit of the initial 24-week treatment period on 31 Aug 2015. In total, 43 subjects (86.0%) completed the 24-week double-blind main study: 23 subjects (92.0%) in the dapagliflozin/exenatide group and 20 subjects (80.0%) in the placebo group.

A total of 39 of the 43 subjects who completed the main study were screened for the optional 28-week open-label extension study, whereof 38 subjects (21 in Dapa+Exe/Dapa+Exe group [Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg]) and 17 in Placebo/Dapa+Exe group [Placebo/ Dapa 10mg+Exe 2mg]) were eligible and received study treatment with dapagliflozin and exenatide (Figure 2 and Table 85, Section 14.1.1). One subject did not meet the eligibility criteria (Subject E114 [Placebo/Dapa+Exe group] had laboratory values indicating diabetes, i.e. exclusion criterion No. 5 was met) and was therefore discontinued from the extension study before receiving any study treatment.

The first subject was enrolled and dosed in the extension study on 04 Jun 2015 (Visit 8/Week 24), and the last subject completed the last visit (Visit 11/Week 52) on 14 Mar 2016.

In total, 33 subjects (84.6% of 39 enrolled) completed the extension study: 16 subjects (76.2% of 21 enrolled) in the group that received dapagliflozin/exenatide in the main study and 17 subjects (94.4% of 18 enrolled) in the group that received placebo in the main study. Subjects that withdrew from the extension study are further discussed in Section 10.1.1.

Figure 2 **Disposition of subjects**
(24-week double-blind main study and 28-week open-label extension study)



DAPA+ExQW=Dapagliflozin+exenatide, ITT=intention to treat, PBO=placebo
*See Section 10.1.1.
Source: Table 13, Table 14, Table 16, Table 17, Table 84, Table 85 and Appendix 16.2.1 to 16.2.3.

10.1.1 Reasons for Premature Withdrawals

Seven subjects (14.0% of the subjects in the main study) were prematurely withdrawn during the 24-week double-blind main study: 2 subjects (8.0%) in the dapagliflozin/exenatide group and 5 subjects (20.0%) in the placebo group (Table 13). 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. One subject (E161; placebo) withdrew consent whereas one subject (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. For more details on the subjects withdrawn from the initial 24-week study period, see the clinical trial report for the 24-week short-term treatment period (version 1.1, dated 11 Jan 2017), provided in Appendix 16.5.

Five subjects (12.8% of the subjects enrolled in the extension study), all in the group that received dapagliflozin/exenatide in the main study, were prematurely withdrawn during the 28-week open-label extension study (Table 14). Four of the 5 subjects (E104, E105, E150 and E155) were prematurely withdrawn due to the occurrence of AEs or SAEs (subjects E104 and E150 were in addition non-compliant to IP, see Section 11.3) and 1 subject (E118) discontinued the study medication on own record due to perceived lack of efficacy (see eCRF, individual subject data listings in Appendix 16.2.1 and 16.2.3, and Section 12.4.4 for more details on withdrawals due to AE).

An individual subject data listing of premature withdrawals from the 28-week open-label extension study is provided in Appendix 16.2.1.

Table 13 Primary reasons for premature withdrawals. Randomized subjects (24-week double-blind main study)

	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.
[b] Subject E129 (placebo) was prematurely withdrawn due to severe non-compliance with the protocol (primary reason for discontinuation. Concomitantly, the IP was withdrawn due to AE.
[c] Subject E161 (placebo) prematurely terminated the study due to withdrawal of consent.
Source: Clinical trial report for the 24-week short-term treatment period (version 1.1, dated 11 Jan 2017), Appendix 16.5.

Table 14 Premature withdrawals. Extension enrolled subjects (28-week open-label extension study)

	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=18)	Total (N=39)
Prematurely withdrawn[1]	5 (23.8%)	0	5 (12.8%)
Primary reason			
Adverse Event[2, 3]	4 (80.0%)		4 (80.0%)
Patient discontinued study medication on own initiative due to perceived lack of efficacy[2, 4]	1 (20.0%)		1 (20.0%)

[1]Percentages are based on the number of enrolled subjects.
[2]Percentages are based on the number of withdrawn subjects.
[3]Subjects E104, E105, E150 and E155 were prematurely withdrawn due to adverse events. The nature and severity of these adverse events are further discussed in Section 12.4.4.
[4]Subject E118

10.2 PROTOCOL DEVIATIONS

10.2.1 Protocol Deviations

Prior to both database locks, all protocol deviations were reviewed for potential effect on the study results by the project manager at PCG 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 any of the analysis data sets.

No major protocol deviations were reported in the extension part of the study (Table 15). A total of 28 protocol deviations, all classified as minor, were reported for 21 subjects (53.8% of the 39 enrolled into extension study) during the entire study period. Most of the minor protocol deviations (24 deviations, 19 subjects) referred to a visit or assessment performed outside the allowed visit window as detailed in the protocol (±3 days) and single reported deviations referred to training (syringe administration) not provided, assessment (anthropometry) not performed and study medication not returned.

A complete list of all protocol deviations registered in the eCRF during entire study for subjects enrolled into the 28-week open-label extension study is provided in Appendix 16.2.2.

Table 15 Protocol deviations. Extension enrolled subjects

	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)		Placebo/ Dapa 10mg+Exe 2mg (N=18)		Total (N=39)	
	n (%)	m	n (%)	m	n (%)	m
Major	0	0	0	0	0	0
Minor	14 (66.7%)	19	7 (38.9%)	9	21 (53.8%)	28

Percentages are based on the number of enrolled subjects.
n is the number of subjects, m is the number of deviations.

10.2.2 Prohibited Medications

Treatment with any drug known to affect body weight within the last month, e.g. systemic glucocorticoids, antipsychotics or orlistat was regarded as prohibited medication.

Four subjects received systemic glucocorticoids for treatment of AEs/SAEs during the study (see the eCRF and individual data listings of concomitant medications, Appendix 16.2.4):

- Subject E122 and E160 received injections of glucocorticoids during the main 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 during the main study. 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). (For more details, see the clinical trial report for the 24-week short-term treatment period (version 1.1, dated 11 Jan 2017), provided in Appendix 16.5.
- Subject E155 received betamethasone sodium phosphate (glucocorticoid, drug name Betapred) as treatment for SAE (angioedema) during the extension part. The SAE caused the subject's withdrawal from the extension 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 ANALYSED

In the 24-week double-blind main part of the study, 3 analysis sets were defined: the safety, FAS (main study) and PPAS (main study). In the 28-week open-label extension part, corresponding extension safety, extension-FAS and extension-PPAS were defined an in addition a 4th analysis set, the full-FAS.

For definitions of the analysis populations, see Section 9.7.2.

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

Individual subject data listings for the extension study populations are provided in Appendix 16.2.1 and 16.2.3.

Individual subject data listings for the main study populations are included in the clinical trial report for the 24-week short-term treatment period (version 1.1, dated 11 Jan 2017), provided in Appendix 16.5.

11.1.1 Data Sets Analysed in the 24-week Double-Blind Main Study

In the analyses of the main study data, all 50 randomized subjects were included in the safety analysis set, 49 subjects were included in the FAS (main study) and 42 subjects were included in the PPAS (main study) (Table 16).

The decision to include or exclude subjects from each analysis set was taken by the Sponsor and the Project manager under blinded conditions (main study only) 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 (main study): 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 (main study) and the PPAS (main study) due to severe non-compliance with the protocol regarding diet instructions. For more details, see the the clinical trial report for the 24-week short-term treatment period (version 1.1, dated 11 Jan 2017), provided in Appendix 16.5.

Table 16 Analysis datasets (24-week double-blind main study)

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 84, Section 14.1.1

11.1.2 Data Sets Analysed in the 28-week Open-Label Extension Study

In the analyses of the extension study data, all 38 eligible subjects were included in the extension safety analysis set as well as the extension-FAS and 30 subjects were included in the extension-PPAS (Table 17).

The extension-PPAS population consisted of subject who:

1. Had sufficiently complied with the protocol, e.g. no major protocol deviations
2. Had available data at 52 weeks for the primary variable
3. Had been compliant, i.e. a duration of at least 22 weeks of IP treatment and 80% to 120% of intended IPs

Eight subjects were excluded from the extension-PPAS (Table 18): 4 subjects (E104, E105, E150 and E155) were withdrawn from the extension study due to AEs (E104 and E155) or SAEs (E105 and E150), 3 subjects (E127, E142, E157) were non-compliant to IP (E104 and E150 were also non-compliant to IP, main reason for exclusion from extension-PPAS was withdrawal due to AE) and 1 subject (E118) was non-compliant to the protocol (as the subject discontinued the study medication on own initiative due to perceived lack of efficacy).

For more details, see Section 10.1.1 (Reasons for premature withdrawals), Section 11.3 (Measurement of treatment compliance) and Section 12.4.4 (Withdrawals due to AEs).

The full-FAS population included all subjects in the FAS (main study) population earlier defined for the main study irrespective of continuation status to the extension part of the study, i.e. 49 subjects (see Section 11.1.1 and Table 16).

Table 17 Analysis datasets (28-week open-label extension study)

Analysis population	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg	Placebo/ Dapa 10mg+Exe 2mg	Total
Extension safety analysis set	21 (100.0%)	17 (94.4%)	38 (97.4%)
Extension full analysis set, Extension-FAS	21 (100.0%)	17 (94.4%)	38 (97.4%)
Extension per-protocol analysis set, Extension-PPAS	15 (71.4%)	15 (83.3%)	30 (76.9%)

Percentages are based on the number of enrolled subjects.
Source: Table 85, Section 14.1.1

Table 18 Summary of main reasons for exclusion of subjects from the extension per protocol analysis set

Subject ID	Treatment group	Reason for exclusion
E104[a]	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg	Prematurely withdrawn due to AE
E105[a]	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg	Prematurely withdrawn due to SAEs
E118[b]	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg	Non-compliant with protocol
E127[c]	Placebo/ Dapa 10mg+Exe 2mg	Non-compliant with IP
E142[c]	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg	Non-compliant with IP
E150[a]	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg	Prematurely withdrawn due to AEs
E155[a]	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg	Prematurely withdrawn due to SAE
E157[c]	Placebo/ Dapa 10mg+Exe 2mg	Non-compliant with IP

[a] Subjects prematurely withdrawn from the study due to AE lacked available efficacy data at week 52 and were excluded from the extension-PPAS:

E104 (eye allergy, mild AE, unlikely related to IP) (also non-compliant with IP, see Section 11.3)
E105 (gastrointestinal haemorrhage, SAE, moderate, unlikely related to IP and adenocarcinoma of colon, SAE, severe, unlikely related to IP)
E150 (dizziness, fatigue and nausea, all AEs of mild intensity and possibly related to IP) (also non-compliant with IP, see Section 11.3)
E155 (angioedema, SAE, severe, possibly related to IP)

[b] Subject E118 discontinued study medication on own initiative due to perceived lack of efficacy

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

AE=adverse event, Dapa=dapagliflozin, Exe=exenatide, IP=Investigational product, PPAS=Per protocol analysis set

Source: Appendix 16.2.1, 16.2.3 and 16.2.7

11.2 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

The results from demographics, body weight and other anthropometric measures at baseline, obesity history (main part only), medical history, concurrent diseases, prior and concomitant procedures and prior and concomitant medications are described in Section 11.2.1 to Section 11.2.8.

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

Summary tables of the demographics and other baseline characteristics are provided for extension-FAS and extension-PPAS in Section 14.1 and individual subject data listings are provided in Appendix 16.2.4.

Summary tables and individual subject data listings for the 24-week double-blind main study are provided in the clinical trial report for the 24-week short-term treatment period (version 1.1, dated 11 Jan 2017), Appendix 16.5.

11.2.1 Demographics

The demographics for the extension-FAS are summarized in Table 19. The corresponding table for the extension safety analysis set is provided in Section 14.1.2 (Table 87). Individual subject data listings of the demographics are provided in Appendix 16.2.4.

All 38 subjects in the extension-FAS, 24 females and 14 males were treated with IP. The ratio of females to males was 13 to 8 in the group that received dapagliflozin/exenatide in the main study and 11 to 6 in the group that received placebo.

In terms of race, the majority of subjects was White (94.7%), 1 subject was Asian (2.6%) and 1 was Iranian (reported as other; 2.6%).

The age of all subjects in the extension study 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 in main study) and 50 years (placebo in main study).

No pregnancies occurred during the main study period or during the extension study period. Eight of 24 female subjects were of child-bearing potential.

Overall, in the main study and the extension study, the demographics were well balanced between the treatment groups.

Table 19 Demographics. Extension full analysis set

	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)	Total (N=38)
Age (years)[1]			
n/nmiss	21/0	17/0	38/0
Mean (SD)	53.4 (14.2)	49.8 (12.9)	51.8 (13.6)
Median	58.0	52.0	53.5
Q1, Q3	42.0, 65.0	43.0, 57.0	42.0, 65.0
Min, Max	20, 69	23, 68	20, 69
Gender[1]			
Female	13 (61.9%)	11 (64.7%)	24 (63.2%)
Male	8 (38.1%)	6 (35.3%)	14 (36.8%)
Race[1]			
American Indian or Alaska Native	0	0	0
Asian	1 (4.8%)	0	1 (2.6%)
Black or African American	0	0	0
Native Hawaiian of other Pacific Islander	0	0	0
White	19 (90.5%)	17 (100.0%)	36 (94.7%)
Other	1 (4.8%)	0	1 (2.6%)
Childbearing potential[1]			
Yes	4 (19.0%)	4 (23.5%)	8 (21.1%)
No	9 (42.9%)	7 (41.2%)	16 (42.1%)
Reason[2]			
Postmenopausal	7 (77.8%)	6 (85.7%)	13 (81.3%)
Surgically sterile	0	1 (14.3%)	1 (6.3%)
Premenarcheal	1 (11.1%)	0	1 (6.3%)
Other	1 (11.1%)	0	1 (6.3%)

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
[1]Percentages are based on the number of subjects in the applicable analysis set.
[2]Percentages are based on the number of females without childbearing potential.

11.2.2 Body Weight and Other Anthropometric Measures at Baseline

The assessments of baseline body weight and other anthropometric measures (waist circumference, BMI and WHR) for the extension-FAS and extension safety analysis sets are provided in the corresponding efficacy results sections (Section 11.4.1 [body weight] and Section 11.4.3.5 [other anthropometric measures]).

The mean body weight at baseline (week 0) was 106.4 kg (SD=15.7) in the group that received dapagliflozin/exenatide in the 24-week main study and 102.9 kg (SD=14.7) in the group that received placebo (Table 22, Section 11.4.1).

The mean waist circumference was 116.4 cm (SD=11.5) and 114.2 cm (SD=12.6) (Table 57, Section 11.4.3.5.1) and the mean BMI was 35.7 kg/m^2 (SD=3.0) and 34.9 kg/m^2 (SD=3.4), in the dapagliflozin/exenatide and the placebo groups, respectively (Table 61, Section 11.4.3.5.3).

The mean WHR at baseline (week 0) was 0.96 in the group that received dapagliflozin/exenatide in the main study and 0.97 in the group that received placebo in the main study (Table 60, Section 11.4.3.5.2).

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

11.2.3 Medical History

Summary tables pertaining to this section are presented in Section 14.1.3 (Table 88 for the extension safety analysis set and Table 89 for the extension-FAS). Individual subject data listings of the medical history are provided in Appendix 16.2.4.

Ten subjects (47.6%) in the group that received dapagliflozin/exenatide in the main study, and 5 subjects (29.4%) in the group that received placebo, reported previous medical history.

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 (maximum 3 subjects in total).

Overall, in the main study and the extension study, 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.

11.2.4 Concurrent Diseases

Summary tables pertaining to this section are presented in Section 14.1.4 (Table 90 for the extension safety analysis set and Table 91 for the extension-FAS). Individual subject data listings of concurrent diseases are provided in Appendix 16.2.4.

Concurrent diseases were reported by 16 subjects (76.2%) that received dapagliflozin/exenatide in the main study and 12 subjects (70.6%) in the group that received placebo. The most common type of concurrent diseases (SOCs) were:

- Musculoskeletal and connective tissue disorders: 4 vs 5 subjects in the Dapa+Exe/Dapa+Exe and Placebo/Dapa+Exe groups, respectively
- Gastrointestinal disorders: 6 vs 2 subjects in the Dapa+Exe/Dapa+Exe and Placebo/Dapa+Exe groups, respectively
- Respiratory, thoracic and mediastinal disorders: 4 vs 3 subjects in the Dapa+Exe/Dapa+Exe and Placebo/Dapa+Exe groups, respectively
- Vascular disorders: 4 vs 1 subject(s) in the Dapa+Exe/Dapa+Exe and Placebo/Dapa+Exe groups, respectively

All other SOCs and PTs were reported by 3 subjects or fewer in each treatment group (maximum of 5 subjects in total).

Overall, in the main study and the extension study, 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.

11.2.5 Prior Procedures

Summary tables pertaining to this section are presented in Section 14.1.5 (Table 92 for the extension safety analysis set and Table 93 for the extension-FAS). Individual subject data listings of prior procedures are provided in Appendix 16.2.4.

Prior surgical or medical procedures were reported by 12 subjects (57.1%) that received dapagliflozin/exenatide in the main study and by 7 subjects (41.2%) that received placebo. The most

common conditions reported as prior procedure, based on PTs, were: appendicectomy (n=7), cholecystectomy (n=3), knee arthroplasty (n=3) and knee operation (n=3).

Overall, in the main study and the extension study, 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.

11.2.6 Concomitant Procedures

Summary tables pertaining to this section are presented in Section 14.1.6 (Table 94 for the extension safety analysis set and Table 95 for the extension-FAS). Individual data listings for the concomitant procedures are provided in Appendix 16.2.4.

Concomitant surgical or medical procedures were reported by 4 subjects (19.0%) that received dapagliflozin/exenatide in the main study and by 4 subjects (23.5%) that received placebo. All procedures were reported by single subjects.

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

11.2.7 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 14.1.7 (Table 96 for the extension safety analysis set and Table 97 for the extension-FAS). Individual data listings of prior medications are provided in Appendix 16.2.4.

Prior medications were reported by 7 subjects (36.3%) that received dapagliflozin/exenatide in the main study and 3 subjects (17.6%) that received placebo. The most common type of prior medications, based on therapeutic main group was:

- Antiobesity preparations (excluding diet products): 4 subjects (19.0%) vs 1 subject (5.9%) in the Dapa+Exe/Dapa+Exe and Placebo/Dapa+Exe groups, respectively. The medications taken were orlistat (n=3) and sibutramine hydrochloride (n=3).

All other prior medications were reported by single subjects.

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.

11.2.8 Concomitant Medication

For definitions of prior and concomitant medications, refer to section 9.4.7. Summary tables pertaining to this section are presented in Section 14.1.8 (Table 98 to Table 100 for the extension safety analysis set and Table 99 to Table 103 for the extension-FAS). Individual subject data listings of concomitant medications are provided in Appendix 16.2.4.

During the 52 weeks study period, 20 subjects (95.2%) that received dapagliflozin/exenatide in the main study and 16 subjects (94.1%) that received placebo reported at least one concomitant medication (Table 100, Section 14.1.8).

The most common types of concomitant medications, based on therapeutic main group and preferred names, during all three study periods (baseline to 24 weeks, 24 weeks to 52 weeks and baseline to 52 weeks) were (Table 98 to Table 100, Section 14.1.8):

- Analgesics:
  10 subjects (47.6%) vs 6 subjects (35.3%), in the groups that received dapagliflozin/exenatide and placebo, respectively, from baseline to 24 weeks;

  2 subjects (9.5%) vs 3 subjects (17.6%) during the 24 weeks to 52 weeks period;

11 subjects (52.4%) vs 8 subjects (47.1%) during the whole 52 week study period.
The most common medication was paracetamol (used by 16 subjects between baseline and week 52).

- Anti-inflammatory and antirheumatic products:
  6 subjects (28.6%) vs 6 subjects (35.3%), in the groups that received dapagliflozin/exenatide and placebo, respectively, from baseline to 24 weeks;

  2 subjects (9.5%) vs 3 subjects (17.6%) during the 24 weeks to 52 weeks period;

  7 subjects (33.3%) vs 8 subjects (47.1%) during the whole 52 week study period.
  The most common medication was ibuprofen (used by 7 subjects between baseline and week 52).

- Drugs for acid-related disorders:
  7 subjects (33.3%) vs 2 subjects (11.8%), in the groups that received dapagliflozin/exenatide and placebo, respectively, from baseline to 24 weeks;

  3 subjects (14.3%) vs 2 subjects (11.8%) during the 24 weeks to 52 weeks period;

  7 subjects (33.3%) vs 3 subjects (17.6%) during the whole 52 week study period.
  The most common medication was omeprazole (used by 6 subjects between baseline and week 52).

No subjects used any antiobesity preparations (e.g. orlistat) during the main study period or the extension study period. For details on the use of prohibited medications during the study, refer to Section 10.2.2.

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

11.3 MEASUREMENTS OF TREATMENT COMPLIANCE

Treatment compliance (number of doses received relative to doses planned) is summarized by treatment group for the extension-FAS in Table 20 (baseline to 24 weeks) and Table 21 (24 weeks to 52 weeks) and for the extension safety analysis set in Section 14.1.9 (Table 104 and Table 105). Individual subject data listings for compliance are provided in Appendix 16.2.5.

Summary tables and individual data listings for the 24-week double-blind main study are provided in the clinical trial report for the 24-week short-term treatment period (version 1.1, dated 11 Jan 2017), Appendix 16.5.

Non-compliance was defined as taking less than 80% or more than 120% of the prescribed dose of IP. Five subjects (E104, E127, E142, E150 and E157) were identified as non-compliant with the protocol during the extension part, as they had taken less than 80% of the planned doses for at least one of the IPs. Subject E104 took 72.1% of the tablets and 78.2% of the injections, subject E127 took 82.8% of the tablets and 75.9% of the injections, subject E142 took 67.0% of the tablets and 94.5% of the injections, subject E150 took 56.4% of the tablets and 50.9% of the injections and subject E157 took 107.1% of the tablets and 75.0% of the injections (see individual data listings for treatment compliance in Appendix 16.2.5).

In general, the compliance was high during the study, the mean was above 98% during the baseline to 24-weeks period and above 93% during the 24 to 52 weeks period, for both IPs (Table 20 and Table 21).

Equal results were obtained for the extension safety analysis set, see Section 14.1.9 (Table 104 and Table 105).

Table 20 Compliance - Baseline to 24 weeks. Extension full analysis set

	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Injection compliance (%)		
n/nmiss	21/0	17/0
Mean (SD)	100.8 (4.0)	100.0 (2.0)
Median	101.8	100.0
Q1, Q3	100.0, 102.9	99.4, 100.6
Min, Max	86, 104	96, 104
Tablet compliance (%)		
n/nmiss	21/0	17/0
Mean (SD)	98.9 (7.8)	99.1 (4.6)
Median	100.6	98.8
Q1, Q3	98.8, 101.2	97.7, 100.6
Min, Max	81, 116	90, 112

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

Table 21 Compliance - 24 to 52 weeks. Extension full analysis set

	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Injection compliance (%)		
n/nmiss	21/0	17/0
Mean (SD)	94.7 (12.0)	97.0 (8.5)
Median	100.0	100.0
Q1, Q3	92.9, 100.5	99.5, 100.5
Min, Max	51, 104	75, 106
Tablet compliance (%)		
n/nmiss	21/0	17/0
Mean (SD)	93.3 (13.5)	98.6 (6.3)
Median	98.0	98.0
Q1, Q3	88.7, 100.5	96.4, 100.0
Min, Max	56, 113	83, 113

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 analyses of the primary, secondary and exploratory efficacy variables are presented in Section 11.4.1 to Section 11.4.3, statistical and analytical issues, tabulation of individual response and by-patient display in Section 11.4.4 to Section 11.4.6. The efficacy conclusions are presented in Section 11.5 and in Section 13.2.1 (overall conclusions).

Data from baseline to week 24, from week 24 to 52 and from baseline to week 52 are presented in the text, however data collected at other time points are available in the tables. Tables for extension-FAS are in general presented in the body text of the report if statistically significant results were obtained. Other extension-FAS tables and all corresponding tables for the extension-PPAS are provided in Section 14.2.

Individual subject data listings for all efficacy variables for the extension-FAS and extension-PPAS are provided in Appendix 16.2.6.

The results of the analyses of the primary and secondary efficacy variables on the full-FAS are summarized in the corresponding sections below and tables are included in Section 14.2.2 and Section 14.2.4. Tables for all primary, secondary and exploratory efficacy results, for full-FAS, are provided in Appendix 16.6.

Tables and individual subject data listings for the main study (FAS and PPAS populations) are provided in the clinical trial report for the 24-week short-term treatment period (version 1.1, dated 11 Jan 2017), Appendix 16.5.

11.4.1 Primary Efficacy Variable

Adjusted mean change in body weight from baseline to week 24, from week 24 to 52 and from baseline to week 52 – Extension-FAS and extension-PPAS

Body weight measurements were performed at screening, at week 0 (baseline) and at weeks 4, 8, 12, 24, 38 and 52.

A statistically significant reduction in mean body weight between baseline (week 0) and week 24 was observed within the group that received dapagliflozin/exenatide (adjusted mean change: -4.3 kg, p<0.0001), but not within the placebo group (adjusted mean change: -0.8 kg) (Table 22).

In the 28 week open-label extension part conducted between week 24 and week 52, there was no further statistically significant weight reduction within the group that had been on active treatment for 24 + 28 weeks (Dapa+Exe/Dapa+Exe group: -1.1 kg) (Table 23). A statistically significant weight reduction was, however, observed within the group that received placebo in the main study and active treatment in the extension study part (Placebo/Dapa+Exe group: -4.8 kg, p<0.0001).

Overall, from baseline (week 0) to week 52, there was a statistically significant reduction in body weight within both groups (Dapa+Exe/Dapa+Exe group: -5.3 kg, p=0.0013; Placebo/Dapa+Exe group: -5.4 kg, p=0.0023) (Table 24). The main weight reduction was observed during the first 12 or 14 weeks (at 38 weeks for Placebo/Dapa+Exe group) of treatment with dapagliflozin/exenatide in both groups.

There were corresponding statistically significant reductions in mean body weight shown within the respective groups for the extension-PPAS, see Section 14.2.1 (Table 106 to Table 108).

Adjusted mean change in body weight from baseline to week 24, from week 24 to 52 and from baseline to week 52 – Full-FAS

For the full-FAS population, a corresponding statistically significant reduction in mean body weight between baseline (week 0) and week 24 was observed within the group that received dapagliflozin/exenatide in the main part (-4.5 kg, p<0.0001), but not within the group that received placebo (-0.34 kg) (Table 109, Section 14.2.2).

Between week 24 and week 52, there was no further statistically significant weight reduction for full-FAS within the Dapa+Exe/Dapa+Exe group (-1.2 kg), however within the Placebo/Dapa+Exe group, a statistically significant weight reduction was observed (-3.8 kg, p=0.0006) (Table 109, Section 14.2.2).

In the full-FAS population, there was a statistically significant reduction in mean body weight from baseline (week 0) to week 52, within both groups (Dapa+Exe/Dapa+Exe group: -5.7 kg, p=0.0003; Placebo/Dapa+Exe group: -4.2 kg, p=0.0088) (Table 109, Section 14.2.2).

Table 22 Body weight (kg) and adjusted mean change from baseline to 24 weeks. Extension full analysis set

Body weight (kg)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Baseline		
n/nmiss	21/0	17/0
Mean (SD)	106.43 (15.73)	102.91 (14.69)
Median	108.10	98.00
Q1, Q3	98.30, 115.00	94.50, 108.60
Min, Max	82.0, 142.8	82.3, 134.0
4 weeks		
n/nmiss	21/0	17/0
Mean (SD)	105.72 (15.97)	102.15 (14.87)
Median	105.70	96.80
Q1, Q3	94.90, 116.10	93.00, 109.40
Min, Max	79.0, 140.8	81.9, 133.6
Adjusted mean change (95% CI)	-0.80 (-1.58, -0.02)	-0.80 (-1.63, 0.04)
p-value	0.0439	0.0622
8 weeks		
n/nmiss	21/0	17/0
Mean (SD)	104.58 (15.82)	102.39 (14.89)
Median	102.30	96.50
Q1, Q3	92.50, 115.90	93.40, 109.90
Min, Max	76.7, 138.7	81.9, 134.8
Adjusted mean change (95% CI)	-1.94 (-3.00, -0.88)	-0.55 (-1.71, 0.61)
p-value	0.0007	0.3392
12 weeks		
n/nmiss	21/0	17/0
Mean (SD)	102.84 (16.41)	102.04 (14.90)
Median	98.70	96.50
Q1, Q3	91.60, 113.50	92.90, 109.60
Min, Max	74.5, 138.1	81.1, 134.8
Adjusted mean change (95% CI)	-3.68 (-5.00, -2.35)	-0.91 (-2.36, 0.55)
p-value	<.0001	0.2153
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	102.19 (17.70)	102.18 (14.50)
Median	98.50	95.60
Q1, Q3	90.40, 112.10	93.80, 109.70
Min, Max	75.0, 141.9	83.3, 134.6
Adjusted mean change (95% CI)	-4.33 (-6.11, -2.55)	-0.76 (-2.72, 1.20)
p-value	<.0001	0.4379

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 23 Body weight (kg) and adjusted mean change from 24 weeks to 52 weeks. Extension full analysis set

Body weight (kg)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	102.19 (17.70)	102.18 (14.50)
Median	98.50	95.60
Q1, Q3	90.40, 112.10	93.80, 109.70
Min, Max	75.0, 141.9	83.3, 134.6
38 weeks		
n/nmiss	19/2	17/0
Mean (SD)	101.12 (18.89)	98.59 (14.00)
Median	98.80	93.90
Q1, Q3	83.30, 119.50	89.30, 105.40
Min, Max	75.1, 140.0	80.9, 132.6
Adjusted mean change (95% CI)	-0.41 (-1.87, 1.05)	-3.76 (-5.33, -2.20)
p-value	0.5742	<.0001
52 weeks		
n/nmiss	17/4	17/0
Mean (SD)	98.71 (20.61)	97.51 (14.08)
Median	95.40	92.60
Q1, Q3	82.30, 109.90	88.40, 105.50
Min, Max	72.2, 143.0	80.5, 134.1
Adjusted mean change (95% CI)	-1.05 (-3.06, 0.95)	-4.84 (-6.93, -2.75)
p-value	0.2937	<.0001

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 24 Body weight (kg) and adjusted mean change from baseline to 52 weeks. Extension full analysis set

Body weight (kg)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)	Placebo/Dapa 10mg+Exe 2mg (N=17)
Baseline		
n/nmiss	21/0	17/0
Mean (SD)	106.43 (15.73)	102.91 (14.69)
Median	108.10	98.00
Q1, Q3	98.30, 115.00	94.50, 108.60
Min, Max	82.0, 142.8	82.3, 134.0
4 weeks		
n/nmiss	21/0	17/0
Mean (SD)	105.72 (15.97)	102.15 (14.87)
Median	105.70	96.80
Q1, Q3	94.90, 116.10	93.00, 109.40
Min, Max	79.0, 140.8	81.9, 133.6
Adjusted mean change (95% CI)	-0.81 (-1.59, -0.03)	-0.78 (-1.62, 0.05)
p-value	0.0434	0.0658
8 weeks		
n/nmiss	21/0	17/0
Mean (SD)	104.58 (15.82)	102.39 (14.89)
Median	102.30	96.50
Q1, Q3	92.50, 115.90	93.40, 109.90
Min, Max	76.7, 138.7	81.9, 134.8
Adjusted mean change (95% CI)	-1.95 (-3.01, -0.88)	-0.54 (-1.71, 0.62)
p-value	0.0007	0.3500
12 weeks		
n/nmiss	21/0	17/0
Mean (SD)	102.84 (16.41)	102.04 (14.90)
Median	98.70	96.50
Q1, Q3	91.60, 113.50	92.90, 109.60
Min, Max	74.5, 138.1	81.1, 134.8
Adjusted mean change (95% CI)	-3.68 (-5.01, -2.36)	-0.90 (-2.36, 0.56)
p-value	<.0001	0.2208
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	102.19 (17.70)	102.18 (14.50)
Median	98.50	95.60
Q1, Q3	90.40, 112.10	93.80, 109.70
Min, Max	75.0, 141.9	83.3, 134.6
Adjusted mean change (95% CI)	-4.33 (-6.11, -2.56)	-0.75 (-2.71, 1.21)
p-value	<.0001	0.4437
38 weeks		
n/nmiss	19/2	17/0
Mean (SD)	101.12 (18.89)	98.59 (14.00)
Median	98.80	93.90
Q1, Q3	83.30, 119.50	89.30, 105.40
Min, Max	75.1, 140.0	80.9, 132.6
Adjusted mean change (95% CI)	-4.51 (-7.08, -1.93)	-4.34 (-7.16, -1.52)

Body weight (kg)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)	Placebo/Dapa 10mg+Exe 2mg (N=17)
p-value	0.0011	0.0036
52 weeks		
n/nmiss	17/4	17/0
Mean (SD)	98.71 (20.61)	97.51 (14.08)
Median	95.40	92.60
Q1, Q3	82.30, 109.90	88.40, 105.50
Min, Max	72.2, 143.0	80.5, 134.1
Adjusted mean change (95% CI)	-5.28 (-8.35, -2.20)	-5.42 (-8.76, -2.08)
p-value	0.0013	0.0023

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

11.4.2 Secondary Efficacy Variable

Mean Percentage Change in Body Weight from Baseline to Week 24, from Week 24 to 52 and from Baseline to Week 52 – Extension-FAS and extension-PPAS

A statistically significant reduction in mean body weight based on percentage change between baseline (week 0) and week 24 was observed within the group that received dapagliflozin/exenatide ($p<0.0001$, adjusted mean percentage change from baseline to week 24: -4.3%), but not within the placebo group (adjusted mean percentage change from baseline to week 24: -0.71%) (Table 25).

Between week 24 and week 52, there was no further statistically significant weight reduction in the group that had been on active treatment for 24 +28 weeks (Dapa+Exe/Dapa+Exe group: -1.4%) (Table 26). A statistically significant weight reduction was, however, observed within the group that received placebo in the main study and active treatment in the extension study (Placebo/Dapa+Exe group: -4.7%, $p<0.0001$).

Overall, from baseline (week 0) to week 52, there was a statistically significant reduction in mean body weight based on percentage change within both groups (Dapa+Exe/Dapa+Exe group: -5.3%, $p=0.0007$; Placebo/Dapa+Exe group: -5.2%, $p=0.0023$) (Table 27).

There were corresponding statistically significant reductions in mean body weight based on percentage change shown within the respective groups for the extension-PPAS, see Section 14.2.3 (Table 110 to Table 112).

Mean Percentage Change in Body Weight from Baseline to Week 24, from Week 24 to 52 and from Baseline to Week 52 – Full-FAS

For the full-FAS population, a corresponding statistically significant reduction in mean body weight based on percentage change between baseline (week 0) and week 24 was observed within the group that received active treatment (-4.5%, $p<0.0001$), but not within the group that received placebo (-0.27%) (Table 113, Section 14.2.4).

Between week 24 and week 52, there was no further statistically significant weight reduction for full-FAS within the Dapa+Exe/Dapa+Exe group (-1.2%) (Table 113, Section 14.2.4), however within the Placebo/Dapa+Exe group (-3.8%, $p=0.0002$).

Overall from baseline (week 0) to week 52, for full-FAS, there was a statistically significant reduction in percentage body weight within both groups (Dapa+Exe/Dapa+Exe group: -5.7%, $p=0.0002$; Placebo/Dapa+Exe group: -4.1%, $p=0.0064$) (Table 113, Section 14.2.4).

Table 25 Body weight (kg) and adjusted mean percentage change from baseline to 24 weeks. Extension full analysis set

Body weight (kg)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Baseline		
n/nmiss	21/0	17/0
Mean (SD)	106.43 (15.73)	102.91 (14.69)
Median	108.10	98.00
Q1, Q3	98.30, 115.00	94.50, 108.60
Min, Max	82.0, 142.8	82.3, 134.0
4 weeks		
n/nmiss	21/0	17/0
Mean (SD)	105.72 (15.97)	102.15 (14.87)
Median	105.70	96.80
Q1, Q3	94.90, 116.10	93.00, 109.40
Min, Max	79.0, 140.8	81.9, 133.6
Adjusted mean percentage change (95% CI)	-0.81 (-1.56, -0.05)	-0.81 (-1.62, 0.01)
p-value	0.0363	0.0516
8 weeks		
n/nmiss	21/0	17/0
Mean (SD)	104.58 (15.82)	102.39 (14.89)
Median	102.30	96.50
Q1, Q3	92.50, 115.90	93.40, 109.90
Min, Max	76.7, 138.7	81.9, 134.8
Adjusted mean percentage change (95% CI)	-1.88 (-2.90, -0.86)	-0.56 (-1.68, 0.55)
p-value	0.0006	0.3120
12 weeks		
n/nmiss	21/0	17/0
Mean (SD)	102.84 (16.41)	102.04 (14.90)
Median	98.70	96.50
Q1, Q3	91.60, 113.50	92.90, 109.60
Min, Max	74.5, 138.1	81.1, 134.8
Adjusted mean percentage change (95% CI)	-3.59 (-4.90, -2.29)	-0.91 (-2.34, 0.53)
p-value	<.0001	0.2083
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	102.19 (17.70)	102.18 (14.50)
Median	98.50	95.60
Q1, Q3	90.40, 112.10	93.80, 109.70
Min, Max	75.0, 141.9	83.3, 134.6
Adjusted mean percentage change (95% CI)	-4.34 (-6.09, -2.60)	-0.71 (-2.64, 1.22)
p-value	<.0001	0.4630

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 26 Body weight (kg) and adjusted mean percentage change from 24 weeks to 52 weeks. Extension full analysis set

Body weight (kg)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	102.19 (17.70)	102.18 (14.50)
Median	98.50	95.60
Q1, Q3	90.40, 112.10	93.80, 109.70
Min, Max	75.0, 141.9	83.3, 134.6
38 weeks		
n/nmiss	19/2	17/0
Mean (SD)	101.12 (18.89)	98.59 (14.00)
Median	98.80	93.90
Q1, Q3	83.30, 119.50	89.30, 105.40
Min, Max	75.1, 140.0	80.9, 132.6
Adjusted mean percentage change (95% CI)	-0.45 (-1.93, 1.03)	-3.65 (-5.23, -2.07)
p-value	0.5386	<.0001
52 weeks		
n/nmiss	17/4	17/0
Mean (SD)	98.71 (20.61)	97.51 (14.08)
Median	95.40	92.60
Q1, Q3	82.30, 109.90	88.40, 105.50
Min, Max	72.2, 143.0	80.5, 134.1
Adjusted mean percentage change (95% CI)	-1.35 (-3.26, 0.57)	-4.65 (-6.66, -2.65)
p-value	0.1618	<.0001

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 27 Body weight (kg) and adjusted mean percentage change from baseline to 52 weeks. Extension full analysis set

Body weight (kg)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Baseline		
n/nmiss	21/0	17/0
Mean (SD)	106.43 (15.73)	102.91 (14.69)
Median	108.10	98.00
Q1, Q3	98.30, 115.00	94.50, 108.60
Min, Max	82.0, 142.8	82.3, 134.0
4 weeks		
n/nmiss	21/0	17/0
Mean (SD)	105.72 (15.97)	102.15 (14.87)
Median	105.70	96.80
Q1, Q3	94.90, 116.10	93.00, 109.40
Min, Max	79.0, 140.8	81.9, 133.6
Adjusted mean percentage change (95% CI)	-0.82 (-1.57, -0.06)	-0.80 (-1.61, 0.01)
p-value	0.0352	0.0525
8 weeks		
n/nmiss	21/0	17/0
Mean (SD)	104.58 (15.82)	102.39 (14.89)
Median	102.30	96.50
Q1, Q3	92.50, 115.90	93.40, 109.90
Min, Max	76.7, 138.7	81.9, 134.8
Adjusted mean percentage change (95% CI)	-1.89 (-2.92, -0.87)	-0.56 (-1.68, 0.56)
p-value	0.0006	0.3150
12 weeks		
n/nmiss	21/0	17/0
Mean (SD)	102.84 (16.41)	102.04 (14.90)
Median	98.70	96.50
Q1, Q3	91.60, 113.50	92.90, 109.60
Min, Max	74.5, 138.1	81.1, 134.8
Adjusted mean percentage change (95% CI)	-3.60 (-4.90, -2.30)	-0.90 (-2.33, 0.53)
p-value	<.0001	0.2090
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	102.19 (17.70)	102.18 (14.50)
Median	98.50	95.60
Q1, Q3	90.40, 112.10	93.80, 109.70
Min, Max	75.0, 141.9	83.3, 134.6
Adjusted mean percentage change (95% CI)	-4.35 (-6.09, -2.61)	-0.70 (-2.63, 1.22)
p-value	<.0001	0.4640
38 weeks		
n/nmiss	19/2	17/0
Mean (SD)	101.12 (18.89)	98.59 (14.00)
Median	98.80	93.90
Q1, Q3	83.30, 119.50	89.30, 105.40
Min, Max	75.1, 140.0	80.9, 132.6
Adjusted mean percentage change (95% CI)	-4.52 (-7.00, -2.05)	-4.13 (-6.84, -1.42)

Body weight (kg)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
p-value	0.0007	0.0038
52 weeks		
n/nmiss	17/4	17/0
Mean (SD)	98.71 (20.61)	97.51 (14.08)
Median	95.40	92.60
Q1, Q3	82.30, 109.90	88.40, 105.50
Min, Max	72.2, 143.0	80.5, 134.1
Adjusted mean percentage change (95% CI)	-5.33 (-8.26, -2.40)	-5.16 (-8.34, -1.97)
p-value	0.0007	0.0023

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

11.4.3 Exploratory Efficacy Variables

Descriptive data and the results of the statistical analyses of the exploratory efficacy variables, for the extension-FAS, are presented in Section 11.4.3.1 (Body fat composition), Section 11.4.3.2 (Haemoglobin A1c, glucose tolerance and insulin), Section 11.4.3.3 (Blood lipid profile) and Section 11.4.3.4 (Vital signs).

11.4.3.1 Body Fat Composition

Descriptive data and the results of the statistical analyses of body fat composition are presented in Section 11.4.3.1.1 (Total, abdominal visceral and abdominal subcutaneous adipose tissue and total lean tissue, Dapa+Exe/Dapa+Exe group only), Section 11.4.3.1.2 (Percentage liver fat and total liver fat, Dapa+Exe/Dapa+Exe group only) and Section 11.4.3.1.3 (Body fat as measured by bioimpedance). A summary is provided in Section 11.4.3.1.4.

The corresponding tables for extension-FAS not presented below and the extension-PPAS tables are provided in Section 14.2.5.1.

11.4.3.1.1 Total, Abdominal Visceral and Abdominal Subcutaneous Adipose Tissue and Total Lean Tissue (Dapa+Exe/Dapa+Exe group only)

A statistically significant reduction of total adipose tissue between baseline and week 24 was observed within the group that received dapagliflozin/exenatide (adjusted mean change:-3.9 L, p=0.0008) (Table 28).

The reduction in total adipose tissue was attributed to statistically significant reductions in abdominal visceral adipose tissue (-0.39 L, p=0.0167) (Table 29) and abdominal subcutaneous adipose tissue (-1.3 L, p=0.0008) (Table 30).

Also a statistically significant reduction of total lean tissue between baseline and week 24 was observed within the dapagliflozin/exenatide group (-0.93 L, p=0.0111) (Table 31).

Between week 24 and week 52, there were no statistically significant reductions in total adipose tissue (Table 114, Section 14.2.5.1.1), abdominal subcutaneous adipose tissue (Table 118, Section 14.2.5.1.1) abdominal visceral adipose tissue (Table 122, Section 14.2.5.1.1) or lean tissue (Table 127, Section 14.2.5.1.1) observed.

Overall, 52 weeks of treatment with dapagliflozin/exenatide, resulted in a statistically significant reduction in total adipose tissue from baseline (week 0) to week 52 (-5.1 L, p=0.0149) (Table 32). This reduction was attributed to a statistically significant reduction in abdominal subcutaneous adipose tissue (-1.6 L, p=0.0053) (Table 33), but not in abdominal visceral adipose tissue (-0.49 L) (Table 123, Section 14.2.5.1.1).

Also a statistically significant reduction of total lean tissue between baseline and week 52 was observed within the Dapa+Exe/Dapa+Exe group (-1.3 L, p=0.0051) (Table 34).

For the extension-PPAS (see Section 14.2.5.1.1), there were corresponding statistically significant reductions between baseline and week 24 observed for total adipose tissue (Table 115) and abdominal subcutaneous adipose tissue (Table 119), but not for abdominal visceral adipose tissue (Table 124,) or for total lean tissue (Table 128). Between week 24 and week 52, similar results (no statistically significant differences) were seen for the extension-PPAS (see Table 116 [total adipose tissue], Table 120 [abdominal subcutaneous adipose tissue], Table 125 [abdominal visceral adipose tissue] and Table 129 [total lean tissue], Section 14.2.5.1.1). Between baseline and week 52, corresponding statistically significant reductions were observed for extension-PPAS in abdominal subcutaneous adipose tissue (Table 121), but not in total adipose tissue (Table 117, Section 14.2.5.1.1), abdominal visceral adipose tissue (Table 126, Section 14.2.5.1.1) or total lean tissue Table 130, Section 14.2.2.5.1.

Table 28 Total adipose tissue (L) and adjusted mean change from baseline to 24 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension full analysis set

Total adipose tissue (L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)
Baseline	
n/nmiss	20/1
Mean (SD)	56.754 (10.537)
Median	55.760
Q1, Q3	48.595, 66.045
Min, Max	42.27, 76.06
24 weeks	
n/nmiss	21/0
Mean (SD)	52.835 (12.944)
Median	51.340
Q1, Q3	42.640, 62.190
Min, Max	33.06, 75.98
Adjusted mean change (95% CI)	-3.929 (-5.967, -1.891)
p-value	0.0008

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

Table 29 Abdominal visceral adipose tissue (L) and adjusted mean change from baseline to 24 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension full analysis set

Abdominal visceral adipose tissue (L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)
Baseline	
n/nmiss	20/1
Mean (SD)	6.179 (3.242)
Median	5.050
Q1, Q3	3.685, 8.900
Min, Max	1.95, 12.50
24 weeks	
n/nmiss	21/0
Mean (SD)	5.748 (3.118)
Median	4.430
Q1, Q3	3.540, 7.720
Min, Max	1.82, 11.90
Adjusted mean change (95% CI)	-0.387 (-0.695, -0.079)
p-value	0.0167

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

Table 30 Abdominal subcutaneous adipose tissue (L) and adjusted mean change from baseline to 24 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension full analysis set

Abdominal subcutaneous adipose tissue (L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)
Baseline	
n/nmiss	20/1
Mean (SD)	13.969 (4.006)
Median	13.020
Q1, Q3	11.505, 16.610
Min, Max	8.24, 25.65
24 weeks	
n/nmiss	21/0
Mean (SD)	12.690 (4.697)
Median	11.610
Q1, Q3	9.030, 16.600
Min, Max	7.19, 25.01
Adjusted mean change (95% CI)	-1.271 (-1.934, -0.609)
p-value	0.0008

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

Table 31 Total lean tissue (L) and adjusted mean change from baseline to 24 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension full analysis set

Total lean tissue (L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)
Baseline	
n/nmiss	20/1
Mean (SD)	42.635 (9.565)
Median	41.235
Q1, Q3	35.675, 50.220
Min, Max	29.46, 61.33
24 weeks	
n/nmiss	21/0
Mean (SD)	41.774 (9.342)
Median	38.700
Q1, Q3	35.360, 46.130
Min, Max	28.09, 60.68
Adjusted mean change (95% CI)	-0.929 (-1.617, -0.241)
p-value	0.0111

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

Table 32 Total adipose tissue (L) and adjusted mean change from baseline to 52 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension full analysis set

Total adipose tissue (L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)
Baseline	
n/nmiss	20/1
Mean (SD)	56.754 (10.537)
Median	55.760
Q1, Q3	48.595, 66.045
Min, Max	42.27, 76.06
24 weeks	
n/nmiss	21/0
Mean (SD)	52.835 (12.944)
Median	51.340
Q1, Q3	42.640, 62.190
Min, Max	33.06, 75.98
Adjusted mean change (95% CI)	-3.667 (-5.980, -1.355)
p-value	0.0042
52 weeks	
n/nmiss	15/6
Mean (SD)	50.571 (17.619)
Median	45.940
Q1, Q3	38.660, 67.140
Min, Max	25.95, 84.15
Adjusted mean change (95% CI)	-5.113 (-9.099, -1.127)
p-value	0.0149

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 33 Abdominal subcutaneous adipose tissue (L) and adjusted mean change from baseline to 52 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension full analysis set

Abdominal subcutaneous adipose tissue (L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)
Baseline	
n/nmiss	20/1
Mean (SD)	13.969 (4.006)
Median	13.020
Q1, Q3	11.505, 16.610
Min, Max	8.24, 25.65
24 weeks	
n/nmiss	21/0
Mean (SD)	12.690 (4.697)
Median	11.610
Q1, Q3	9.030, 16.600
Min, Max	7.19, 25.01
Adjusted mean change (95% CI)	-1.227 (-1.881, -0.573)
p-value	0.0010
52 weeks	
n/nmiss	15/6
Mean (SD)	12.225 (5.525)
Median	11.350
Q1, Q3	7.480, 17.660
Min, Max	5.75, 23.52
Adjusted mean change (95% CI)	-1.574 (-2.620, -0.529)
p-value	0.0053

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 34 Total lean tissue (L) and adjusted mean change from baseline to 52 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension full analysis set

Total lean tissue (L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)
Baseline	
n/nmiss	20/1
Mean (SD)	42.635 (9.565)
Median	41.235
Q1, Q3	35.675, 50.220
Min, Max	29.46, 61.33
24 weeks	
n/nmiss	21/0
Mean (SD)	41.774 (9.342)
Median	38.700
Q1, Q3	35.360, 46.130
Min, Max	28.09, 60.68
Adjusted mean change (95% CI)	-1.007 (-1.713, -0.300)
p-value	0.0079
52 weeks	
n/nmiss	15/6
Mean (SD)	40.219 (8.725)
Median	37.860
Q1, Q3	33.780, 43.540
Min, Max	28.45, 60.69
Adjusted mean change (95% CI)	-1.340 (-2.206, -0.474)
p-value	0.0051

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

11.4.3.1.2 Percentage Liver Fat and Total Liver Fat (Dapa+Exe/Dapa+Exe group only)

A statistically significant reduction in total liver fat was observed between week 24 and week 52 following 52 weeks of treatment with dapagliflozin/exenatide (adjusted mean change: -0.04 L p=0.0265) (Table 35). No corresponding statistically significant result was observed for the extension-PPAS (Table 134, Section 14.2.5.1.2).

In contrast, no statistically significant changes in total liver fat were observed from baseline to week 24 or from baseline to week 52 (Table 131 and Table 132, Section 14.2.5.1.2). Similar results were obtained for the extension-PPAS (Table 133 and Table 135, Section 14.2.5.1.2).

No statistically significant changes in percentage liver fat were observed at any of the time points in either extension-FAS or extension-PPAS (Table 136 to Table 138, Section 14.2.5.1.2). Similar results were obtained for the extension-PPAS (Table 139 to Table 141, Section 14.2.5.1.2).

Table 35 Total liver fat (L) and adjusted mean change from 24 weeks to 52 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension full analysis set

Total liver fat (L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)
24 weeks	
n/nmiss	20/1
Mean (SD)	0.235 (0.317)
Median	0.095
Q1, Q3	0.040, 0.315
Min, Max	0.02, 1.38
52 weeks	
n/nmiss	14/7
Mean (SD)	0.202 (0.243)
Median	0.080
Q1, Q3	0.040, 0.310
Min, Max	0.00, 0.82
Adjusted mean change (95% CI)	-0.043 (-0.079, -0.006)
p-value	0.0265

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

11.4.3.1.3 Body Fat Percentage as Measured by Bioimpedance

No statistically significant changes in percentage body fat were observed within the Dapa+Exe/Dapa+Exe group or within the Placebo/Dapa+Exe group, at any of the time points (from baseline to 24 weeks, from 24 weeks to 52 weeks or from baseline to 52 weeks) (Table 142 to Table 144, Section 14.2.5.1.3).

Similar results were obtained for the extension-PPAS (Table 145 to Table 147, Section 14.2.5.1.3).

11.4.3.1.4 Summary - Body Fat Composition

Statistically significant differences within the group that received dapagliflozin/exenatide for 24 +28 weeks were observed in total adipose tissue (from baseline to week 24, from baseline to week 52), in abdominal visceral adipose tissue (from baseline to week 24), in abdominal subcutaneous adipose tissue (from baseline to week 24, from baseline to week 52), in total lean tissue (from baseline to week 24, from baseline to week 52) and in total liver fat (from week 24 to week 52) (Table 36).

There were no statistically significant differences within the Dapa+Exe/Dapa+Exe group with regard to total adipose tissue (from week 24 to week 52), abdominal visceral adipose tissue (from week 24 to week 52, from baseline to week 52), abdominal subcutaneous adipose tissue (from week 24 to week 52), total lean tissue (from week 24 to week 52), percentage liver fat (all time points), and total liver fat (from week 24 to week 52) (Table 36).

For body fat percentage (only parameter tested within both groups), no statistically significant reductions were observed from baseline to week 24, between week 24 and 52 or from baseline to week 52, within any of the groups (Table 36).

Table 36 Summary of within group differences in body fat composition. Extension full analysis set

Variable[a]	Unit		Adjusted mean change[b]	(95% CI)	p-value
Total adipose tissue	**L**	**Baseline to Week 24**	**-3.929**	**(-5.967 to -1.891)**	**p=0.0008**
	L	Week 24 to Week 52	-1.566	**(-3.185 to 0.053)**	p=0.0567
	L	**Baseline to Week 52**	**-5.113**	**(-9.099 to -1.127)**	**p=0.0149**
Abdominal visceral adipose tissue	**L**	**Baseline to Week 24**	**-0.387**	**(-0.695 to -0.079)**	**p=0.0167**
	L	Week 24 to Week 52	-0.211	(-0.516 to 0.094)	p=0.1573
	L	Baseline to Week 52	-0.494	(-1.010 to 0.022)	p=0.0596
Abdominal subcutaneous adipose tissue	**L**	**Baseline to Week 24**	**-1.271**	**(-1.934 to -0.609)**	**p=0.0008**
	L	Week 24 to Week 52	-0.362	(-0.971 to 0.246)	p=0.2190
	L	**Baseline to Week 52**	**-1.574**	**(-2.620 to -0.529)**	**p=0.0053**
Total lean tissue	**L**	**Baseline to Week 24**	**-0.929**	**(-1.617 to -0.241)**	**p=0.0111**
	L	Week 24 to Week 52	-0.679	(-1.618 to 0.259)	p=0.1408
	L	**Baseline to Week 52**	**-1.340**	**(-2.206 to -0.474)**	**p=0.0051**
Body fat (bioimpedance)	%	Baseline to Week 24	-0.84	(-1.77 to 0.08)	p=0.0732
	%	Week 24 to Week 52	-0.26	(-1.67 to 1.14)	p=0.7066
	%	Baseline to Week 52	-1.15	(-2.77 to 0.47)	p=0.1590
(Placebo/Dapa+Exe group)	%	Baseline to Week 24	0.17	(-0.95 to 1.29)	p=0.7610
(Placebo/Dapa+Exe group)	%	Week 24 to Week 52	-0.97	(-2.44 to 0.51)	p=0.1909
(Placebo/Dapa+Exe group)	%	Baseline to Week 52	-0.82	(-2.56 to 0.93)	p=0.3504
Liver fat	%	Baseline to Week 24	-1.09	(-2.65 to 0.46)	p=0.1554
	%	Week 24 to Week 52	-0.89	(-2.22 to 0.45)	p=0.1695
	%	Baseline to Week 52	-1.47	(-3.19 to 0.25)	p=0.0867
Total liver fat	L	Baseline to Week 24	-0.011	(-0.048 to 0.026)	p=0.5374
	L	**Week 24 to Week 52**	**-0.043**	**(-0.079 to -0.006)**	**p=0.0265**
	L	Baseline to Week 52	-0.023	(-0.081 to 0.035)	p=0.3864

a All variables were measured by MRI except percentage body fat which was assessed by bioimpedance.
b Adjusted mean change during baseline to week 24, week 24 to week 52 or baseline to week 52, within the Dapa+Exe/Dapa+Exe group or within the Placebo/Dapa+Exe group.
Source: Table 28 to Table 35, Table 114 to Table 144 (extension-FAS tables).

11.4.3.2 Haemoglobin A1c, Glucose Tolerance and Insulin

Descriptive data and the results of the statistical analyses for the extension-FAS are presented in Section 11.4.3.2.1 (HbA1c), Section 11.4.3.2.2 (Glucose), Section 11.4.3.2.3 (IFG, Dapa+Exe/Dapa+Exe group only), Section 11.4.3.2.4 (IGT, Dapa+Exe/Dapa+Exe group only), Section 11.4.3.2.5 (IFG and/or IGT) and Section 11.4.3.2.6 (Insulin). Descriptive data of plasma glucose, insulin, C-peptide and ketones in blood (all fasting) are summarized in Section 11.4.3.2.7. A summary is provided in Section 11.4.3.2.8.

The corresponding tables for extension-FAS not presented below and the extension-PPAS are provided in Section 14.2.5.2. Individual data pertaining to this section are provided in Appendix 16.2.6.

11.4.3.2.1 Haemoglobin A1c

Statistically significant reductions in mean HbA1c levels between baseline (screening) and week 24 were observed within both groups (Dapa+Exe/Dapa+Exe group: -3.9 mmol/mol, p<0.0001; Placebo/Dapa+Exe group: -1.6 mmol/mol, p=0.0041) (Table 37).

Between week 24 and week 52, a statistically significant reduction in mean HbA1c levels was observed within the Placebo/Dapa+Exe group (-1.4 mmol/mol, p=0.0038) (Table 38), but not within the Dapa+Exe/Dapa+Exe group (0.4 mmol/mol).

Overall, from baseline (screening) to week 52, there were statistically significant reductions in mean HbA1c levels observed within both groups (both groups: -3.1 mmol/mol, p<0.0001) (Table 39).

There were corresponding statistically significant reductions in mean HbA1c levels shown within the respective group for the extension-PPAS, see Section 14.2.5.2.1 (Table 148 to Table 150)

Table 37 HbA1c (mmol/mol) and adjusted mean change from baseline to 24 weeks. Extension full analysis set

HbA1c (mmol/mol)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Screening		
n/nmiss	21/0	17/0
Mean (SD)	37.2 (3.8)	37.2 (2.6)
Median	36.0	37.0
Q1, Q3	35.0, 40.0	35.0, 39.0
Min, Max	29, 47	33, 42
12 weeks		
n/nmiss	21/0	17/0
Mean (SD)	34.5 (3.4)	36.9 (2.8)
Median	34.0	37.0
Q1, Q3	32.0, 36.0	35.0, 39.0
Min, Max	28, 42	32, 41
Adjusted mean change (95% CI)	-2.7 (-3.7, -1.7)	-0.3 (-1.4, 0.9)
p-value	<.0001	0.6365
24 weeks		
n/nmiss	20/1	17/0
Mean (SD)	33.1 (4.1)	35.6 (2.6)
Median	32.0	35.0
Q1, Q3	30.5, 36.0	33.0, 38.0
Min, Max	27, 43	32, 40
Adjusted mean change (95% CI)	-3.9 (-4.8, -2.9)	-1.6 (-2.6, -0.5)
p-value	<.0001	0.0041

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 38 HbA1c (mmol/mol) and adjusted mean change from 24 weeks to 52 weeks. Extension full analysis set

HbA1c (mmol/mol)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
24 weeks		
n/nmiss	20/1	17/0
Mean (SD)	33.1 (4.1)	35.6 (2.6)
Median	32.0	35.0
Q1, Q3	30.5, 36.0	33.0, 38.0
Min, Max	27, 43	32, 40
52 weeks		
n/nmiss	17/4	16/1
Mean (SD)	34.1 (4.1)	33.8 (2.2)
Median	34.0	34.0
Q1, Q3	31.0, 36.0	32.0, 35.0
Min, Max	27, 45	31, 38
Adjusted mean change (95% CI)	0.4 (-0.5, 1.3)	-1.4 (-2.3, -0.5)
p-value	0.3973	0.0038

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

Table 39 HbA1c (mmol/mol) and adjusted mean change from baseline to 52 weeks. Extension full analysis set

HbA1c (mmol/mol)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)	Placebo/Dapa 10mg+Exe 2mg (N=17)
Screening		
n/nmiss	21/0	17/0
Mean (SD)	37.2 (3.8)	37.2 (2.6)
Median	36.0	37.0
Q1, Q3	35.0, 40.0	35.0, 39.0
Min, Max	29, 47	33, 42
12 weeks		
n/nmiss	21/0	17/0
Mean (SD)	34.5 (3.4)	36.9 (2.8)
Median	34.0	37.0
Q1, Q3	32.0, 36.0	35.0, 39.0
Min, Max	28, 42	32, 41
Adjusted mean change (95% CI)	-2.7 (-3.7, -1.7)	-0.3 (-1.4, 0.9)
p-value	<.0001	0.6480
24 weeks		
n/nmiss	20/1	17/0
Mean (SD)	33.1 (4.1)	35.6 (2.6)
Median	32.0	35.0
Q1, Q3	30.5, 36.0	33.0, 38.0
Min, Max	27, 43	32, 40
Adjusted mean change (95% CI)	-3.9 (-4.8, -2.9)	-1.5 (-2.6, -0.5)
p-value	<.0001	0.0039
52 weeks		
n/nmiss	17/4	16/1
Mean (SD)	34.1 (4.1)	33.8 (2.2)
Median	34.0	34.0
Q1, Q3	31.0, 36.0	32.0, 35.0
Min, Max	27, 45	31, 38
Adjusted mean change (95% CI)	-3.1 (-4.0, -2.2)	-3.1 (-4.1, -2.2)
p-value	<.0001	<.0001

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

11.4.3.2.2 Glucose

Fasting Plasma Glucose

A statistically significant reduction in mean FPG between baseline (screening) and week 24 was observed within the Dapa+Exe/Dapa+Exe group (-0.42 mmol/L, p<0.0001), but not within the Placebo/Dapa+Exe group (0.14 mmol/L) (Table 40).

Between week 24 and week 52, a statistically significant reduction in mean FPG levels was observed within the Placebo/Dapa+Exe group (-0.27 mmol/L, p=0.0046), but not within the Dapa+Exe/Dapa+Exe group (0.01 mmol/L) (Table 41).

Overall, from baseline (screening) to week 52, statistically significant reductions in mean FPG were

observed within both groups (Dapa+Exe/Dapa+Exe group: -0.31 mmol/L, p=0.0006; Placebo/Dapa+Exe group: -0.29 mmol/L, p=0.0012) (Table 42).

There were corresponding statistically significant reductions in mean FPG shown within the respective group for the extension-PPAS, see Section 14.2.5.2.2 (Table 151 to Table 153).

Table 40 Fasting plasma glucose (mmol/L) and adjusted mean change from baseline to 24 weeks. Extension full analysis set

Glucose (mmol/L)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Screening		
n/nmiss	21/0	17/0
Mean (SD)	5.91 (0.64)	5.78 (0.42)
Median	5.80	5.70
Q1, Q3	5.40, 6.10	5.50, 6.00
Min, Max	5.0, 7.2	5.1, 6.6
12 weeks		
n/nmiss	21/0	17/0
Mean (SD)	5.65 (0.54)	5.97 (0.38)
Median	5.70	5.80
Q1, Q3	5.20, 5.90	5.70, 6.30
Min, Max	4.7, 6.8	5.6, 6.7
Adjusted mean change (95% CI)	-0.23 (-0.38, -0.09)	0.17 (0.02, 0.33)
p-value	0.0024	0.0320
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	5.47 (0.54)	5.94 (0.47)
Median	5.40	5.80
Q1, Q3	5.20, 5.70	5.70, 6.20
Min, Max	4.7, 7.1	5.1, 6.9
Adjusted mean change (95% CI)	-0.42 (-0.58, -0.25)	0.14 (-0.04, 0.33)
p-value	<.0001	0.1193

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 41 Fasting plasma glucose (mmol/L) and adjusted mean change from 24 weeks to 52 weeks. Extension full analysis set

Glucose (mmol/L)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	5.47 (0.54)	5.94 (0.47)
Median	5.40	5.80
Q1, Q3	5.20, 5.70	5.70, 6.20
Min, Max	4.7, 7.1	5.1, 6.9
52 weeks		
n/nmiss	17/4	17/0
Mean (SD)	5.54 (0.50)	5.51 (0.33)
Median	5.50	5.60
Q1, Q3	5.10, 5.80	5.30, 5.70
Min, Max	4.8, 6.8	4.9, 6.2
Adjusted mean change (95% CI)	0.01 (-0.16, 0.18)	-0.27 (-0.45, -0.09)
p-value	0.8932	0.0046

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

Table 42 Fasting plasma glucose (mmol/L) and adjusted mean change from baseline to 52 weeks. Extension full analysis set

Glucose (mmol/L)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Screening		
n/nmiss	21/0	17/0
Mean (SD)	5.91 (0.64)	5.78 (0.42)
Median	5.80	5.70
Q1, Q3	5.40, 6.10	5.50, 6.00
Min, Max	5.0, 7.2	5.1, 6.6
12 weeks		
n/nmiss	21/0	17/0
Mean (SD)	5.65 (0.54)	5.97 (0.38)
Median	5.70	5.80
Q1, Q3	5.20, 5.90	5.70, 6.30
Min, Max	4.7, 6.8	5.6, 6.7
Adjusted mean change (95% CI)	-0.22 (-0.36, -0.08)	0.18 (0.02, 0.34)
p-value	0.0038	0.0296
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	5.47 (0.54)	5.94 (0.47)
Median	5.40	5.80
Q1, Q3	5.20, 5.70	5.70, 6.20
Min, Max	4.7, 7.1	5.1, 6.9
Adjusted mean change (95% CI)	-0.41 (-0.57, -0.24)	0.15 (-0.04, 0.33)
p-value	<.0001	0.1107
52 weeks		
n/nmiss	17/4	17/0
Mean (SD)	5.54 (0.50)	5.51 (0.33)
Median	5.50	5.60
Q1, Q3	5.10, 5.80	5.30, 5.70
Min, Max	4.8, 6.8	4.9, 6.2
Adjusted mean change (95% CI)	-0.31 (-0.47, -0.14)	-0.29 (-0.45, -0.12)
p-value	0.0006	0.0012

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Post-challenge Plasma Glucose 120 min (Dapa+Exe/Dapa+Exe group only)

A statistically significant reduction in 120 minutes post-challenge plasma glucose levels between baseline (screening) and week 24 was observed within the Dapa+Exe/Dapa+Exe group (-1.8 mmol/L, p=0.0002) (Table 43).

Between week 24 and week 52, no further statistically significant change in 120 minutes post-challenge plasma glucose levels was observed (Table 154, Section 14.2.5.2.2).

Overall, from baseline (screening) to week 52, a statistically significant reduction in 120 minutes post-challenge plasma glucose levels was observed within the Dapa+Exe/Dapa+Exe group (-2.2 mmol/L, p<0.0001) (Table 44).

Similar results were observed within the group for the extension-PPAS, see Section 14.2.5.2.2 (Table 155 to Table 157).

Table 43 Glucose (mmol/L) 120 min and adjusted mean change from baseline to 24 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension full analysis set

Glucose (mmol/L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)
Screening	
n/nmiss	21/0
Mean (SD)	7.82 (2.19)
Median	7.30
Q1, Q3	6.30, 9.20
Min, Max	4.3, 12.8
24 weeks	
n/nmiss	21/0
Mean (SD)	5.95 (1.75)
Median	5.50
Q1, Q3	4.70, 6.60
Min, Max	3.8, 10.8
Adjusted mean change (95% CI)	-1.84 (-2.67, -1.00)
p-value	0.0002

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

Table 44 Glucose (mmol/L) 120 min and adjusted mean change from baseline to 52 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension full analysis set

Glucose (mmol/L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)
Screening	
n/nmiss	21/0
Mean (SD)	7.82 (2.19)
Median	7.30
Q1, Q3	6.30, 9.20
Min, Max	4.3, 12.8
24 weeks	
n/nmiss	21/0
Mean (SD)	5.95 (1.75)
Median	5.50
Q1, Q3	4.70, 6.60
Min, Max	3.8, 10.8
Adjusted mean change (95% CI)	-1.87 (-2.71, -1.03)
p-value	0.0002
52 weeks	
n/nmiss	15/6
Mean (SD)	5.59 (1.85)
Median	5.30
Q1, Q3	4.00, 6.80
Min, Max	2.8, 9.7
Adjusted mean change (95% CI)	-2.21 (-3.01, -1.40)
p-value	<.0001

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Area under the Curve (0-3h) Plasma Glucose (Dapa+Exe/Dapa+Exe group only)

A statistically significant reduction in mean AUC_{0-3h} for plasma glucose between baseline (screening) and week 24 was observed within the Dapa+Exe/Dapa+Exe group (-218.0 mmol/L x 180 min, p=0.0002) (Table 45).

Between week 24 and week 52, no further statistically significant change in mean AUC_{0-3h} for plasma glucose was observed (Table 158, Section 14.2.5.2.2).

Overall, from baseline (screening) to week 52, a statistically significant reduction in mean AUC_{0-3h} for plasma glucose was observed within the Dapa+Exe/Dapa+Exe group (-248.7 mmol/L x 180 min, p<0.0001) (Table 46).

Similar results were seen within the group for the extension-PPAS, see Section 14.2.5.2.2 (Table 159 to Table 161).

Table 45 **Glucose area under the curve (180 min*mmol/L) and adjusted mean change from baseline to 24 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension full analysis set**

Glucose AUC (180 min*mmol/L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)
Screening	
n/nmiss	20/1
Mean (SD)	1421.925 (300.392)
Median	1515.750
Q1, Q3	1208.250, 1629.750
Min, Max	851.25, 1936.50
24 weeks	
n/nmiss	20/1
Mean (SD)	1170.675 (225.907)
Median	1121.250
Q1, Q3	1003.500, 1307.625
Min, Max	899.25, 1674.75
Adjusted mean change (95% CI)	-218.047 (-312.498, -123.596)
p-value	0.0002

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

Table 46 Glucose area under the curve (180 min*mmol/L) and adjusted mean change from baseline to 52 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension full analysis set

Glucose AUC (180 min*mmol/L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)
Screening	
n/nmiss	20/1
Mean (SD)	1421.925 (300.392)
Median	1515.750
Q1, Q3	1208.250, 1629.750
Min, Max	851.25, 1936.50
24 weeks	
n/nmiss	20/1
Mean (SD)	1170.675 (225.907)
Median	1121.250
Q1, Q3	1003.500, 1307.625
Min, Max	899.25, 1674.75
Adjusted mean change (95% CI)	-238.406 (-336.002, -140.809)
p-value	0.0001
52 weeks	
n/nmiss	14/7
Mean (SD)	1166.946 (257.917)
Median	1104.000
Q1, Q3	1013.250, 1291.500
Min, Max	800.25, 1631.25
Adjusted mean change (95% CI)	-248.655 (-334.152, -163.157)
p-value	<.0001

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

11.4.3.2.3 Impaired Fasting Glucose (Dapa+Exe/Dapa+Exe group only)

The IFG was assessed at Time 0 of the 3h-OGTT at screening, at week 24 and at week 52. The threshold for IFG was categorized as FPG levels ≥5.6 mmol/L (i.e., subjects with FPG <5.6 mmol/L were categorized as having a normal FPG).

Within the Dapa+Exe/Dapa+Exe group, there was a statistically significant reduction in the proportion of subjects with IFG at week 24 (p=0.0082) (Table 47). Between baseline (screening) and week 24, 33.3% shifted from raised to normal and 0% shifted from normal to raised status. No statistically significant reductions were seen between baseline (screening) and week 52 or between week 24 and week 52. However, 35.3% shifted from raised to normal between baseline (screening) and week 52 and 11.8% shifted from raised to normal between 24 weeks and 52 weeks, respectively.

For the extension-PPAS, statistically significant reductions in the proportion of subjects with IFG, were observed between baseline (screening) and week 24 and between baseline (screening) and week 52, respectively, but not between week 24 and week 52 (Table 162, Section 14.2.5.2.3).

Table 47 Impaired fasting glucose. Extension full analysis set

	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)
Screening	
Normal	7 (33.3%)
Raised	14 (66.7%)
24 weeks	
Normal	14 (66.7%)
Raised	7 (33.3%)
Shift in categories	
Normal to normal	7 (33.3%)
Normal to raised	0
Raised to normal	7 (33.3%)
Raised to raised	7 (33.3%)
p-value[1], change from baseline	0.0082
52 weeks	
Normal	11 (64.7%)
Raised	6 (35.3%)
Shift in categories	
From baseline, Normal to normal	5 (29.4%)
From baseline, Normal to raised	1 (5.9%)
From baseline, Raised to normal	6 (35.3%)
From baseline, Raised to raised	5 (29.4%)
From 24 weeks, Normal to normal	9 (52.9%)
From 24 weeks, Normal to raised	3 (17.6%)
From 24 weeks, Raised to normal	2 (11.8%)
From 24 weeks, Raised to raised	3 (17.6%)
p-value[1], change from baseline	0.0588
p-value[1], change from 24 weeks	0.6547

[1]P-value based on a paired McNemar test.
Percentages are based on the number of subjects in the applicable analysis set with non-missing values.

11.4.3.2.4 Impaired Glucose Tolerance (Dapa+Exe/Dapa+Exe group only)

IGT was assessed at Time 120 minutes during the 3h-OGTT at screening, at week 24 and at week 52. The threshold for IGT was categorized as plasma glucose at Time 120 min ≥7.8 mmol/L (*i.e.*, subjects with plasma glucose <7.8 mmol/L were categorized as having a normal glucose tolerance).

Within the Dapa+Exe/Dapa+Exe group, statistically significant reductions in the proportion of subjects with IGT were observed between baseline (screening) and week 24 (p=0.0196) and week 52 (p=0.0253), respectively (Table 48). No statistically significant reductions were seen between week 24 and week 52.

A total of 38.1% shifted from raised to normal and 4.8% (1 subject) shifted from normal to raised between baseline (screening) and week 24 while 33.3% shifted from raised to normal and 0% shifted from normal to raised status between baseline (screening) and week 52. Between 24 weeks and 52 weeks, 6.7% (1 subject) shifted from raised to normal IGT status and 0% shifted from normal to raised status.

For the extension-PPAS, a statistically significant reduction in the proportion of subjects with IGT was observed, between baseline (screening) and week 52, but not between baseline (screening) and week 24 or between week 24 and week 52 (Table 163, Section 14.2.5.2.4).

Table 48 Impaired glucose tolerance. Extension full analysis set

	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)
Screening	
Normal	11 (52.4%)
Raised	10 (47.6%)
24 weeks	
Normal	18 (85.7%)
Raised	3 (14.3%)
Shift in categories	
Normal to normal	10 (47.6%)
Normal to raised	1 (4.8%)
Raised to normal	8 (38.1%)
Raised to raised	2 (9.5%)
p-value[1], change from baseline	0.0196
52 weeks	
Normal	13 (86.7%)
Raised	2 (13.3%)
Shift in categories	
From baseline, Normal to normal	8 (53.3%)
From baseline, Normal to raised	0
From baseline, Raised to normal	5 (33.3%)
From baseline, Raised to raised	2 (13.3%)
From 24 weeks, Normal to normal	12 (80.0%)
From 24 weeks, Normal to raised	0
From 24 weeks, Raised to normal	1 (6.7%)
From 24 weeks, Raised to raised	2 (13.3%)
p-value[1], change from baseline	0.0253
p-value[1], change from 24 weeks	0.3173

[1]P-value based on a paired McNemar test.
Percentages are based on the number of subjects in the applicable analysis set with non-missing values.

11.4.3.2.5 Impaired Fasting Glucose and/or Impaired Glucose Tolerance

The number of subjects with IFG and/or IGT as defined in Section 11.4.3.2.3 and Section 11.4.3.2.4 was summarized in order to estimate the proportion of subjects who were prediabetic at baseline, at week 24 and at week 52.

There was a statistically significant difference in the proportion of subjects with IFG and/or IGT in the Dapa+Exe/Dapa+Exe group compared to the Placebo/Dapa+Exe group between baseline (screening) and week 24 (p=0.0031, Cochran–Mantel–Haenszel test, Table 164, Section 14.2.5.2.5). The proportion of subjects with raised status was lower in the Dapa+Exe/Dapa+Exe group (33.3%) than in the Placebo/Dapa+Exe group (82.4%) at week 24.

Within the Dapa+Exe/Dapa+Exe group, there was a statistically significant reduction in the proportion of subjects with IFG and/or IGT between baseline (screening) and week 24 (p=0.0047, McNemar's test), 38.1% shifted from raised IFG and/or IGT status at baseline (screening) to normal at week 24 and 0% shifted from normal to raised (Table 164, Section 14.2.5.2.5). Within the Placebo/Dapa+Exe group, no statistically significant difference was shown, 5.9% (1 subject) shifted from raised status at baseline (screening) to normal at week 24 and 5.9% (1 subject) shifted from normal to raised.

At week 52 there was a statistically significant reduction in the proportion of subjects with IFG and/or IGT shown within the Dapa+Exe/Dapa+Exe group (p=0.0143, McNemar's test), 28.6% shifted from raised to normal and 0% shifted from normal to raised status.

The models did not allow for corresponding calculations for the Placebo/Dapa+Exe group since this group did not perform OGTT in the extension part.

Similar results were obtained for the extension-PPAS, see Section 14.2.5.2.5 (Table 165).

11.4.3.2.6 Insulin

Between week 24 and week 52, a statistically significant reduction in mean fasting insulin was observed within the Dapa+Exe/Dapa+Exe group (-4.9 mU/L, p=0.0006) (Table 49), but not within the Placebo/Dapa+Exe group (1.1 mU/L).

No statistically significant differences in mean fasting insulin were observed within any of the groups, between baseline (screening) and week 24 (Table 166, Section 14.2.5.2.6) or between baseline (screening) and week 52 (Table 167, Section 14.2.5.2.6). The adjusted mean change in fasting insulin was 2.3 mU/L and 2.2 mU/L in the Dapa+Exe/Dapa+Exe and Placebo/Dapa+Exe group, respectively, at week 24, and -2.5 mU/L and 3.1 mU/L, respectively at week 52.

Similar results were observed for the extension-PPAS, see Section 14.2.5.2.6 (Table 168 to Table 170).

Table 49 Fasting insulin (mU/L) and adjusted mean change from 24 weeks to 52 weeks. Extension full analysis set

Insulin (mU/L)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/Dapa 10mg+Exe 2mg (N=17)
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	14.99 (14.57)	15.49 (11.45)
Median	12.60	13.00
Q1, Q3	7.60, 14.40	7.90, 18.80
Min, Max	3.1, 72.0	4.0, 50.0
52 weeks		
n/nmiss	16/5	14/3
Mean (SD)	9.96 (6.11)	16.85 (9.31)
Median	10.15	13.35
Q1, Q3	4.90, 12.80	11.30, 19.40
Min, Max	0.2, 25.0	7.7, 41.0
Adjusted mean change (95% CI)	-4.90 (-7.49, -2.31)	1.13 (-1.68, 3.94)
p-value	0.0006	0.4152

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

Area under the Curve (0-3h) Insulin (Dapa+Exe/Dapa+Exe group only)

No statistically significant changes in mean AUC_{0-3h} for insulin were observed within the Dapa+Exe/Dapa+Exe group at any of the time points (Table 171 to Table 173, Section 14.2.5.2.6). Similar results were observed for the extension-PPAS (Table 174 to Table 176, Section 14.2.5.2.6).

11.4.3.2.7 Descriptive Statistics OGTT Variables

Descriptive statistics of plasma glucose, insulin, C-peptide, ketones in blood (all fasting) and U-glucose are summarized in Section 14.2.5.2.7 (Plasma glucose, Table 177 and Table 178), Section 14.2.5.2.8 (Insulin, Table 179 and Table 180), Section 14.2.5.2.9 (C-peptide, Table 181 and Table 182), Section 14.2.5.2.10 (Ketones, Table 183 and Table 184) and Section 14.2.5.2.11 (U-glucose, Table 185).

The variables are presented as summary statistics by treatment group including mean change from baseline to weeks 12, 24 and 52, and corresponding 95% confidence intervals for the extension-FAS and extension-PPAS.

No apparent differences between the treatment groups, or relevant changes in mean values from screening to week 12, week 24 or week 52, were observed for any of the variables (plasma glucose, insulin, C-peptide and ketones) in either extension-FAS or extension-PPAS (Table 177 to Table 184, Section 14.2.5.2.7 to Section 14.2.5.2.10).

For U-glucose, the mean value was 52.3 mmol (SD=31.8) at week 24, in the group that was treated with dapagliflozin/exenatide, as compared to 0.082 mmol (SD=0.056) in the group that received placebo (Table 185, Section 14.2.5.2.11). At week 52, the mean value of U-glucose was 45.7 mmol (SD=29.3), in the Dapa+Exe/Dapa+Exe group (U-glucose was not analysed for the Placebo/Dapa+Exe group at week 52).

11.4.3.2.8 Summary – Haemoglobin A1c, Glucose Tolerance and Insulin

Statistically significant differences within the group that received dapagliflozin/exenatide for 24 +28 weeks (Dapa+Exe/Dapa+Exe), were observed for HbA1c (from baseline to week 24 and from baseline to week 52), for glucose (FPG, 120 min, AUC_{0-3h}; from baseline to week 24 and from baseline to week 52) and for insulin (from week 24 to week 52) (Table 50).

Statistically significant differences within the group that received placebo for 24 weeks and dapagliflozin/exenatide for the following 28 weeks (Placebo/Dapa+Exe), were observed for HbA1c (from baseline to week 24, from week 24 to week 52 and from baseline to week 52) and for glucose (FPG) (from week 24 to week 52 and from baseline to week 52). Only a selected number of analyses (HbA1c, FPG and insulin) were performed for subjects in the Placebo/Dapa+Exe group.

Statistically significant differences in the proportion of subjects with IFG and/or IGT were observed, between the Dapa+Exe/Dapa+Exe group and the Placebo/Dapa+Exe group (from baseline to week 24, Cochran–Mantel–Haenszel test). The proportion of subjects with raised status was lower in the Dapa+Exe/Dapa+Exe group (33.3%) than in the Placebo/Dapa+Exe group (82.4%) at week 24 and also at week 52 (28.6% vs 52.9%). Also, within the Dapa+Exe/Dapa+Exe group, there were statistically significant reductions in the proportion of subjects with IFG and/or IGT shown (from baseline to week 24 and from baseline to week 52, McNemar's test).

Only descriptive statistical analyses were performed for the other OGTT variables (plasma glucose, , insulin, C-peptide and ketones) and no apparent differences between the treatment groups, or relevant changes in mean values from screening to week 12, week 24 or week 52 (where applicable), were observed for any of the other variables.

Table 50 Summary of within group differences in haemoglobin, glucose tolerance, insulin secretion and insulin sensitivity. Extension-full analysis set

Variable	Time period	Unit	Adjusted mean change[a]	(95% CI)	p-value
HbA1c	**Baseline to Week 24**	mmol/L	**-3.9**	**(-4.8 to -2.9)**	**p<0.0001**
	Week 24 to Week 52	mmol/L	0.4	(-0.5 to 1.3)	p=0.3973
	Baseline to Week 52	mmol/L	**-3.1**	**(-4.0 to -2.2)**	**p<0.0001**
(Placebo/Dapa+Exe)	**Baseline to Week 24**	mmol/L	**-1.6**	**(-2.6 to -0.5)**	**p=0.0041**
(Placebo/Dapa+Exe)	**Week 24 to Week 52**	mmol/L	**-1.4**	**(-2.3 to -0.5)**	**p=0.0038**
(Placebo/Dapa+Exe)	**Baseline to Week 52**	mmol/L	**-3.1**	**(-4.1 to -2.2)**	**p<0.0001**
Glucose (FPG)	**Baseline to Week 24**	mmol/L	**-0.42**	**(-0.58 to -0.25)**	**p<0.0001**
	Week 24 to Week 52	mmol/L	0.01	(-0.16 to 0.18)	p=0.8932
	Baseline to Week 52	mmol/L	**-0.31**	**(-0.47 to -0.14)**	**p=0.0006**
(Placebo/Dapa+Exe)	Baseline to Week 24	mmol/L	0.14	(-0.04 to 0.33)	p=0.1193
(Placebo/Dapa+Exe)	**Week 24 to Week 52**	mmol/L	**-0.27**	**(-0.45 to -0.09)**	**p=0.0046**
(Placebo/Dapa+Exe)	**Baseline to Week 52**	mmol/L	**-0.29**	**(-0.45 to -0.12)**	**p=0.0012**
Glucose 120 min	**Baseline to Week 24**	mmol/L	**-1.84**	**(-2.67 to -1.00)**	**p=0.0002**
	Week 24 to Week 52	mmol/L	-0.30	(-1.04 to 0.43)	p=0.3883
	Baseline to Week 52	mmol/L	**-2.21**	**(-3.01 to -1.40)**	**p<0.0001**
Glucose AUC_{0-3h}	**Baseline to Week 24**	mmol/L x 180 min	**-218.047**	**(-312.498 to -123.596)**	**p=0.0002**
	Week 24 to Week 52	mmol/L x 180 min	0.579	(-77.507 to 78.665)	p=0.9871
	Baseline to Week 52	mmol/L x 180 min	**-248.655**	**(-334.152 to -163.157)**	**p<0.0001**
Insulin	Baseline to Week 24	mU/L	2.27	(-2.43 to 6.96)	p=0.3329
	Week 24 to Week 52	mU/L	**-4.90**	**(-7.49 to -2.31)**	**p=0.0006**
	Baseline to Week 52	mU/L	-2.53	(-5.39 to 0.33)	p=0.0813
(Placebo/Dapa+Exe)	Baseline to Week 24	mU/L	2.20	(-3.03 to 7.44)	p=0.3978
(Placebo/Dapa+Exe)	Week 24 to Week 52	mU/L	1.13	(-1.68 to 3.94)	p=0.4152
(Placebo/Dapa+Exe)	Baseline to Week 52	mU/L	3.05	(-0.08 to 6.17)	p=0.0555
Insulin AUC_{0-3h}	Baseline to Week 24	mU/L x 180 min	-590.161	(-2328.55 to 1148.232)	p=0.4804
	Week 24 to Week 52	mU/L x 180 min	-985.668	(-3175.79 to 1204.455)	p=0.3352
	Baseline to Week 52	mU/L x 180 min	-1544.88	(-3924.18 to 834.411)	p=0.1753

a Adjusted mean change during baseline to week 24, week 24 to week 52 or baseline to week 52, within the Dapa+Exe/Dapa+Exe group or within the Placebo/Dapa+Exe group.
Source: Table 37 to Table 49, Table 154 to Table 168 (extension-FAS tables).

11.4.3.3 Blood Lipid Profile

The blood lipid profile was assessed at screening (baseline), weeks 12, 24 and 52.

Descriptive data of the blood lipid profile are summarized for the extension-FAS and extension-PPAS in Section 14.2.5.3.1 (TC [Table 186 and Table 187]), Section 14.2.5.3.2 (LDL-C [Table 188 and Table 189]), Section 14.2.5.3.3 (HDL-C [Table 190 and Table 191]) and Section 14.2.5.3.4 (TG [Table 192 and Table 193]).

The variables are presented as summary statistics by treatment group including mean change from baseline to weeks 12, 24 and 52, and corresponding 95% confidence intervals for the extension-FAS and extension-PPAS. Individual data pertaining to this section are provided in Appendix 16.2.6.

No apparent differences between the treatment groups, or relevant changes in mean values from screening to week 12, week 24 or week 52, were observed for any of the blood lipid profile variables (TC, LDL-C, HDL-C and TG), in either extension-FAS or extension-PPAS (Table 186, Section 14.2.5.3.1 to Table 193, Section 14.2.5.3.4).

11.4.3.3.1 Summary – Blood Lipid Profile

No apparent differences between the treatment groups, or relevant changes in mean values from screening to week 12, week 24 or week 52, were observed for any of the blood lipid profile variables (TC, LDL-C, HDL-C and TG) (Table 51).

Table 51 Summary of blood lipid profile variables at week 24 and week 52. Extension-full analysis set

Variable	Unit		Mean change[a]	(95% CI)	p-value
TC	mmol/L	24 weeks	-0.11	(-0.34 to 0.12)	NA
	mmol/L	52 weeks	-0.28	(-0.56 to 0.01)	NA
(Placebo/Dapa+Exe)	mmol/L	24 weeks	-0.28	(-0.62 to 0.06)	NA
(Placebo/Dapa+Exe)	mmol/L	52 weeks	-0.35	(-0.69 to -0.02)	NA
LDL-C	mmol/L	24 weeks	-0.12	(-0.33 to 0.09)	NA
	mmol/L	52 weeks	-0.34	(-0.55 to -0.13)	NA
(Placebo/Dapa+Exe)	mmol/L	24 weeks	-0.22	(-0.50 to 0.06)	NA
(Placebo/Dapa+Exe)	mmol/L	52 weeks	-0.33	(-0.64 to -0.02)	NA
HDL-C	mmol/L	24 weeks	0.033	(-0.062 to 0.128)	NA
	mmol/L	52 weeks	-0.006	(-0.160 to 0.149)	NA
(Placebo/Dapa+Exe)	mmol/L	24 weeks	-0.085	(-0.170 to 0.000)	NA
(Placebo/Dapa+Exe)	mmol/L	52 weeks	0.012	(-0.074 to 0.099)	NA
TG	mmol/L	24 weeks	-0.114	(-0.337 to 0.109)	NA
	mmol/L	52 weeks	-0.261	(-0.464 to -0.057)	NA
(Placebo/Dapa+Exe)	mmol/L	24 weeks	-0.060	(-0.294 to 0.174)	NA
(Placebo/Dapa+Exe)	mmol/L	52 weeks	-0.141	(-0.372 to 0.090)	NA

a Mean change from baseline to week 24 or week 52, within the Dapa+Exe/Dapa+Exe group or within the Placebo/Dapa+Exe group.

HDL-C= high-density lipoprotein cholesterol, LDL-C= low-density lipoprotein cholesterol, NA= not applicable, TC= total cholesterol, TG= triglycerides

Source: Table 186 to Table 192 (extension-FAS tables).

11.4.3.4 Vital Signs

Vital signs (blood pressure and pulse) were assessed at screening, week 0 (baseline), weeks 4, 8, 12, 24, 38 and 52.

Descriptive data and the results of the statistical analyses for the extension-FAS are presented in Section 11.4.3.4.1 (systolic blood pressure), Section 11.4.3.4.2 (diastolic blood pressure) and Section 11.4.3.4.3 (pulse). A summary is provided in Section 11.4.3.4.4.

The corresponding tables for extension-FAS not presented in the sections below and the extension-PPAS are provided in Section 14.2.5.4. Individual data pertaining to this section are provided in Appendix 16.2.6.

11.4.3.4.1 Systolic Blood Pressure

A statistically significant reduction in mean systolic blood pressure between baseline (week 0) and week 24 was observed within the dapagliflozin/exenatide group (-8.8 mmHg, p=0.0004) but not within the placebo group (-2.4 mmHg) (Table 52).

There was no statistically significant mean change in systolic blood pressure between week 24 and 52 within either group (Dapa+Exe/Dapa+Exe group: -4.4 mmHg; Placebo/Dapa+Exe group: -4.1 mmHg) (Table 194, Section 14.2.5.4.1).

Between baseline (week 0) and week 52, there were statistically significant reductions in mean systolic blood pressure within both groups (Dapa+Exe/Dapa+Exe group: -13.0 mmHg, p<0.0001; Placebo/Dapa+Exe group: -8.6 mmHg, p=0.0045) (Table 53).

Extension-PPAS results for systolic blood pressure were similar, except between week 24 and week 52 when the Dapa+Exe/Dapa+Exe group showed a statistically significant reduction (Table 195 to Table 197, Section 14.2.5.4.1).

Table 52 Systolic blood pressure (mmHg) and adjusted mean change from baseline to 24 weeks. Extension full analysis set

Systolic blood pressure (mmHg)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Baseline		
n/nmiss	21/0	17/0
Mean (SD)	132.71 (12.77)	137.38 (13.79)
Median	129.50	137.50
Q1, Q3	122.50, 140.00	132.50, 145.00
Min, Max	114.0, 162.5	112.5, 161.0
4 weeks		
n/nmiss	21/0	17/0
Mean (SD)	129.02 (16.83)	136.38 (12.37)
Median	128.00	136.00
Q1, Q3	117.00, 143.50	127.00, 141.00
Min, Max	102.5, 159.0	118.0, 161.5
Adjusted mean change (95% CI)	-4.21 (-9.75, 1.34)	0.25 (-5.91, 6.41)
p-value	0.1324	0.9344
8 weeks		
n/nmiss	21/0	17/0
Mean (SD)	123.00 (13.37)	133.09 (12.32)
Median	124.00	132.00
Q1, Q3	114.00, 130.50	123.00, 142.50
Min, Max	100.0, 150.0	112.5, 157.5
Adjusted mean change (95% CI)	-10.23 (-14.15, -6.31)	-3.04 (-7.40, 1.32)
p-value	<.0001	0.1653
12 weeks		
n/nmiss	21/0	17/0
Mean (SD)	123.12 (13.06)	131.44 (12.31)
Median	123.50	133.00
Q1, Q3	110.00, 133.00	128.00, 141.50
Min, Max	105.0, 151.5	100.0, 147.5
Adjusted mean change (95% CI)	-10.11 (-14.40, -5.83)	-4.69 (-9.45, 0.08)
p-value	<.0001	0.0535
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	124.45 (11.39)	133.71 (11.43)
Median	121.00	135.00
Q1, Q3	117.00, 133.00	127.00, 141.00
Min, Max	97.0, 142.5	111.0, 151.0
Adjusted mean change (95% CI)	-8.78 (-13.32, -4.24)	-2.42 (-7.47, 2.63)
p-value	0.0004	0.3352

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 53 Systolic blood pressure (mmHg) and adjusted mean change from baseline to 52 weeks. Extension full analysis set

Systolic blood pressure (mmHg)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Baseline		
n/nmiss	21/0	17/0
Mean (SD)	132.71 (12.77)	137.38 (13.79)
Median	129.50	137.50
Q1, Q3	122.50, 140.00	132.50, 145.00
Min, Max	114.0, 162.5	112.5, 161.0
4 weeks		
n/nmiss	21/0	17/0
Mean (SD)	129.02 (16.83)	136.38 (12.37)
Median	128.00	136.00
Q1, Q3	117.00, 143.50	127.00, 141.00
Min, Max	102.5, 159.0	118.0, 161.5
Adjusted mean change (95% CI)	-4.30 (-9.84, 1.25)	0.12 (-6.03, 6.28)
p-value	0.1250	0.9676
8 weeks		
n/nmiss	21/0	17/0
Mean (SD)	123.00 (13.37)	133.09 (12.32)
Median	124.00	132.00
Q1, Q3	114.00, 130.50	123.00, 142.50
Min, Max	100.0, 150.0	112.5, 157.5
Adjusted mean change (95% CI)	-10.32 (-14.24, -6.40)	-3.17 (-7.52, 1.18)
p-value	<.0001	0.1477
12 weeks		
n/nmiss	21/0	17/0
Mean (SD)	123.12 (13.06)	131.44 (12.31)
Median	123.50	133.00
Q1, Q3	110.00, 133.00	128.00, 141.50
Min, Max	105.0, 151.5	100.0, 147.5
Adjusted mean change (95% CI)	-10.20 (-14.49, -5.91)	-4.82 (-9.58, -0.06)
p-value	<.0001	0.0474
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	124.45 (11.39)	133.71 (11.43)
Median	121.00	135.00
Q1, Q3	117.00, 133.00	127.00, 141.00
Min, Max	97.0, 142.5	111.0, 151.0
Adjusted mean change (95% CI)	-8.87 (-13.43, -4.31)	-2.55 (-7.61, 2.50)
p-value	0.0004	0.3114
38 weeks		
n/nmiss	19/2	17/0
Mean (SD)	122.45 (16.05)	127.29 (8.63)
Median	121.00	125.00
Q1, Q3	107.00, 136.50	121.00, 135.00
Min, Max	95.5, 150.0	112.5, 144.0
Adjusted mean change (95% CI)	-10.77 (-15.66, -5.88)	-8.96 (-14.24, -3.69)

Systolic blood pressure (mmHg)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
p-value	<.0001	0.0015
52 weeks		
n/nmiss	17/4	17/0
Mean (SD)	121.44 (15.55)	127.68 (7.95)
Median	123.00	127.50
Q1, Q3	110.50, 128.00	120.50, 135.00
Min, Max	98.5, 160.0	114.0, 138.5
Adjusted mean change (95% CI)	-13.03 (-18.50, -7.56)	-8.58 (-14.30, -2.86)
p-value	<.0001	0.0045

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

11.4.3.4.2 Diastolic Blood Pressure

No statistically significant changes in diastolic blood pressure were observed within the Dapa+Exe/Dapa+Exe group or within the Placebo/Dapa+Exe group, at any of the time points (from baseline to 24 weeks, from 24 weeks to 52 weeks and from baseline to 52 weeks) (Table 198 to Table 200, Section 14.2.5.4.2).

Similar results were obtained for the extension-PPAS (Table 201 to Table 203, Section 14.2.5.4.2).

11.4.3.4.3 Pulse

A statistically significant increase in mean pulse between week 24 and week 52 was observed within the Placebo/Dapa+Exe group (2.0 beats/min, p=0.0096) but not within the Dapa+Exe/Dapa+Exe group (adjusted mean change: 5.9 beats/min) (Table 54).

Overall, from baseline (week 0) to week 52, there was also a statistically significant difference in mean pulse observed within the Placebo/Dapa+Exe group (2.4 beats/min, p=0.0107), but not within the Dapa+Exe/Dapa+Exe group (5.6 beats/min) (Table 55).

From baseline (week 0) to week 24, there were no statistically significant differences observed within any of the groups (Dapa+Exe/Dapa+Exe group: 2.1 beats/min; Placebo/Dapa+Exe group: -0.6 beats/min) (Table 204, Section 14.2.5.4.3).

Similar results were observed for the extension-PPAS, see Section 14.2.5.4.3 (Table 205 to Table 207).

Table 54 Pulse (beats/min) and adjusted mean change from 24 weeks to 52 weeks. Extension full analysis set

Pulse (beats/min)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	68.8 (10.0)	65.6 (9.6)
Median	66.0	64.0
Q1, Q3	62.0, 72.0	60.0, 70.0
Min, Max	52, 100	54, 86
38 weeks		
n/nmiss	19/2	17/0
Mean (SD)	69.2 (8.0)	72.9 (11.6)
Median	68.0	72.0
Q1, Q3	62.0, 76.0	60.0, 82.0
Min, Max	57, 82	58, 96
Adjusted mean change (95% CI)	2.8 (-1.7, 7.3)	7.0 (2.3, 11.8)
p-value	0.2171	0.0048
52 weeks		
n/nmiss	17/4	17/0
Mean (SD)	68.5 (10.7)	71.8 (7.8)
Median	62.0	72.0
Q1, Q3	60.0, 78.0	65.0, 78.0
Min, Max	58, 96	59, 85
Adjusted mean change (95% CI)	2.0 (-2.3, 6.4)	5.9 (1.6, 10.3)
p-value	0.3499	0.0096

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 55 Pulse (beats/min) and adjusted mean change from baseline to 52 weeks. Extension full analysis set

Pulse (beats/min)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Baseline		
n/nmiss	21/0	17/0
Mean (SD)	67.1 (9.8)	66.4 (9.5)
Median	66.0	64.0
Q1, Q3	60.0, 72.0	60.0, 70.0
Min, Max	52, 88	52, 94
4 weeks		
n/nmiss	21/0	17/0
Mean (SD)	70.3 (8.2)	65.8 (7.6)
Median	68.0	66.0
Q1, Q3	64.0, 76.0	60.0, 70.0
Min, Max	58, 92	56, 82
Adjusted mean change (95% CI)	3.7 (0.7, 6.6)	-0.4 (-3.7, 2.9)
p-value	0.0163	0.8270
8 weeks		
n/nmiss	21/0	17/0
Mean (SD)	70.0 (10.0)	68.4 (10.2)
Median	68.0	70.0
Q1, Q3	64.0, 72.0	62.0, 78.0
Min, Max	55, 96	48, 82
Adjusted mean change (95% CI)	3.4 (-0.9, 7.8)	2.2 (-2.6, 7.1)
p-value	0.1195	0.3590
12 weeks		
n/nmiss	21/0	17/0
Mean (SD)	66.7 (7.9)	63.1 (8.1)
Median	66.0	62.0
Q1, Q3	62.0, 70.0	58.0, 68.0
Min, Max	52, 88	50, 78
Adjusted mean change (95% CI)	0.1 (-3.0, 3.2)	-3.1 (-6.5, 0.4)
p-value	0.9665	0.0786
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	68.8 (10.0)	65.6 (9.6)
Median	66.0	64.0
Q1, Q3	62.0, 72.0	60.0, 70.0
Min, Max	52, 100	54, 86
Adjusted mean change (95% CI)	2.2 (-0.7, 5.1)	-0.5 (-3.7, 2.7)
p-value	0.1279	0.7646
38 weeks		
n/nmiss	19/2	17/0
Mean (SD)	69.2 (8.0)	72.9 (11.6)
Median	68.0	72.0
Q1, Q3	62.0, 76.0	60.0, 82.0
Min, Max	57, 82	58, 96
Adjusted mean change (95% CI)	3.3 (-0.9, 7.5)	6.8 (2.3, 11.2)

Pulse (beats/min)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
p-value	0.1198	0.0042
52 weeks		
n/nmiss	17/4	17/0
Mean (SD)	68.5 (10.7)	71.8 (7.8)
Median	62.0	72.0
Q1, Q3	60.0, 78.0	65.0, 78.0
Min, Max	58, 96	59, 85
Adjusted mean change (95% CI)	2.4 (-1.9, 6.6)	5.6 (1.4, 9.9)
p-value	0.2660	0.0107

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

11.4.3.4.4 Summary – Vital Signs

Statistically significant reductions in systolic blood pressure were observed within the group that received dapagliflozin/exenatide for 24 + 28 weeks (from baseline to week 24 and from baseline to week 52) (see summary in Table 56). No statistically significant differences within the group with regard to diastolic blood pressure or pulse were observed.

Within the group that received placebo for 24 weeks and dapagliflozin/exenatide for the following 28 weeks, statistically significant differences were observed for systolic blood pressure (reduction from baseline to week 52) and for pulse (increase between week 24 and week 52 and from baseline to week 52). No statistically significant difference within the group with regard to diastolic blood pressure was observed.

Table 56 Summary of within group differences in vital signs. Extension full analysis set

Variable	Time period	Unit	Adjusted mean change[a]	(95% CI)	p-value
Systolic blood pressure	**Baseline to Week 24**	**mmHg**	**-8.78**	**(-13.32 to -4.2)**	**p=0.0004**
	Week 24 to Week 52	mmHg	-4.36	(-9.37 to 0.64)	p=0.0853
	Baseline to Week 52	**mmHg**	**-13.03**	**(-18.50 to -7.56)**	**p<0.0001**
(Placebo/Dapa+Exe)	Baseline to Week 24	mmHg	-2.42	(-7.47 to 2.63)	p=0.3352
(Placebo/Dapa+Exe)	Week 24 to Week 52	mmHg	-4.12	(-9.10 to 0.85)	p=0.1009
(Placebo/Dapa+Exe)	**Baseline to Week 52**	**mmHg**	**-8.58**	**(-14.30 to -2.86)**	**p=0.0045**
Diastolic blood pressure	Baseline to Week 24	mmHg	1.51	(-3.29 to 6.31)	p=0.5270
	Week 24 to Week 52	mmHg	-1.42	(-5.43 to 2.60)	p=0.4781
	Baseline to Week 52	mmHg	0.41	(-3.65 to 4.47)	p=0.8376
(Placebo/Dapa+Exe)	Baseline to Week 24	mmHg	2.05	(-3.32 to 7.42)	p=0.4449
(Placebo/Dapa+Exe)	Week 24 to Week 52	mmHg	0.26	(-3.73 to 4.26)	p=0.8933
(Placebo/Dapa+Exe)	Baseline to Week 52	mmHg	0.96	(-3.42 to 5.35)	p=0.6585
Pulse	Baseline to Week 24	beats/min	2.1	(-0.7 to 5.0)	p=0.1407
	Week 24 to Week 52	beats/min	2.0	(-2.3 to 6.4)	p=0.3499
	Baseline to Week 52	beats/min	2.4	(-1.9 to 6.6)	p=0.2660
(Placebo/Dapa+Exe)	Baseline to Week 24	beats/min	-0.6	(-3.7 to 2.6)	p=0.7267
(Placebo/Dapa+Exe)	**Week 24 to Week 52**	**beats/min**	**5.9**	**(1.6 to 10.3)**	**p=0.0096**
(Placebo/Dapa+Exe)	**Baseline to Week 52**	**beats/min**	**5.6**	**(1.4 to 9.9)**	**p=0.0107**

a Adjusted mean change during baseline to week 24, week 24 to week 52 or baseline to week 52, within the Dapa+Exe /Dapa+Exe dapagliflozin/exenatide group or within the Placebo/Dapa+Exe group.

Source: Table 52 to Table 55, Table 194 to Table 204 (extension-FAS tables).

11.4.3.5 Other Anthropometric Measurements

Measurements of waist and hip circumference (cm) were assessed at screening, week 0 (baseline), and weeks 4, 8, 12, 24 and 52.

Descriptive data and the results of the statistical analyses for the extension-FAS are presented in Section 11.4.3.5.1 (waist circumference), Section 11.4.3.5.2 (waist-hip ratio) and Section 11.4.3.5.3 (BMI). A summary is provided in Section 11.4.3.5.4.

The corresponding tables for extension-FAS not presented in the sections below and the extension-PPAS are provided in Section 14.2.5.5. Individual data pertaining to this section are provided in Appendix 16.2.6.

11.4.3.5.1 Waist Circumference

A statistically significant reduction in mean waist circumference between baseline (week 0) and week 24 was observed within the Dapa+Exe/Dapa+Exe group (-5.3 cm, p<0.0001) but not within the Placebo/Dapa+Exe group (-2.6 cm) (Table 57).

Between week 24 and week 52, a statistically significant reduction in mean waist circumference was observed within the Placebo/Dapa+Exe group (-4.8 cm, p=0.0020), but not within the Dapa+Exe/Dapa+Exe group (-2.1 cm) (Table 58).

Overall, from baseline (week 0) to week 52, there were statistically significant reductions in mean waist circumference observed within both groups (Dapa+Exe/Dapa+Exe group: -7.3 cm, p<0.0001; Placebo/Dapa+Exe group: -7.2 cm, p=0.0003) (Table 59).

Similar results were observed for the extension-PPAS, see Section 14.2.5.5.1 (Table 208 to Table 210).

Table 57 Waist circumference (cm) and adjusted mean change from baseline to 24 weeks. Extension full analysis set

Waist circumference (cm)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Baseline		
n/nmiss	21/0	17/0
Mean (SD)	116.43 (11.45)	114.21 (12.57)
Median	115.00	109.50
Q1, Q3	110.00, 122.00	107.00, 120.00
Min, Max	93.5, 148.5	94.0, 143.0
4 weeks		
n/nmiss	21/0	17/0
Mean (SD)	115.00 (10.67)	112.29 (11.72)
Median	114.00	111.00
Q1, Q3	108.50, 120.50	103.50, 114.50
Min, Max	96.0, 143.0	98.5, 141.5
Adjusted mean change (95% CI)	-0.98 (-2.74, 0.78)	-1.77 (-3.70, 0.16)
p-value	0.2661	0.0711
8 weeks		
n/nmiss	21/0	17/0
Mean (SD)	114.88 (11.02)	114.76 (11.72)
Median	113.00	113.00
Q1, Q3	107.50, 119.50	107.50, 117.00
Min, Max	95.0, 147.5	101.0, 144.0
Adjusted mean change (95% CI)	-1.10 (-2.77, 0.58)	0.70 (-1.14, 2.54)
p-value	0.1917	0.4453
12 weeks		
n/nmiss	21/0	17/0
Mean (SD)	112.62 (11.37)	111.47 (12.19)
Median	112.50	109.00
Q1, Q3	105.00, 119.00	104.00, 116.50
Min, Max	91.5, 145.0	96.5, 142.0
Adjusted mean change (95% CI)	-3.36 (-5.46, -1.26)	-2.60 (-4.91, -0.28)
p-value	0.0025	0.0289
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	110.69 (12.24)	111.47 (13.40)
Median	111.00	111.00
Q1, Q3	102.00, 117.00	102.50, 117.00
Min, Max	88.0, 143.0	94.0, 138.0
Adjusted mean change (95% CI)	-5.29 (-7.69, -2.88)	-2.60 (-5.25, 0.06)

Waist circumference (cm)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
p-value	<.0001	0.0552

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 58 Waist circumference (cm) and adjusted mean change from 24 weeks to 52 weeks. Extension full analysis set

Waist circumference (cm)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	110.69 (12.24)	111.47 (13.40)
Median	111.00	111.00
Q1, Q3	102.00, 117.00	102.50, 117.00
Min, Max	88.0, 143.0	94.0, 138.0
38 weeks		
n/nmiss	19/2	17/0
Mean (SD)	108.76 (14.15)	107.47 (11.68)
Median	110.00	107.00
Q1, Q3	97.00, 119.50	101.00, 110.00
Min, Max	85.0, 140.0	87.0, 133.0
Adjusted mean change (95% CI)	-1.51 (-3.89, 0.87)	-4.16 (-6.73, -1.59)
p-value	0.2065	0.0024
52 weeks		
n/nmiss	17/4	17/0
Mean (SD)	107.18 (14.57)	106.79 (12.16)
Median	107.00	106.00
Q1, Q3	97.00, 120.00	98.00, 110.50
Min, Max	85.0, 140.0	87.0, 135.0
Adjusted mean change (95% CI)	-2.06 (-4.81, 0.70)	-4.84 (-7.76, -1.91)
p-value	0.1380	0.0020

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 59 Waist circumference (cm) and adjusted mean change from baseline to 52 weeks. Extension full analysis set

Waist circumference (cm)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Baseline		
n/nmiss	21/0	17/0
Mean (SD)	116.43 (11.45)	114.21 (12.57)
Median	115.00	109.50
Q1, Q3	110.00, 122.00	107.00, 120.00
Min, Max	93.5, 148.5	94.0, 143.0
4 weeks		
n/nmiss	21/0	17/0
Mean (SD)	115.00 (10.67)	112.29 (11.72)
Median	114.00	111.00
Q1, Q3	108.50, 120.50	103.50, 114.50
Min, Max	96.0, 143.0	98.5, 141.5
Adjusted mean change (95% CI)	-0.97 (-2.73, 0.80)	-1.73 (-3.66, 0.21)
p-value	0.2742	0.0785
8 weeks		
n/nmiss	21/0	17/0
Mean (SD)	114.88 (11.02)	114.76 (11.72)
Median	113.00	113.00
Q1, Q3	107.50, 119.50	107.50, 117.00
Min, Max	95.0, 147.5	101.0, 144.0
Adjusted mean change (95% CI)	-1.08 (-2.76, 0.59)	0.74 (-1.09, 2.58)
p-value	0.1970	0.4161
12 weeks		
n/nmiss	21/0	17/0
Mean (SD)	112.62 (11.37)	111.47 (12.19)
Median	112.50	109.00
Q1, Q3	105.00, 119.00	104.00, 116.50
Min, Max	91.5, 145.0	96.5, 142.0
Adjusted mean change (95% CI)	-3.35 (-5.44, -1.25)	-2.55 (-4.86, -0.24)
p-value	0.0026	0.0312
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	110.69 (12.24)	111.47 (13.40)
Median	111.00	111.00
Q1, Q3	102.00, 117.00	102.50, 117.00
Min, Max	88.0, 143.0	94.0, 138.0
Adjusted mean change (95% CI)	-5.28 (-7.67, -2.88)	-2.55 (-5.19, 0.09)
p-value	<.0001	0.0579
38 weeks		
n/nmiss	19/2	17/0
Mean (SD)	108.76 (14.15)	107.47 (11.68)
Median	110.00	107.00
Q1, Q3	97.00, 119.50	101.00, 110.00
Min, Max	85.0, 140.0	87.0, 133.0
Adjusted mean change (95% CI)	-6.74 (-9.91, -3.56)	-6.55 (-9.99, -3.11)

Waist circumference (cm)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
p-value	0.0001	0.0004
52 weeks		
n/nmiss	17/4	17/0
Mean (SD)	107.18 (14.57)	106.79 (12.16)
Median	107.00	106.00
Q1, Q3	97.00, 120.00	98.00, 110.50
Min, Max	85.0, 140.0	87.0, 135.0
Adjusted mean change (95% CI)	-7.25 (-10.62, -3.88)	-7.23 (-10.83, -3.63)
p-value	<.0001	0.0003

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

11.4.3.5.2 Waist-hip Ratio

Overall, from baseline (week 0) to week 52, there were statistically significant reductions in mean waist-hip ratio observed within both groups (Dapa+Exe/Dapa+Exe group: -0.03, p=0.0049; Placebo/Dapa+Exe group: -0.03, p=0.0140) (Table 60).

No statistically significant reductions in mean waist-hip ratio were observed within any of the groups, between baseline (week 0) and week 24 or between week 24 and week 52 (Table 211 and Table 212, Section 14.2.5.5.2).

Similar results were observed for the extension-PPAS, see Section 14.2.5.5.2 (Table 213 to Table 215).

Table 60 Waist-hip ratio and adjusted mean change from baseline to 52 weeks. Extension full analysis set

Waist-hip ratio	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Baseline		
n/nmiss	21/0	17/0
Mean (SD)	0.957 (0.088)	0.974 (0.098)
Median	0.960	0.970
Q1, Q3	0.890, 1.020	0.890, 1.030
Min, Max	0.79, 1.13	0.79, 1.18
4 weeks		
n/nmiss	21/0	17/0
Mean (SD)	0.956 (0.091)	0.962 (0.100)
Median	0.960	0.980
Q1, Q3	0.900, 1.010	0.890, 1.020
Min, Max	0.79, 1.14	0.81, 1.18
Adjusted mean change (95% CI)	0.002 (-0.012, 0.016)	-0.005 (-0.021, 0.011)
p-value	0.7869	0.5218
8 weeks		
n/nmiss	21/0	17/0
Mean (SD)	0.955 (0.089)	0.974 (0.084)

Waist-hip ratio	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Median	0.940	0.980
Q1, Q3	0.920, 1.000	0.920, 1.030
Min, Max	0.80, 1.11	0.84, 1.10
Adjusted mean change (95% CI)	0.000 (-0.015, 0.016)	0.007 (-0.011, 0.025)
p-value	0.9585	0.4121
12 weeks		
n/nmiss	21/0	17/0
Mean (SD)	0.948 (0.081)	0.959 (0.098)
Median	0.940	0.950
Q1, Q3	0.900, 0.990	0.880, 1.040
Min, Max	0.80, 1.12	0.81, 1.09
Adjusted mean change (95% CI)	-0.007 (-0.025, 0.012)	-0.008 (-0.029, 0.013)
p-value	0.4639	0.4447
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	0.939 (0.107)	0.956 (0.112)
Median	0.950	0.990
Q1, Q3	0.860, 0.990	0.850, 1.040
Min, Max	0.77, 1.15	0.80, 1.14
Adjusted mean change (95% CI)	-0.016 (-0.037, 0.005)	-0.011 (-0.034, 0.013)
p-value	0.1361	0.3561
38 weeks		
n/nmiss	19/2	17/0
Mean (SD)	0.927 (0.103)	0.945 (0.100)
Median	0.940	0.970
Q1, Q3	0.840, 1.020	0.870, 1.000
Min, Max	0.77, 1.12	0.79, 1.10
Adjusted mean change (95% CI)	-0.027 (-0.047, -0.008)	-0.022 (-0.043, -0.001)
p-value	0.0075	0.0437
52 weeks		
n/nmiss	17/4	17/0
Mean (SD)	0.919 (0.089)	0.939 (0.097)
Median	0.910	0.960
Q1, Q3	0.850, 1.000	0.860, 1.000
Min, Max	0.78, 1.07	0.78, 1.08
Adjusted mean change (95% CI)	-0.030 (-0.050, -0.010)	-0.027 (-0.049, -0.006)
p-value	0.0049	0.0140

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

11.4.3.5.3 Body Mass Index

A statistically significant reduction in mean BMI between baseline (week 0) and week 24 was observed within the Dapa+Exe/Dapa+Exe group (-1.4 kg/m^2, p<0.0001) but not within the Placebo/Dapa+Exe group (-0.2 kg/m^2) (Table 61).

Between week 24 and week 52, a statistically significant reduction in mean BMI was observed within the Placebo/Dapa+Exe group (-1.6 kg/m^2, p<0.0001), but not within the Dapa+Exe/Dapa+Exe group (-0.35 kg/m^2) (Table 62).

Overall, from baseline (week 0) to week 52, there were statistically significant reductions in mean BMI observed within both groups (Dapa+Exe/Dapa+Exe group: -1.7 kg/m^2, p=0.0014; Placebo/Dapa+Exe group: -1.8 kg/m^2, p=0.0026) (Table 63).

Similar results were observed for the extension-PPAS, see Section 14.2.5.5.3 (Table 216 to Table 218).

Table 61 BMI and adjusted mean change from baseline to 24 weeks. Extension full analysis set

Body mass index (BMI) (kg/m^2)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Baseline		
n/nmiss	21/0	17/0
Mean (SD)	35.686 (2.993)	34.876 (3.373)
Median	35.490	33.710
Q1, Q3	33.740, 37.550	33.230, 35.750
Min, Max	30.85, 44.07	30.79, 44.77
4 weeks		
n/nmiss	21/0	17/0
Mean (SD)	35.450 (3.202)	34.608 (3.389)
Median	35.330	33.810
Q1, Q3	32.990, 37.320	32.530, 34.830
Min, Max	29.78, 43.46	30.64, 44.64
Adjusted mean change (95% CI)	-0.247 (-0.508, 0.015)	-0.268 (-0.557, 0.020)
p-value	0.0638	0.0673
8 weeks		
n/nmiss	21/0	17/0
Mean (SD)	35.077 (3.329)	34.688 (3.383)
Median	35.240	34.110
Q1, Q3	32.410, 37.190	32.660, 34.580
Min, Max	28.87, 42.81	30.64, 45.04
Adjusted mean change (95% CI)	-0.620 (-0.972, -0.267)	-0.188 (-0.578, 0.202)
p-value	0.0010	0.3337
12 weeks		
n/nmiss	21/0	17/0
Mean (SD)	34.487 (3.654)	34.569 (3.433)
Median	35.210	33.660
Q1, Q3	31.290, 36.800	32.470, 35.030
Min, Max	27.59, 42.62	30.34, 45.04
Adjusted mean change (95% CI)	-1.209 (-1.655, -0.763)	-0.307 (-0.802, 0.187)
p-value	<.0001	0.2155
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	34.260 (4.171)	34.642 (3.440)
Median	34.900	34.050
Q1, Q3	30.820, 36.560	32.460, 35.310
Min, Max	26.05, 43.80	31.16, 44.97
Adjusted mean change (95% CI)	-1.436 (-2.028, -0.844)	-0.234 (-0.891, 0.423)

Body mass index (BMI) (kg/m²)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
p-value	<.0001	0.4738

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 62 BMI and adjusted mean change from 24 weeks to 52 weeks. Extension full analysis set

Body mass index (BMI) (kg/m²)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	34.260 (4.171)	34.642 (3.440)
Median	34.900	34.050
Q1, Q3	30.820, 36.560	32.460, 35.310
Min, Max	26.05, 43.80	31.16, 44.97
38 weeks		
n/nmiss	19/2	17/0
Mean (SD)	33.947 (4.643)	33.440 (3.549)
Median	34.590	32.710
Q1, Q3	30.490, 37.090	31.180, 33.700
Min, Max	24.76, 43.21	29.62, 44.30
Adjusted mean change (95% CI)	-0.106 (-0.580, 0.367)	-1.272 (-1.778, -0.765)
p-value	0.6510	<.0001
52 weeks		
n/nmiss	17/4	17/0
Mean (SD)	33.356 (5.277)	33.108 (3.902)
Median	33.730	32.080
Q1, Q3	29.650, 35.560	30.310, 34.230
Min, Max	23.88, 44.14	29.20, 44.81
Adjusted mean change (95% CI)	-0.347 (-0.973, 0.280)	-1.603 (-2.256, -0.951)
p-value	0.2677	<.0001

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 63 BMI and adjusted mean change from baseline to 52 weeks. Extension full analysis set

Body mass index (BMI) (kg/m²)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Baseline		
n/nmiss	21/0	17/0
Mean (SD)	35.686 (2.993)	34.876 (3.373)
Median	35.490	33.710
Q1, Q3	33.740, 37.550	33.230, 35.750
Min, Max	30.85, 44.07	30.79, 44.77
4 weeks		
n/nmiss	21/0	17/0
Mean (SD)	35.450 (3.202)	34.608 (3.389)
Median	35.330	33.810
Q1, Q3	32.990, 37.320	32.530, 34.830
Min, Max	29.78, 43.46	30.64, 44.64
Adjusted mean change (95% CI)	-0.238 (-0.501, 0.026)	-0.265 (-0.554, 0.025)
p-value	0.0759	0.0720
8 weeks		
n/nmiss	21/0	17/0
Mean (SD)	35.077 (3.329)	34.688 (3.383)
Median	35.240	34.110
Q1, Q3	32.410, 37.190	32.660, 34.580
Min, Max	28.87, 42.81	30.64, 45.04
Adjusted mean change (95% CI)	-0.610 (-0.965, -0.256)	-0.185 (-0.577, 0.207)
p-value	0.0013	0.3451
12 weeks		
n/nmiss	21/0	17/0
Mean (SD)	34.487 (3.654)	34.569 (3.433)
Median	35.210	33.660
Q1, Q3	31.290, 36.800	32.470, 35.030
Min, Max	27.59, 42.62	30.34, 45.04
Adjusted mean change (95% CI)	-1.200 (-1.650, -0.750)	-0.304 (-0.802, 0.195)
p-value	<.0001	0.2241
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	34.260 (4.171)	34.642 (3.440)
Median	34.900	34.050
Q1, Q3	30.820, 36.560	32.460, 35.310
Min, Max	26.05, 43.80	31.16, 44.97
Adjusted mean change (95% CI)	-1.427 (-2.024, -0.830)	-0.231 (-0.893, 0.432)
p-value	<.0001	0.4840
38 weeks		
n/nmiss	19/2	17/0
Mean (SD)	33.947 (4.643)	33.440 (3.549)
Median	34.590	32.710
Q1, Q3	30.490, 37.090	31.180, 33.700
Min, Max	24.76, 43.21	29.62, 44.30
Adjusted mean change (95% CI)	-1.473 (-2.320, -0.626)	-1.433 (-2.361, -0.505)

Body mass index (BMI) (kg/m²)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
p-value	0.0012	0.0035
52 weeks		
n/nmiss	17/4	17/0
Mean (SD)	33.356 (5.277)	33.108 (3.902)
Median	33.730	32.080
Q1, Q3	29.650, 35.560	30.310, 34.230
Min, Max	23.88, 44.14	29.20, 44.81
Adjusted mean change (95% CI)	-1.729 (-2.743, -0.714)	-1.765 (-2.867, -0.663)
p-value	0.0014	0.0026

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

11.4.3.5.4 Summary - Other Anthropometric Measurements

Statistically significant differences within the group that received dapagliflozin/exenatide for 24 + 28 weeks, were observed for waist circumference (from baseline to week 24 and from baseline to week 52), for waist-hip ratio (from baseline to week 52) and for BMI (from baseline to week 24 and from baseline to week 52) (see summary in Table 64).

Within the group that received placebo for 24 weeks and dapagliflozin/exenatide for the following 28 weeks, statistically significant differences were observed for waist circumference (from week 24 to week 52 and from baseline to week 52), for waist-hip ratio (from baseline to week 52) and for BMI (from week 24 to week 52 and from baseline to week 52).

Table 64 Summary of within group differences in other anthropometric measurements. Extension full analysis set

Variable	Time period	Unit	Adjusted mean change[a]	(95% CI)	p-value
Waist circumference	**Baseline to Week 24**	cm	**-5.29**	**(-7.69 to -2.88)**	**p<0.0001**
	Week 24 to Week 52	cm	-2.06	(-4.81 to 0.70)	p=0.1380
	Baseline to Week 52	cm	**-7.25**	**(-10.62 to -3.88)**	**p<0.0001**
(Placebo/Dapa+Exe)	Baseline to Week 24	cm	-2.60	(-5.25 to 0.06)	p=0.0552
(Placebo/Dapa+Exe)	**Week 24 to Week 52**	**cm**	**-4.84**	**(-7.76 to -1.91)**	**p=0.0020**
(Placebo/Dapa+Exe)	**Baseline to Week 52**	cm	**-7.23**	**(-10.83 to -3.63)**	**p=0.0003**
Waist-hip ratio	Baseline to Week 24	-	-0.016	(-0.036 to 0.005)	p=0.1379
	Week 24 to Week 52	-	-0.016	(-0.037 to 0.004)	p=0.1202
	Baseline to Week 52	**-**	**-0.030**	**(-0.050 to -0.010)**	**p=0.0049**
(Placebo/Dapa+Exe)	Baseline to Week 24	-	-0.010	(-0.034 to 0.013)	p=0.3717
(Placebo/Dapa+Exe)	Week 24 to Week 52	-	-0.016	(-0.038 to 0.006)	p=0.1410
(Placebo/Dapa+Exe)	**Baseline to Week 52**	**-**	**-0.027**	**(-0.049 to -0.006)**	**p=0.0140**
Body mass index	**Baseline to Week 24**	**kg/m²**	**-1.436**	**(-2.028 to -0.844)**	**p<0.0001**
	Week 24 to Week 52	kg/m²	-0.347	(-0.973 to 0.280)	p=0.2677
	Baseline to Week 52	**kg/m²**	**-1.729**	**(-2.743 to -0.714)**	**p=0.0014**
(Placebo/Dapa+Exe)	Baseline to Week 24	kg/m²	-0.234	(-0.891 to 0.423)	p=0.4738
(Placebo/Dapa+Exe)	**Week 24 to Week 52**	**kg/m²**	**-1.603**	**(-2.256 to -0.951)**	**p<0.0001**
(Placebo/Dapa+Exe)	**Baseline to Week 52**	**kg/m²**	**-1.765**	**(-2.867 to -0.663)**	**p=0.0026**

[a] Adjusted mean change during baseline to week 24, week 24 to week 52 or baseline to week 52, within the Dapa+Exe/Dapa+Exe group or within the Placebo/Dapa+Exe group. Source: Table 57 to Table 63 and Table 208 to Table 215 (extension-FAS tables), Section 14.2.5.5.

11.4.4 Statistical/Analytical Issues

11.4.4.1 Adjustments for Covariates

The MMRM was adjusted for treatment, week, treatment-by-week interaction, gender and baseline value as covariates.

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 any of the analysis sets (FAS, extension-FAS, full-FAS, PPAS, extension-PPAS, safety and extension safety).

For continuous variables for which analyses were performed using the 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 Mixed Model for Repeat Measures

In the MMRM analyses, on the full-FAS, it has not been taken into account that subjects that were on placebo treatment for the initial 24 weeks (main study part) changed to active treatment during the following 28 weeks (extension study part). This may lead to underestimation of change in body weight during the extension study part for placebo subjects not electing to continue after 24 weeks.

11.4.4.4 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.

11.4.4.5 Multiple Comparison/Multiplicity

No control for multiplicity of endpoints was performed.

11.4.4.6 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 for the FAS (main study) and PPAS (main study) in Section 14.2.2.4 (Figure 16 to Figure 19) of the clinical trial report for the 24-week short-term treatment period (version 1.1, dated 11 Jan 2017), Appendix 16.5.

11.5 EFFICACY CONCLUSIONS

Primary Efficacy Variable

Mean Change in Body Weight (kg)

- **Extension-FAS and extension-PPAS**: A statistically significant reduction in mean body weight (kg) of 4.3 kg (p<0.0001) between baseline (week 0) and week 24 was observed within the group that had been on active treatment with dapagliflozin and exenatide for 24 weeks in the main study (Dapa+Exe/Dapa+Exe group) but not within the group that had been on placebo (Placebo/Dapa+Exe group). Similar results were obtained for the extension-PPAS.

  During the following 28-week open label extension study period, no further statistically significant weight reduction was observed within the Dapa+Exe/Dapa+Exe group whereas a statistically significant reduction in mean body weight by 4.8 kg (p<0.0001) was evident within the Placebo/Dapa+Exe group. Similar results were obtained for the extension-PPAS.

  Overall, from baseline (week 0) to week 52, there was a statistically significant reduction in body weight, within both groups (p=0.0013, Dapa+Exe/Dapa+Exe group; p=0.0023, Placebo/Dapa+Exe group). The adjusted mean change from baseline to week 52 was -5.3 kg in the group who received active treatment for 52 weeks and -5.4 kg in the group who received placebo for 24 weeks and active treatment for 28 weeks. The main weight reduction was observed during the first 12 weeks or 14 weeks of treatment with dapagliflozin/exenatide in both groups. Similar results were obtained for the extension-PPAS.

- **Full FAS:** When data from all subjects were included in the analyses, irrespective of continuation in the extension part of the study, corresponding statistically significant reductions in mean body weight (kg) were observed between baseline (week 0) and week 24 within the Dapa+Exe/Dapa+Exe group (-4.5 kg, p<0.0001, full FAS), between week 24 and week 52 within the placebo group (-3.8 kg, p=0.0006, full FAS) and between baseline and week 52 within both groups (-5.7 kg, p=0.0003, Dapa+Exe/Dapa+Exe group [full FAS]; -4.2 kg, p=0.0088, Placebo/Dapa+Exe group [full FAS]).

Secondary Efficacy Variable

Percentage Change in Body Weight

- **Extension-FAS and extension-PPAS**: A statistically significant reduction in mean body weight of 4.3% based on percentage change between baseline (week 0) and week 24 was observed within the Dapa+Exe/Dapa+Exe group (p<0.0001), but not within the Placebo/Dapa+Exe group.

  During the following 28-week open label extension study period, a statistically significant reduction in mean body weight of 4.7% was observed within the Placebo/Dapa+Exe group (p<0.0001). No further statistically significant decrease was observed within the Dapa+Exe/Dapa+Exe group.

  Overall, from baseline (week 0) to week 52, there was a statistically significant reduction in mean body weight (%) within both groups (p=0.0007, Dapa+Exe/Dapa+Exe group; p=0.0023, Placebo/Dapa+Exe group). The adjusted mean percentage change was -5.3% and -5.2% in the respective groups.
- **Full-FAS:** Corresponding statistically significant reductions in mean body weight (%) were observed between baseline (week 0) and week 24 within the Dapa+Exe/Dapa+Exe group (-4.5%, p<0.0001, full FAS), between week 24 and week 52 within the placebo group (-3.8%, p=0.0002, full FAS) and between baseline (week 0) and week 52 within both groups (-5.7%, p=0.0002, Dapa+Exe/Dapa+Exe group [full FAS]; -4.1%, p=0.0064, Placebo/Dapa+Exe group [full FAS]).

Exploratory Variables

Body fat composition

- Statistically significant differences within the group that received dapagliflozin/exenatide for 24 +28 weeks were observed in total adipose tissue (from baseline to week 24: -3.9 L, p=0.0008; from baseline to week 52: -5.1 L, p=0.0149), in abdominal visceral adipose tissue (from baseline to week 24: -0.39 L, p=0.0167), in abdominal subcutaneous adipose tissue (from baseline to week 24: -1.3 L, p=0.0008; from baseline to week 52: -1.6 L, p=0.0053), in total lean tissue (from baseline to week 24: -0.93 L, p=0.0111; from baseline to week 52: -1.3 L, p=0.0051) and in total liver fat (from week 24 to week 52: -0.043 L, p=0.0265).

Haemoglobin A1c

- Statistically significant reductions of HbA1c levels were observed within the Dapa+Exe/Dapa+Exe group (from baseline to week 24: -3.9 mmol/L, p<0.0001; from baseline to week 52: -3.1 mmol/L, p<0.0001) and within Placebo/Dapa+Exe group (from baseline to week 24: -1.6 mmol/L, p=0.0041; from week 24 to week 52: -1.4 mmol/L, p=0.0038; from baseline to week 52: -3.1 mmol/L, p<0.0001).

Glucose

- Statistically significant reductions of glucose (FPG) levels were observed within Dapa+Exe/Dapa+Exe group (from baseline to week 24: -0.42 mmol/L, p<0.0001; from baseline to week 52: -0.31 mmol/L, p=0.0006) and within Placebo/Dapa+Exe group (from week 24 to week 52: -0.27 mmol/L, p=0.0046; from baseline to week 52: -0.29 mmol/L, p=0.0012).

  Statistically significant reductions of 120 minutes post-challenge plasma glucose levels were observed within Dapa+Exe/Dapa+Exe group (from baseline to week 24: -218.0 mmol/L x 180 min, p=0.0002; from baseline to week 52: -2.2 mmol/L, p<0.0001). Also, statistically significant reductions in mean AUC_{0-3h} for plasma glucose were observed (from baseline to week 24: -1.8 mmol/L, p=0.0002; from baseline to week 52: -248.7 mmol/L x 180 min, p<0.0001).

Impaired fasting plasma glucose and impaired glucose tolerance

- The proportion of subject with IFG (FPG ≥5.6 mmol/L) was significantly lower within the Dapa+Exe/Dapa+Exe group between baseline (screening) and week 24 (p=0.0082). Between baseline (screening) and week 24, 33.3% of the subjects shifted from raised to normal IFG status and at week 52, 35.3% shifted from raised to normal.

  There were statistically significant reductions observed in the proportion of subjects with IGT (post-challenge plasma glucose ≥7.8 mmol/L at Time 120 minutes during the 3h-OGTT) within the Dapa+Exe/Dapa+Exe group, between baseline (screening) and week 24 (p=0.0196) and week 52 (p=0.0253), respectively. A proportion of 38.1% shifted from raised to normal IGT status between baseline (screening) and week 24, 33.3% between baseline (screening) and week 52, and 6.7% shifted from raised to normal IGT status between 24 weeks and 52 weeks.

  There were statistically significant differences in the proportion of subjects with IFG and/or IGT observed in the Dapa+Exe/Dapa+Exe group compared to the Placebo/Dapa+Exe group, between baseline (screening) and week 24 (p=0.0031, Cochran–Mantel–Haenszel test). The proportion of subjects with raised status was lower in the Dapa+Exe/Dapa+Exe group (33.3%) than in the Placebo/Dapa+Exe group (82.4%) at week 24 and also at week 52 (28.6% vs 52.9%).

Within the Dapa+Exe/Dapa+Exe group, there was a statistically significant reduction in the proportion of subjects with IFG and/or IGT between baseline (screening) and week 24 (p=0.0047, McNemar's test) and between baseline (screening) to week 52 (p=0.0143, McNemar's test).

Insulin secretion and insulin sensitivity

- A statistically significant reduction in mean fasting insulin was observed within the Dapa+Exe/Dapa+Exe group between week 24 and week 52 (p=0.0006), but not within the Placebo/Dapa+Exe group. The adjusted mean change in fasting insulin was -4.9 mU/L and 1.1 mU/L in the respective group. No statistically significant changes in mean AUC_{0-3h} for insulin were observed within the Dapa+Exe/Dapa+Exe group at any of the time points.

Other variables

- No apparent differences between the treatment groups, or relevant changes in mean values from screening to week 12, week 24 or week 52 (where applicable) (descriptive statistics only), were observed for any of the variables (plasma glucose, insulin, C-peptide and ketones).

Blood lipid profile

- No apparent differences between the treatment groups, or relevant changes in mean values from screening to week 12, week 24 or week 52 (descriptive statistics only), were observed for any of the blood lipid profile variables (TC, LDL-C, HDL-C and TG).

Vital signs

- Statistically significant reductions in mean systolic blood pressure were observed within Dapa+Exe/Dapa+Exe group (from baseline to week 24: -8.8 mmHg, p=0.0004; from baseline to week 52: -13.0 mmHg, p<0.0001) and within the Placebo/Dapa+Exe group (from baseline to week 52: -8.6 mmHg, p=0.0045). Also, significant increases in mean pulse were observed within the Placebo/Dapa+Exe group (between week 24 and week 52: 5.9 bets/min, p=0.0096; from baseline to week 52: 5.6 beats/min, p=0.0107).

Other anthropometric measurements

- Statistically significant reductions in waist circumference were observed within the Dapa+Exe/Dapa+Exe group (from baseline to week 24: -5.3 cm, p<0.0001; from baseline to week 52: -7.3 cm, p<0.0001) and within the Placebo/Dapa+Exe group (from week 24 to week 52: -4.8 cm, p=0.0020; from baseline to week 52: -7.2 cm, p=0.0003).

  Statistically significant reductions in waist-hip ratio were observed within the Dapa+Exe/Dapa+Exe group (from baseline to week 52: -0.03, p=0.0049) and within the Placebo/Dapa+Exe group (from baseline to week 52: -0.03, p=0.0140)

  Statistically significant reductions in BMI were observed within the Dapa+Exe/Dapa+Exe group (from baseline to week 24: -1.4 kg/m^2, p<0.0001; from baseline to week 52: -1.7 kg/m^2, p=0.0014) and within the Placebo/Dapa+Exe group (from week 24 to week 52: -1.6 kg/m^2, p<0.0001; from baseline to week 52: -1.8 kg/m^2, p=0.0026).

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, from week 24 to week 52 and from baseline to week 52 are presented, per treatment group, in Section 11.4.3.4.

Summary tables for the extension safety analysis set are provided in the below sections or in Section 14.3. Individual subject data listings for the safety variables for the extension safety analysis set, are provided in Appendix 16.2.5 (exposure), Appendix 16.2.7 (AEs) and Appendix 16.2.8 (laboratory measurements).

12.1 EXTENT OF EXPOSURE

The extent of exposure to IP expressed as duration of exposure to exenatide injections (weekly) and duration of exposure to dapagliflozin tablets (daily), is summarized for each treatment group in Table 65 to Table 68. 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 the subjects that participated in the extension study (extension safety analysis set), the mean duration of treatment with exenatide or matching placebo (weekly injections) during the 24 week main study part was 24.3 weeks (SD=0.74) and 24.1 weeks (SD=0.26) in the group that received dapagliflozin/exenatide and in the group that received placebo, respectively (Table 65). During the 28-week extension study period, the mean duration of exenatide treatment (weekly injections) was 25.4 weeks (SD=6.7) and 28.2 weeks (SD=0.46) in the two groups, respectively (Table 66).

The mean duration of treatment with dapagliflozin or matching placebo (daily administration) during the 24 week main study was 170.1 days (SD=5.21) and 168.8 days (SD=1.85) in the group that received dapagliflozin/exenatide and in the group that received placebo, respectively (Table 67).

During the 28-week extension study period, the mean duration of dapagliflozin treatment (daily administration) was 178.0 days (SD=46.9) and 197.5 days (SD=3.24) in the two groups, respectively (Table 68).

Thus, during the 28-week extension period, there was a difference of approximately 20 days in mean duration of exposure between the groups: 25.4 vs 28.0 weeks for exenatide and 178 vs 198 days for dapagliflozin. The difference in duration of exposure reflects the lower drop-out rate in the Placebo/Dapa+Exe group (0%) compared to the Dapa+Exe/Dapa+Exe group (23.8%), as presented in Section 10.1.

Table 65 Duration of exposure to Exenatide injections (weekly) - Baseline to 24 weeks. Extension safety analysis set

	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Duration of exposure (weeks)		
n/nmiss	21/0	17/0
Mean (SD)	24.29 (0.74)	24.12 (0.26)
Median	24.14	24.00
Q1, Q3	24.00, 24.43	24.00, 24.43
Min, Max	23.4, 26.9	23.9, 24.7

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

Table 66 Duration of exposure to Exenatide injections (weekly) - 24 to 52 weeks. Extension safety analysis set

	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Duration of exposure (weeks)		
n/nmiss	21/0	17/0
Mean (SD)	25.43 (6.70)	28.22 (0.46)
Median	28.00	28.00
Q1, Q3	27.86, 28.14	28.00, 28.43
Min, Max	7.7, 30.4	27.6, 29.1

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

Table 67 Duration of exposure to Dapagliflozin tablets (daily) - Baseline to 24 weeks. Extension safety analysis set

	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Duration of exposure (days)		
n/nmiss	21/0	17/0
Mean (SD)	170.05 (5.21)	168.82 (1.85)
Median	169.00	168.00
Q1, Q3	168.00, 171.00	168.00, 171.00
Min, Max	164.0, 188.0	167.0, 173.0

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

Table 68 Duration of exposure to Dapagliflozin tablets (daily) - 24 to 52 weeks. Extension safety analysis set

	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Duration of exposure (days)		
n/nmiss	21/0	17/0
Mean (SD)	178.00 (46.92)	197.53 (3.24)
Median	196.00	196.00
Q1, Q3	195.00, 197.00	196.00, 199.00
Min, Max	54.0, 213.0	193.0, 204.0

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

Descriptive data of the clinical laboratory variables are summarized in Section 12.2.1 (Laboratory values over time), Section 12.2.2 (Individual clinically significant abnormalities), Section 12.2.3 (Derived safety variable - creatinine clearance) and Section 12.2.4 (Derived safety variable - eGFR).

The corresponding summary statistics tables for the extension safety analysis set are provided in Section 14.3.1.

Listings of individual laboratory data for haematology, clinical chemistry and urinalysis 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 to be reported as AEs (see Section 12.2.2).

12.2.1 Laboratory Values over Time

Descriptive statistics of haematology data (B-haemoglobin) and clinical chemistry data (albumin, ALP, ALT, AST, total bilirubin, total calcium, CK, creatinine, CRP, potassium and sodium) are presented by treatment group including mean change from baseline to weeks 12, 24 and 52 and corresponding 95% confidence interval for the extension safety analysis set, in Section 14.3.1.1 (haematology Table 219) and Section 14.3.1.2 (clinical chemistry, Table 220 to Table 230).

Haematology

An increase in mean and median haemoglobin values between screening and weeks 12 and 24 was indicated based on descriptive data in the Dapa+Exe/Dapa+Exe group, as well as between week 24 and week 52 in the Placebo/Dapa+Exe group (Table 219, Section 14.3.1.1). This is consistent with previous findings following dapagliflozin administration.

Clinical chemistry

A transient elevation of the mean CRP levels was observed at week 12 in the Dapa+Exe/Dapa+Exe group (9.6 mg/L [SD=20.1]) compared to the Placebo/Dapa+Exe group (3.4 mg/L [SD=2.5]) (Table 228, Section 14.3.1.2). As reported in the main study report (Clinical trial report for the 24-week short-term treatment period [version 1.1, dated 11 Jan 2017], Appendix 16.5) 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). For all other subjects, CRP levels were considered normal at all time points.

No apparent differences between the treatment groups, or clinically significant changes in mean values from screening to week 12, 24 or 52, were observed for any of the other clinical chemistry laboratory variables (albumin, ALP, ALT, AST, total bilirubin, total calcium, CK, creatinine, potassium and sodium), see Section 14.3.1.2 (Table 220 to Table 227, Table 229 to Table 230).

12.2.2 Individual Clinically Significant Abnormalities

During the 28 weeks open label extension part of the study, no abnormal clinically significant laboratory finding was reported as AE and assessed as related to IP.

Two subjects had an abnormal clinically significant laboratory finding assessed as related to IP reported, during the 24 weeks double blind main study part:

- Subject E121 (Placebo/Dapa+Exe group): Progression of hyperlipidaemia (PT hyperlipidaemia) was reported 13 weeks after start of treatment with placebo (24-week double-blind main study). 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 24-week double blind main study

and also the 28-week open-label extension, but had not recovered from the AE at the last visit (Visit 11, week 28) (see eCRF, Table 240, Table 243 and Appendix 16.2.7).

- Subject E129 (Placebo, participated only in the 24-week double-blind main study): 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. 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. (Data provided in the clinical trial report for the 24-week short-term treatment period [version 1.1, dated 11 Jan 2017], Appendix 16.5).

12.2.3 Derived Safety Variable - Creatinine Clearance

At baseline (screening), the mean value of creatinine clearance was similar in both treatment groups (146.4 mL/min [SD=44.8] vs 144.1 mL/min [SD=37.0]). Twenty-four weeks of exposure to dapagliflozin/exenatide led to a reduction of the creatinine clearance rate compared to the group exposed to placebo. The mean change from baseline to week 24 was -7.4 mL/min and 0.8 mL/min in the Dapa+Exe/Dapa+Exe and Placebo/Dapa+Exe group, respectively (Table 231, Section 14.3.1.3). Between baseline and week 52, the mean change was -4.2 mL/min and -7.7 mL/min in the respective group.

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

12.2.4 Derived Safety Variable - Estimated Glomerular Filtration Rate

There were no apparent differences between the treatment groups, or clinically significant changes observed, in mean values of eGFR, from baseline (screening) to week 12, 24 or 52 (Table 232, Section 14.3.1.3).

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, 8, 12, 24, 38 and 52. Vital signs were included as an exploratory efficacy variable and data are presented as mean change from baseline to week 24, between week 24 and week 52 and from baseline to week 52, per treatment group, in Section 11.4.3.4.

Individual subject data listings of vital signs are provided in Appendix 16.2.6.

Statistically significant differences within the group that received dapagliflozin/exenatide for 24 +28 weeks were observed for systolic blood pressure (decrease from baseline to week 24 and from baseline to week 52) (Table 52 and Table 53, Section 11.4.3.4.1).

Within the group that received placebo for 24 weeks and dapagliflozin/exenatide for the following 28 weeks, statistically significant differences were observed for systolic blood pressure (reduction from baseline to week 52) (Table 53, Section 11.4.3.4.1) and for pulse (increase between week 24 and week 52 and from baseline to week 52) (Table 54 and Table 55, Section 11.4.3.4.3).

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

The AEs are presented for the extension safety analysis data set in Section 12.4.1 (Brief summary of AEs), Section 12.4.2 (Display of AEs), Section 12.4.3 (Analysis of AEs) and Section 12.4.4 (Withdrawals due to AEs).

The corresponding summary statistics tables not presented in the sections below are provided in Section 14.3.2. 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

Overviews of AEs, including intensity, relationship to IP (causality), SAEs and AEs leading to withdrawal, are presented by treatment group, from baseline to week 24 in Table 69, from week 24 to week 52 in Table 70 and from baseline to week 52 in Table 233 (Section 14.3.2.1).

All 38 subjects (100.0%) that participated in the extension study, reported AEs and in both groups, the main part of AEs were reported during the initial 24-week main study period (Table 74). A total of 238 AEs, whereof 147 AEs reported by 21 subjects (100.0%) in the Dapa+Exe/Dapa+Exe group and 91 AEs reported by 17 subjects (100.0%) in the Placebo/Dapa+Exe group, where reported between baseline and weeks 24. Between week 24 and week 52, a total of 103 AEs were reported; 61 AEs reported by 17 subjects (81.0%) in the Dapa+Exe/Dapa+Exe group and 42 AEs reported by 16 subjects (94.1%) in the Placebo/Dapa+Exe group) (Table 70).

Three of the subjects that participated in the extension part of the study (all in the Dapa+Exe/Dapa+Exe group), had SAEs during the study (Table 233). Subject E135 reported head trauma (PT injury) during the initial 24-week double blind study period and Subject E105 reported adenocarcinoma in the sigmoideum (PT adenocarcinoma of colon) and gastrointestinal haemorrhage (PT gastrointestinal haemorrhage) and Subject E155 reported Quincke's oedema (PT angioedema) during the 28-week open-label extension study period. See more details in Section 12.5.1.2.

One subject that did not participate in the extension part (Subject E153, Placebo group) experienced 2 SAEs (PTs dyspnoea and fatigue) during the initial 24 weeks main study. The subject was withdrawn from the main study due to the events. See more details in the clinical trial report for the 24-week short-term treatment period (version 1.1, dated 11 Jan 2017), Appendix 16.5.

Four subjects (all in the Dapa+Exe/Dapa+Exe group) were withdrawn due to AEs, during the 28-week open-label extension study period (Table 70). Subject E104 was withdrawn due to eye allergy, Subject E105 due to gastrointestinal haemorrhage and adenocarcinoma of colon (SAEs), Subject E150 due to dizziness, fatigue and nausea and Subject E155 due to angioedema (SAE). See more details in Section 12.4.4.

Six subjects were prematurely withdrawn due to AEs, during the initial 24 weeks main study; 2 subjects in the dapagliflozin/exenatide group reporting 3 AEs (abdominal pain, injection site pruritus and injection site mass) and 4 subjects in the placebo group, reporting 6 AEs (skin ulcer, vasculitis, malaise, blood ketone body increased [main reason for withdrawal was severe non-compliance with the protocol], dyspnoea [SAE] and fatigue [SAE]). See more details in the clinical trial report for the 24-week short-term treatment period (version 1.1, dated 11 Jan 2017), Appendix 16.5.

Over the 52-week study period, most AEs were of mild severity in both groups (251 AEs in total; 148 AEs reported by 21 subjects [100.0%] in the Dapa+Exe/Dapa+Exe group and 103 AEs reported by 17 subjects [100.0%] in the Placebo/Dapa+Exe group (Table 233). Moderate AEs (83 in total) were reported by 15 and 10 subjects in the Dapa+Exe/Dapa+Exe and Placebo/Dapa+Exe groups, respectively. Severe AEs (6 in total) were reported by 4 subjects (19.0%) in the Dapa+Exe/Dapa+Exe group and by 2 subjects (11.8%) in the Placebo/Dapa+Exe group.

In both treatment groups, most AEs were assessed as possibly related to treatment, 210 AEs in total (128 AEs reported by 20 subjects [95.2%] in the Dapa+Exe/Dapa+Exe group and 82 AEs reported by 17 subjects [100.0%] in the Placebo/Dapa+Exe group) or to have an unlikely relationship to treatment, 123 AEs in total (74 AEs reported by 18 subjects [85.7%] in the Dapa+Exe/Dapa+Exe group and 49 AEs reported by 15 subjects [88.2%] in the Placebo/Dapa+Exe group) (Table 233). In total, 7 AEs were assessed as related to treatment (5 AEs reported by 5 subjects [23.8%] in the Dapa+Exe/Dapa+Exe group and 2 AEs reported by 2 subjects [11.8%] in the Placebo/Dapa+Exe group).

Overall, there were no major differences in AE severity or relationship to IP between the groups.

Table 69 Overview of adverse events - Baseline to 24 weeks. Extension safety analysis set

	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)		Placebo/ Dapa 10mg+Exe 2mg (N=17)	
	n (%)	m	n (%)	m
Any adverse events	21 (100.0%)	147	17 (100.0%)	91
Any serious adverse events	1 (4.8%)	1	0	0
Adverse events leading to withdrawal	0	0	0	0
Severity of adverse events				
Mild	21 (100.0%)	110	17 (100.0%)	68
Moderate	14 (66.7%)	36	9 (52.9%)	22
Severe	1 (4.8%)	1	1 (5.9%)	1
Causality of adverse events				
Unlikely related	17 (81.0%)	53	14 (82.4%)	35
Possibly related	19 (90.5%)	89	15 (88.2%)	54
Related	5 (23.8%)	5	2 (11.8%)	2

n is the number of subjects, m is the number of events.
Percentages are based on the number of subjects in the extension safety analysis set.

Table 70 Overview of adverse events - 24 to 52 weeks. Extension safety analysis set

	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)		Placebo/ Dapa 10mg+Exe 2mg (N=17)	
	n (%)	m	n (%)	m
Any adverse events	17 (81.0%)	61	16 (94.1%)	42
Any serious adverse events	2 (9.5%)	3	0	0
Adverse events leading to withdrawal	4 (19.0%)	7	0	0
Severity of adverse events				
Mild	15 (71.4%)	39	16 (94.1%)	35
Moderate	5 (23.8%)	19	5 (29.4%)	6
Severe	3 (14.3%)	3	1 (5.9%)	1
Causality of adverse events				
Unlikely related	10 (47.6%)	22	8 (47.1%)	14
Possibly related	11 (52.4%)	39	14 (82.4%)	28
Related	0	0	0	0

n is the number of subjects, m is the number of events.
Percentages are based on the number of subjects in the extension safety analysis set.

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 234 to Table 236, by severity in Table 237 to Table 239 (Dapa+Exe/Dapa+Exe group) and Table 240 to Table 242 (Placebo/Dapa+Exe group), and by relationship to IP in Table 243 to Table 245.

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) and AEs 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

All reported AEs are summarized for the extension safety analysis set, by SOC and PT and by treatment group, in Table 234 (baseline to 24 weeks), Table 235 (24 weeks to 52 weeks) and Table 236 (baseline to 52 weeks), in Section 14.3.2.

The most common SOCs reported by ≥20% of the subjects in any group between baseline and week 52, are summarized in Table 71 and the most common PTs (reported by ≥10% of the subjects in any group) are summarized in Table 72.

The most common SOCs were:

- General disorders and administration site conditions: 16 subjects (76.2%) vs 13 subjects (76.5%) in the Dapa+Exe/Dapa+Exe and Placebo/Dapa+Exe groups, respectively.
- Gastrointestinal disorders: 15 subjects (71.4%) vs 13 subjects (76.5%) in the respective groups.

- Infections and infestations: 13 subjects (61.9%) vs 9 subjects (52.9%) in the respective groups.

The most common reported PTs differed between the groups. In the Dapa+Exe/Dapa+Exe group, most common PTs were:

- Nausea (Gastrointestinal disorders): 16 events reported by 9 subjects (42.9%) vs 4 events reported by 4 subjects (23.5%) in the Placebo/Dapa+Exe group.
- Nasopharyngitis (Infections and infestations): 8 events reported by 8 subjects (38.1%) vs 3 events reported by 3 subjects (17.6%) in the Placebo/Dapa+Exe group.
- Dizziness (Nervous system disorders): 8 events reported by 7 subjects (33.3%) vs 3 events reported by 3 subjects (17.6%) in the Placebo/Dapa+Exe group.
- Decreased appetite (Metabolism and nutrition disorders): 7 events reported by 7 subjects (33.3%) vs 3 events reported by 2 subjects (11.8%) in the Placebo/Dapa+Exe group.

The most common PTs reported in the Placebo/Dapa+Exe group were:

- Pollakiuria (Renal and urinary disorders): 11 events reported by 11 subjects (64.7%) vs 5 events reported by 5 subjects (23.8%) in the Dapa+Exe/Dapa+Exe group.
- Injection site mass (General disorders and administration site conditions): 6 events reported by 6 subjects (35.3%) vs 6 events reported by 6 subjects (28.6%) in the Dapa+Exe/Dapa+Exe group.
- Fatigue (General disorders and administration site conditions): 6 events reported by 6 subjects (35.3%) vs 6 events reported by 4 subjects (19.0%) in the Dapa+Exe/Dapa+Exe group.

Table 71 Most common adverse event by system organ classes, reported by ≥20% of the subjects in any treatment group – Baseline to 52 weeks. Extension safety analysis set

	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)		Placebo/ Dapa 10mg+Exe 2mg (N=17)	
System organ class	**n (%)**	**m**	**n (%)**	**m**
Infections and infestations	13 (61.9%)	23	9 (52.9%)	15
Metabolism and nutrition disorders	11 (52.4%)	12	5 (29.4%)	6
Nervous system disorders	12 (57.1%)	28	7 (41.2%)	11
Vascular disorders	2 (9.5%)	2	5 (29.4%)	5
Respiratory, thoracic and mediastinal disorders	5 (23.8%)	8	3 (17.6%)	3
Gastrointestinal disorders	15 (71.4%)	50	13 (76.5%)	22
Skin and subcutaneous tissue disorders	9 (42.9%)	12	3 (17.6%)	3
Musculoskeletal and connective tissue disorders	9 (42.9%)	13	7 (41.2%)	12
Renal and urinary disorders	6 (28.6%)	6	12 (70.6%)	12
General disorders and administration site conditions	16 (76.2%)	38	13 (76.5%)	29
Injury, poisoning and procedural complications	4 (19.0%)	5	4 (23.5%)	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 Extension safety analysis set
Source: Table 236, Section 14.3.2.1.

Table 72 Most common adverse event by preferred terms reported by ≥10% of the subjects in any treatment group - Baseline to 52 weeks. Extension safety analysis set

System organ class/Preferred term	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21) n (%)	m	Placebo/ Dapa 10mg+Exe 2mg (N=17) n (%)	m
Infections and infestations				
Influenza	1 (4.8%)	1	3 (17.6%)	3
Nasopharyngitis	8 (38.1%)	8	3 (17.6%)	3
Metabolism and nutrition disorders				
Decreased appetite	7 (33.3%)	7	2 (11.8%)	3
Nervous system disorders				
Dizziness	7 (33.3%)	8	3 (17.6%)	3
Headache	6 (28.6%)	13	4 (23.5%)	5
Tremor	3 (14.3%)	4	2 (11.8%)	2
Vascular disorders				
Hypertension	1 (4.8%)	1	3 (17.6%)	3
Respiratory, thoracic and mediastinal disorders				
Oropharyngeal pain	3 (14.3%)	4	0	0
Gastrointestinal disorders				
Abdominal distension	2 (9.5%)	2	2 (11.8%)	3
Abdominal pain upper	3 (14.3%)	4	4 (23.5%)	4
Constipation	3 (14.3%)	3	2 (11.8%)	2
Diarrhoea	3 (14.3%)	6	3 (17.6%)	3
Dyspepsia	3 (14.3%)	3	0	0
Gastrooesophageal reflux disease	2 (9.5%)	2	2 (11.8%)	2
Nausea	9 (42.9%)	16	4 (23.5%)	4
Vomiting	3 (14.3%)	7	2 (11.8%)	2
Skin and subcutaneous tissue disorders				
Hyperhidrosis	3 (14.3%)	4	2 (11.8%)	2
Musculoskeletal and connective tissue disorders				
Arthralgia	3 (14.3%)	3	4 (23.5%)	4
Back pain	3 (14.3%)	3	2 (11.8%)	3
Renal and urinary disorders				
Pollakiuria	5 (23.8%)	5	11 (64.7%)	11
General disorders and administration site conditions				
Fatigue	4 (19.0%)	6	6 (35.3%)	6
Feeling hot	1 (4.8%)	1	2 (11.8%)	2
Hunger	1 (4.8%)	1	2 (11.8%)	2
Injection site mass	6 (28.6%)	6	6 (35.3%)	6
Injection site pruritus	6 (28.6%)	6	2 (11.8%)	2
Peripheral swelling	1 (4.8%)	3	2 (11.8%)	2
Pyrexia	3 (14.3%)	3	1 (5.9%)	1
Thirst	2 (9.5%)	2	3 (17.6%)	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 extension safety analysis set
Source: Table 236, Section 14.3.2.1.

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.[12] Reference listings of PTs, grouped into these 4 different categories, were provided by AstraZeneca and are included in Appendix 16.1.1.

Summary tables of reported AEs of special interest are presented by SOC and PT in Table 73 (urinary tract infections), Table 74 (genital infections) and Table 75 (volume depletion). There were no reported AEs related to renal impairment.

Urinary tract infections

Urinary tract infections were reported by 1 subject (4.8%) in the Dapa+Exe/Dapa+Exe group (PT urinary tract infection fungal, mild, possibly related to IP) and by 1 subject (5.9%) in the Placebo/Dapa+Exe group (PT urinary tract infection, mild, possibly related to IP) (Table 73). Both events were reported during the first 24 weeks of treatment (see individual AE listings Appendix 16.2.7). No other urinary tract infections were reported during the study.

Genital infections

Genital infections were reported by 2 subjects (9.5%) in the Dapa+Exe/Dapa+Exe group (PT vaginal infection, 6 events; 5 mild, 1 moderate; all possibly related) and by 1 subject (5.9%) in the Placebo/Dapa+Exe group (PT genital infection fungal, 1 event, mild, possibly related to IP) during the 24 to 52 weeks period (Table 74). All genital infections were reported for subjects that were on active treatment at the time for the event (see individual AE listings Appendix 16.2.7).

Events possibly related to volume depletion

Hypotension could be a sign of a volume depletion. One subject (5.9%) in the Placebo/Dapa+Exe group, reported PT hypotension (mild, possibly related to IP) during the first 24 weeks of treatment, i.e. the subject was on placebo treatment (Table 75 and individual AE listings, Appendix 16.2.7).

In summary, during the entire study, 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 239 and Table 242). 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.[12]

Table 73 Adverse events related to urinary tract infections - Baseline to 52 weeks. Extension safety analysis set

	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)		Placebo/ Dapa 10mg+Exe 2mg (N=17)	
System organ class/Preferred term	**n (%)**	**m**	**n (%)**	**m**
Infections and infestations				
Urinary tract infection[a]	0	0	1 (5.9%)	1
Urinary tract infection fungal[a]	1 (4.8%)	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 extension safety analysis set
Source: Table 236 in Section 14.3.2.1 and listings of dapagliflozin-related side-effects in Appendix 16.1.1.

Table 74 Adverse events related to genital infections – Baseline to 52 weeks. Extension safety analysis set

	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)		Placebo/ Dapa 10mg+Exe 2mg (N=17)	
System organ class/Preferred term	**n (%)**	**m**	**n (%)**	**m**
Infections and infestations				
Genital infection fungal	0	0	1 (5.9%)	1
Vaginal infection	2 (9.5%)	6	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 extension safety analysis set
Source: Table 236 in Section 14.3.2.1 and listings of dapagliflozin-related side-effects in Appendix 16.1.1.

Table 75 Adverse events possibly related to volume depletion – Baseline to 52 weeks. Extension safety analysis set

	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)		Placebo/ Dapa 10mg+Exe 2mg (N=17)	
System organ class/Preferred term	**n (%)**	**m**	**n (%)**	**m**
Vascular disorders				
Hypotension	0	0	1 (5.9%)	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 extension safety analysis set
Source: Table 236 in Section 14.3.2.1 and listings of dapagliflozin-related side-effects in Appendix 16.1.1.

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.[13] A reference listing of the gastrointestinal symptoms frequently observed in response to exenatide treatment was provided by AstraZeneca and is included in Appendix 16.1.1. This predefined list of MedDRA PTs consisted of a subset of relevant terms out of the full SOC Gastrointestinal disorders. In addition, all terms (PTs) included in the MedDRA high level term (HLT) category Gastrointestinal and abdominal pains (excl oral and throat) in SOC Gastrointestinal disorders were included as predefined terms. 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 76 (gastrointestinal AEs) and Table 77 (injection site-related AEs).

Gastrointestinal adverse events

In the Dapa+Exe/Dapa+Exe group, 13 of 21 subjects (61.9%) reported in total 43 gastrointestinal AEs based on a predefined lists of MedDRA terms (Table 76 and individual subject listing of AEs, Appendix 16.2.7). In the Placebo/Dapa+Exe group, 13 of 17 subjects (76.5%) reported in total 20 such AEs. Twelve of the events were reported during the first 24 weeks of treatment, i.e. the subjects were on placebo treatment at the time for the event (see individual subject listing of AEs, Appendix 16.2.7).

The most common gastrointestinal AEs (PTs) were nausea (42.9% in the Dapa+Exe/Dapa+Exe group vs 23.5% in the Placebo/Dapa+Exe group), abdominal pain upper (14.3% vs 23.5%) and diarrhoea (14.3% vs 17.6%).

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. All injection site reactions were reported during the 24-week main study except 1 (injection site mass reported by 1 subject in the Placebo/Dapa+Exe group). In the Dapa+Exe/Dapa+Exe group, 9 of 21 subjects (42.8%) reported in total 16 injection site-related AEs (Table 77 and individual subject listing of AEs, Appendix 16.2.7). In the Placebo/Dapa+Exe group, 7 of 17 subjects (41.2%) reported in total 11 injection site-related AEs, of which 10 were reported during the 24-week main study when the subjects received placebo. Over 52 weeks, there were no difference in frequency of reported injection site-related AEs between the two groups.

The most common injection site-related AEs (PTs) were injection site mass (28.6% in the Dapa+Exe/Dapa+Exe group vs 35.3% in the Placebo/Dapa+Exe group), injection site pruritus (28.6% vs 11.8%) and injection site erythema (9.5% vs 5.9%).

Table 76 Adverse events related to gastrointestinal symptoms – Baseline to 52 weeks. Extension safety analysis set

	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)		Placebo/ Dapa 10mg+Exe 2mg (N=17)	
System organ class/Preferred term	**n (%)**	**m**	**n (%)**	**m**
Gastrointestinal disorders				
Abdominal distension	2 (9.5%)	2	2 (11.8%)	3
Abdominal pain upper	3 (14.3%)	4	4 (23.5%)	4
Constipation	3 (14.3%)	3	2 (11.8%)	2
Diarrhoea	3 (14.3%)	6	3 (17.6%)	3
Dyspepsia	3 (14.3%)	3	0	0
Gastrooesophageal reflux disease	2 (9.5%)	2	2 (11.8%)	2
Nausea	9 (42.9%)	16	4 (23.5%)	4
Vomiting	3 (14.3%)	7	2 (11.8%)	2

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 extension safety analysis set.
Source: Table 236 in Section 14.3.2.1, listing of preferred terms in MedDRA high level term Gastrointestinal and abdominal pains (excl oral and throat) and listing of exenatide-related side-effects in Appendix 16.1.1.

Table 77 Adverse events related to injection – Baseline to 52 weeks. Extension safety analysis set

System organ class/Preferred term	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21) n (%)	m	Placebo/ Dapa 10mg+Exe 2mg (N=17) n (%)	m
General disorders and administration site conditions				
Injection site erythema	2 (9.5%)	2	1 (5.9%)	1
Injection site mass	6 (28.6%)	6	6 (35.3%)	6
Injection site nodule	2 (9.5%)	2	0	0
Injection site pruritus	6 (28.6%)	6	2 (11.8%)	2
Injection site rash	0	0	1 (5.9%)	1
Injection site swelling	0	0	1 (5.9%)	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 extension safety analysis set.
Source: Table 236 in Section 14.3.2.1 and injection site-related preferred terms in MedDRA system organ class General disorders and administration site conditions.

12.4.3.1.3 Adverse Events Related to Regulation of Appetite

The AEs related to appetite regulation were evaluated based on all terms related to appetite or hunger in MedDRA SOCs Metabolism and nutrition disorders and General disorders and administration site conditions. In the Dapa+Exe/Dapa+Exe group, 9 of 21 subjects (42.8%) reported 10 AEs related to appetite regulation, while 3 of 17 subjects (17.6%) in the Placebo/Dapa+Exe group reported 6 AEs related to appetite regulation of which 4 were reported during the 24 week main study when the subjects were on placebo treatment (Table 78).

The appetite regulation events reported were decreased appetite, reported by 33.3% vs 11.8% in the Dapa+Exe/Dapa+Exe and Placebo/Dapa+Exe group, respectively, hunger/increased appetite (14.3% vs 17.6%). All the events related to appetite regulation were of mild intensity (Table 239 and Table 242).

Table 78 Adverse events related to regulation of appetite – Baseline to 52 weeks. Extension safety analysis set

System organ class/Preferred term	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21) n (%)	m	Placebo/ Dapa 10mg+Exe 2mg (N=17) n (%)	m
Metabolism and nutrition disorders				
Decreased appetite	7 (33.3%)	7	2 (11.8%)	3
Increased appetite	2 (9.5%)	2	1 (5.9%)	1
General disorders and administration site conditions				
Hunger	1 (4.8%)	1	2 (11.8%)	2

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 extension safety analysis set
Source: Table 236 in Section 14.3.2.1

12.4.3.2 Adverse Events by Severity

All reported AEs are summarized by SOC, PT and severity (mild, moderate and severe) for the Dapa+Exe/Dapa+Exe group in Section 14.3.2.3 (Table 237 to Table 239), and the Placebo/Dapa+Exe group in Section 14.3.2.4 (Table 240 to Table 242).

Between baseline and week 24, the majority of the reported AEs was of mild intensity in both groups: 110 of 147 reported AEs (74.8%) in the Dapa+Exe/Dapa+Exe group and 68 of 91 reported AEs (74.7%) in the Placebo/Dapa+Exe group (Table 69, Section 12.4.1). There were 58 AEs of moderate severity: 36 of 147 reported AEs (24.5%) in the Dapa+Exe/Dapa+Exe group and 22 of 91 reported AEs (24.2%) in the Placebo/Dapa+Exe group. One AE in each group (0.7% of the AEs reported in the Dapa+Exe/Dapa+Exe group and 1.1% of the AEs reported the Placebo/Dapa+Exe group) was assessed as severe.

Also between week 24 and week 52, the majority of the reported AEs was mild: 39 of 61 reported AEs (63.9%) in the Dapa+Exe/Dapa+Exe group and 35 of 42 reported AEs (83.3%) in the Placebo/Dapa+Exe group (Table 70, Section 12.4.1). There were 25 AEs of moderate severity: 19 of 61 reported AEs (31.1%) in the Dapa+Exe/Dapa+Exe group and 6 of 42 reported AEs (14.3%) in the Placebo/Dapa+Exe group. Further, there were 4 AEs of severe intensity reported during this period: 3 of 61 reported AEs (4.9%) in the Dapa+Exe/Dapa+Exe group and 1 of 42 reported AEs (2.4%) in the Placebo/Dapa+Exe group.

In the Dapa+Exe/Dapa+Exe group, the 4 AEs assessed as severe were adenocarcinoma of colon (Subject E101, SAE, assessed as unlikely related to IP), hip arthroplasty (Subject E126, unlikely related to IP), injury due to head trauma (Subject E135, SAE, unlikely related to IP) and angioedema (Subject E155, SAE, possibly related to IP) (Table 239, Section 14.3.2.3 and individual AE listings in Appendix 16.2.7).

In the Placebo/Dapa+Exe group, the 2 AEs assessed as severe were meniscus operation reported during the 24 weeks main study part (Subject E133, unlikely related to IP) and skin neoplasm excision reported during 28 weeks extension study part (Subject E149, unlikely related to IP) (Table 242, Section 14.3.2.4 and individual AE listings in Appendix 16.2.7). See more details on SAEs in Section 12.5.1.2.

In summary, most AEs were of mild intensity all through the study. The proportion of subjects reporting moderate AEs were similar in both groups (23.8% vs 29.4%) and few AEs were assessed as severe (1 AE reported by 1 subject in each group).

12.4.3.3 Adverse Events by Relationship to Investigational Product

All reported AEs are summarized by SOC, PT and relationship to IP (not related and related, i.e. assessed as related or possibly related) in Table 243 to Table 245, Section 14.3.2.5.

Between baseline and week 24, the majority of the reported AEs in both groups was assessed as possibly related to the IP: 89 of 147 reported AEs (60.5%) in the Dapa+Exe/Dapa+Exe group and 54 of 91 reported AEs (59.3%) in the Placebo/Dapa+Exe group (Table 69, Section 12.4.1). Five of 147 reported AEs (3.4%) in the Dapa+Exe/Dapa+Exe group and 2 of 91 reported AEs (2.2%) in the Placebo/Dapa+Exe group, were assessed as related to the IP.

Also between week 24 and week 52, the majority of the reported AEs was assessed as possibly related to the IP: 39 of 61 reported AEs (63.9%) in the Dapa+Exe/Dapa+Exe group and 28 of 42 reported AEs (66.6%) in the Placebo/Dapa+Exe group (Table 70, Section 12.4.1). No AE reported during this period was assessed as related to the IP.

Seven AEs, all reported during the 24 weeks main study part, were assessed as related to IP, all were of mild intensity. In the Dapa+Exe/Dapa+Exe group, 5 AEs were reported; nausea (Subject E101), skin mass (Subject E117), injection site erythema (Subject E118) and injection site nodule (Subject E150

and Subject E160). In the Placebo/Dapa+Exe group, 2 AEs (1.5% of reported AEs) were reported during 24 week main part; fatigue (Subject E106) and injection site pruritus (Subject E157) (Table 69, Section 12.4.1 and individual AE listings in Appendix 16.2.7).

In general, 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

During the 28-week open-label extension study, 4 subjects, all in the Dapa+Exe/Dapa+Exe group, were prematurely withdrawn due to the occurrence of AEs or SAEs, see overviews in Table 79 (and Table 246, Section 14.3.2.6) and details in Table 80.

Subject E104 had eye allergy (PT eye allergy) assessed as mild and unlikely related to IP that started 9 days before inclusion in the 28-week study. The subject completed all the visits in the extension study, however was also non-compliant with the IP during the study period (the subject took 72.1% of the tablets and 78.2% of the injections, see Section 11.3). The primary reason for discontinuation from the study (given in the eCRF) was the AE.

Subject E105 was withdrawn after Visit 9 due to SAEs; gastrointestinal haemorrhage (PT gastrointestinal haemorrhage, assessed as moderate and unlikely related to IP) and adenocarcinoma in the sigmoideum (PT adenocarcinoma of colon, assessed as severe and unlikely related to IP).

Subject E150 was withdrawn after Visit 9 due to feeling tired and dizzy (PTs fatigue and dizziness, both assessed as mild and possibly related to IP) and nausea after taking study medication (PT nausea, assessed as mild and possibly related to IP).

Subject E155 was withdrawn after Visit 10 due to SAE, Quincke's oedema (PT angioedema, assessed as severe and possibly related to IP).

See more details on SAEs in Section 12.5.1.2 and SAE narratives in Section 12.5.2.

Complete CRFs for subjects withdrawn due to AEs are provided in Appendix 16.3.1.

Table 79 Adverse events leading to withdrawal of IP - 24 to 52 weeks. Extension safety analysis set

System organ class/Preferred term	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21) n (%)	m	Placebo/ Dapa 10mg+Exe 2mg (N=17) n (%)	m
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (4.8%)	1	0	0
Adenocarcinoma of colon	1 (4.8%)	1	0	0
Nervous system disorders	1 (4.8%)	1	0	0
Dizziness	1 (4.8%)	1	0	0
Eye disorders	1 (4.8%)	1	0	0
Eye allergy	1 (4.8%)	1	0	0
Gastrointestinal disorders	2 (9.5%)	2	0	0
Gastrointestinal haemorrhage	1 (4.8%)	1	0	0
Nausea	1 (4.8%)	1	0	0
Skin and subcutaneous tissue disorders	1 (4.8%)	1	0	0
Angioedema	1 (4.8%)	1	0	0
General disorders and administration site conditions	1 (4.8%)	1	0	0
Fatigue	1 (4.8%)	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 extension safety analysis set

Table 80 Detailed summary of withdrawals due to adverse events. Extension safety analysis set.

Treatment group	Subject ID	AE (PT/SOC)	Start date	Stop date	Onset after first dose (days)	Intensity/ Relation-ship	Action taken	Concom-itant treatment given	Outcome	Date of withdrawal	Concomitant AEs (PT)
Dapa+Exe/ Dapa+Exe	E104	Eye allergy/ Eye disorders	20 Jun 2015	Ongoing	156	Mild/ Unlikely related	Not applicable*	Lomudal	Recovering/ Resolving	12 Jan 2016	-
Dapa+Exe/ Dapa+Exe	E105	Gastrointestinal haemorrhage (SAE)/ Gastrointestinal disorders	17 Aug 2015	19 Aug 2015	213	Moderate/ Unlikely related	Drug withdrawn*	Cyklo-kapron	Recovered/ Resolved	25 Aug 2015	Anaemia Dizziness Decreased appetite
		Adenocarcinoma of colon (SAE)/ Neoplasms benign, malignant and unspecified (incl cysts and polyps)	17 Aug 2015	Ongoing	213	Severe/ Unlikely related	Drug withdrawn	-	Not recovered/ not resolved		
Dapa+Exe/ Dapa+Exe	E150	Dizziness/ Nervous system disorders	27 Aug 2015	04 Oct 2015	171	Mild/ Possibly related	Drug withdrawn*	-	Recovered/ Resolved	20 Oct 2015	Injection site nodule Injection site pruritus Pollakiuria
		Fatigue/ General disorders and administration site conditions	27 Aug 2015	04 Oct 2015	171	Mild/ Possibly related	Drug withdrawn*	-	Recovered/ Resolved		
		Nausea/ Gastrointestinal disorders	27 Aug 2015	28 Sep 2015	171	Mild/ Possibly related	Drug withdrawn*	-	Recovered/ Resolved		
Dapa+Exe/ Dapa+Exe	E155	Angioedema (SAE)/ Skin and subcutaneous tissue disorders	24 Nov 2015	25 Nov 2015	258	Severe/ Possibly related	Drug withdrawn*	Lora-tadine Betapred	Recovered/ Resolved	02 Dec 2015	Injection site mass Increased appetite

*Adverse event given as primary reason for discontinuation from study, however action taken with study treatment was set as "Dose not changed" in the eCRF.
Source: Based on eCRF 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 of the subjects (all in the Dapa+Exe/Dapa+Exe group) that participated in the 28-week open-label extension study part reported 4 SAEs during the entire study (baseline to 52 weeks), see summaries in Table 81 to Table 83.

During the initial 24-week double-blind main study part, subject E135 was hospitalised due to head trauma (PT injury, assessed as severe and unlikely related to IP). The subject temporarily stopped with the study treatment, but completed the 24-week main study and also the 28-week open-label extension study period.

During the 28-week open-label extension study part, subject E105 was hospitalised due to adenocarcinoma in the sigmoideum (PT adenocarcinoma of colon, assessed as severe and unlikely related to IP) and gastrointestinal haemorrhage (PT gastrointestinal haemorrhage, assessed as moderate and unlikely related to IP). Subject E155 was hospitalised due to Quincke's oedema (PT angioedema, assessed as severe and possibly related to IP). Both subjects were withdrawn from the study due to the events. The SAE for subject E155 (PT angioedema) was assessed by the Investigator and Sponsor as expected in regard to the study medication and therefore not reported as a suspected unexpected serious adverse reaction (SUSAR).

Narratives of the SAEs are provided in Section 12.5.2. Complete CRFs for subjects with SAEs are provided in Appendix 16.3.1.

Table 81 Serious adverse events - Baseline to 24 weeks. Extension safety analysis set

	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)		Placebo/ Dapa 10mg+Exe 2mg (N=17)	
System organ class/Preferred term	**n (%)**	**m**	**n (%)**	**m**
Injury, poisoning and procedural complications	1 (4.8%)	1	0	0
Injury	1 (4.8%)	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 extension safety analysis set

Table 82 Serious adverse events - 24 to 52 weeks. Extension safety analysis set

System organ class/Preferred term	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21) n (%)	m	Placebo/ Dapa 10mg+Exe 2mg (N=17) n (%)	m
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (4.8%)	1	0	0
Adenocarcinoma of colon	1 (4.8%)	1	0	0
Gastrointestinal disorders	1 (4.8%)	1	0	0
Gastrointestinal haemorrhage	1 (4.8%)	1	0	0
Skin and subcutaneous tissue disorders	1 (4.8%)	1	0	0
Angioedema	1 (4.8%)	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 extension safety analysis set

Table 83 Serious adverse events - Baseline to 52 weeks. Extension safety analysis set

System organ class/Preferred term	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21) n (%)	m	Placebo/ Dapa 10mg+Exe 2mg (N=17) n (%)	m
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (4.8%)	1	0	0
Adenocarcinoma of colon	1 (4.8%)	1	0	0
Gastrointestinal disorders	1 (4.8%)	1	0	0
Gastrointestinal haemorrhage	1 (4.8%)	1	0	0
Skin and subcutaneous tissue disorders	1 (4.8%)	1	0	0
Angioedema	1 (4.8%)	1	0	0
Injury, poisoning and procedural complications	1 (4.8%)	1	0	0
Injury	1 (4.8%)	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 extension safety analysis set

12.5.1.3 Other Significant Adverse Events

At all visits, subjects were to be asked about the occurrence of symptoms indicative of hypoglycaemia (e.g. fatigue, dizziness, tremor, palpitations and sweating) and in the eCRF (Adverse events log) the Investigator was to answer the question “Is the Adverse Event suggestive of hypoglycaemia?”

No AE was suggestive of hypoglycaemia and no event of hypoglycaemia was reported (see Table 236, Section 14.3.2.1), however for two subjects it was noted in the eCRF by the Investigator that hypoglycaemia could not be excluded (see individual subject AE listing in Appendix 16.2.7):

- Subject E142 (Dapa+Exe/Dapa+Exe group): Hyperhidrosis and tremor were reported as AEs on 20 Aug 2015 (Visit 8) and it was commented that hypoglycaemia could not be excluded

("The patient becomes shaky and sweaty once a week. Could be hypoglycaemia."). Both events were assessed as mild and possibly related to IP, but the dose was not changed. The subject completed the extension study, but was not recovered from the events at the last study visit (Visit 11), 7 Mar 2015.

- Subject E144 (Dapa+Exe/Dapa+Exe group): Asthenia, dizziness and tremor were reported as AEs on 13 Apr 2015 (between Visit 4 and Visit 5) and it was commented that hypoglycaemia could not be excluded ("The patient feels weakness, dizziness, and tremor everyday around four a clock in the afternoon. Hypoglycaemia cannot be excluded."). All events were assessed as mild and possibly related to IP, but the dose was not changed. The subject recovered from the events on 24 Aug 2015 (Visit 7), continued in the extension study that was completed 7 Mar 2015. According to query resolution in the eCRF, hypoglycaemia was ruled out because of the duration and characteristics, however no blood glucose laboratory data were available.

No other significant AEs occurred in the study.

12.5.2 Narratives of Deaths, Other Serious Adverse Events, and Certain Other Significant Adverse Events

Narratives for subjects with SAEs (E105, E135 and E155) are provided below.

For more details, see eCRF, CRFs provided in Appendix 16.3.1 and individual subject data listings in Appendix 16.2.7.

Subject E105 (Dapa+Exe/Dapa+Exe group) - Adenocarcinoma of colon and gastrointestinal haemorrhage

Subject E105, a 58-year old White male, with obesity problems since 1990. Previous medical history included appendectomy (1967), hemiparesis (ongoing since 1969), hemianopia homonymous (ongoing since 1969), tendon operation because of muscle spasticity (1976), cerebral haemorrhage (1969) and anaemia (ongoing since unknown date).

The subject entered the initial 24-week double-blind study on 08 Jan 2015, was randomized to treatment with dapagliflozin/exenatide 16 Jan 2015 and continued in the 28-week open-label study on 02 Jul 2015.

On 17 Aug 2015 (between study visit 9 and visit 10), the subject was investigated for anaemia and examined by coloscopy and biopsy. Later the same day (17 Aug 2015), when the subject was at home, he experienced blood in stool, went to the emergency room and was admitted to the hospital (18 Aug 2015) with diagnosis gastrointestinal haemorrhage (PT gastrointestinal haemorrhage, assessed as moderate and unlikely related to IP). The subject received IV treatment with Cyklokapron (tranexamic acid) (100 mg daily, 18-19 Aug 2015). The bleeding stopped, the subject was discharged from the hospital on 19 Aug 2015 and was recovered from the event (duration: 2 days).

Colonoscopy and biopsy showed signs of malignancy and the subject was diagnosed with adenocarcinoma in the sigmoideum (PT adenocarcinoma of colon, assessed as severe and unlikely related to IP). No medication or treatment was given at the time for the event, however the subject was undergoing a sigmoideum resection 8 Sep 2015.

The moderate gastrointestinal haemorrhage and the severe adenocarcinoma of colon were both assessed as unlikely related to treatment by the Investigator, while the underlying anaemia was assessed to be the reason for both events. However, at an unscheduled visit 25 Aug 2015, the Investigator decided to withdraw the subject from the study and the gastrointestinal haemorrhage was given as the primary reason for discontinuation. The subject was not recovered from the adenocarcinoma of colon at the time for discontinuation.

At the time for the events, the subject reported ongoing events of decreased appetite (since 20 Feb 2015, mild, possibly related to IP), dizziness (since 20 Feb 2015, mild, possibly related to IP) and progress of anaemia (PT anaemia) (since 29 Apr 2015, moderate, unlikely related to IP), treated with Duroferon (ferrous sulphate, 200 mg daily dose, since 29 Apr 2015). The subject was also taking Behepan (cyanocobalamin, 1 mg daily dose, since 9 Oct 2013) for vitamin B12 deficiency.

Subject E135 (Dapa+Exe/Dapa+Exe group) - Injury

Subject E135, a 69-year old White female, with obesity problems since 2010, but no other reported medical history. The subject entered the initial 24-week double-blind study on 17 Feb 2015, was randomized to treatment with dapagliflozin/exenatide 26 Feb 2015 and continued in the 28-week open-label study on 13 Aug 2015.

On 19 May 2015 (between study visit 5 and visit 6) the subject experienced head trauma (PT injury). The SAE criterion was hospitalisation. Briefly, the subject 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 intravenous 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 to 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 24-week double-blind main study as well as the 28-week open-label extension study. The subject recovered from the event (end date: 13 Aug 2015, duration: 86 days).

At the time for the event, the subject reported ongoing events of dry mouth (since 27 Feb 2015, mild, possibly related), injection site mass (since 27 Feb 2015, mild, possibly related), decreased appetite (since 27 Feb 2015, mild, possibly related) and constipation (since 27 Feb 2015, mild, possibly related) but was not taking any other concomitant medications.

Subject E155 (Dapa+Exe/Dapa+Exe group) - Angioedema

Subject E155, a 51-year old White male, with obesity problems since 1995. Previous medical history included tendon rupture (2012) and shoulder surgery (2012).

The subject entered the initial 24-week double-blind study on 04 Mar 2015, was randomized to treatment with dapagliflozin/exenatide 11 Mar 2015 and continued in the 28-week open-label study on 27 Aug 2015.

In the morning, 24 Nov 2015 (before Visit 10), the subject felt itching in the left eye and became swollen around the left eye and went to the clinic (Metabolmottagningen) for advice. At the clinic, the subject's felt swelling of the right half of the tongue and a tight feeling in the throat, and he went to the emergency room. At the time of the examination the subject felt better and the swelling had subsided somewhat. He had taken the dapagliflozin tablet as usual in the morning. According to report, the subject informed that he had not eaten anything he knew he was allergic to, although he had had up to seven previous allergic reactions with itching and swelling of the face, but this reaction was three times worse. The subject showed stable vital signs, but was admitted to the hospital for observation, however was discharged after midnight (00:20) on 25 Nov 2015. The subject recovered from the event (end date: 25 Nov 2015, duration: 1 day). The subject received Betapred

(betamethasone sodium phosphate, 6 mg once) and Loratadine (10 mg once) as treatment of the event.

The event was reported as Quincke's oedema (PT angioedema) and assessed by the Investigator as severe in intensity, possibly related to treatment and as expected in regard to the study medication. The subject did not stop with the study treatment due to the event, however at Visit 10 (02 Dec 2015), the subject was withdrawn from the study with AE angioedema as primary reason for discontinuation.

At the time for the event, the subject reported ongoing events of injection site mass (since 11 Mar 2015, mild, possibly related), increased appetite (since 01 Sep 2015, mild, possibly related) and previous events of dizziness in the morning (01 Sep 2015 to 25 Nov 2015, mild, possibly related) but was not taking any other concomitant medications.

12.5.3 Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

There were no deaths or any AEs assessed as significant reported during the 52-week study period.

A majority of the reported SAEs (gastrointestinal haemorrhage, adenocarcinoma of colon and injury) were assessed by the Investigator as unlikely related to IP. One SAE (angioedema) was assessed as possibly related to IP but further also assessed as expected by the Investigator and Sponsor, i.e. no SUSAR was reported (for details, see Section 12.5.1.2).

12.6 SAFETY CONCLUSIONS

- No new safety concerns based on clinical laboratory tests, creatinine clearance, vital signs and AEs/SAEs, were identified for the combined treatment with dapagliflozin (10 mg once daily) and exenatide (2 mg weekly injections), in obese non-diabetic subjects, during the initial 24 weeks of treatment or during the continuing 28 weeks extended treatment.

Extent of exposure

- During the 24-week double-blind main study period, the mean duration of exposure and treatment compliance was largely similar in both groups, however during the 28-week extension period, there was a difference of approximately 18 days in mean duration of exposure between the groups: 25.4 vs 28.0 weeks for exenatide and 178 vs 196 days for dapagliflozin. This was due to the lower drop-out rate in the Placebo/Dapa+Exe group.

Clinical laboratory evaluation

- There were no major changes in mean laboratory values or no apparent differences between treatment groups observed during the entire 52-week study. A numerical decrease in the creatinine clearance rate (-7.4 mL/min) between baseline and week 24, was observed in the Dapa+Exe/Dapa+Exe group, however not in the Placebo/Dapa+Exe group (0.8 mL/min). Between baseline and week 52, the mean change was -4.2 mL/min and -7.7 mL/min in the respective group. As body weight is included as one of the variables in the formula for calculation of creatinine clearance, the reduced creatinine clearance observed in both groups, after exposure to dapagliflozin/exenatide, is likely to in part be attributable to the reduced mean body weight.

Summary of adverse events

- All 38 subjects that participated in the extension study (extension safety analysis set), reported AEs and in both groups, the main part of AEs were reported during the initial 24-week main study period; 238 AEs, whereof 147 AEs reported by 21 subjects (100.0%) in the Dapa+Exe/Dapa+Exe group and 91 AEs reported by 17 subjects (100.0%) in the Placebo/Dapa+Exe group.

  Between week 24 and week 52, a total of 103 AEs were reported; 61 AEs reported by 17 subjects (81.0%) in the Dapa+Exe/Dapa+Exe group and 42 AEs reported by 16 subjects (94.1%) in the Placebo/Dapa+Exe group).

Adverse events by severity and relationship to investigational product

- Between baseline and week 24, the majority of the reported AEs were of mild intensity (74.8% of reported AEs in the Dapa+Exe/Dapa+Exe group and 74.7% in the Placebo/Dapa+Exe group), 24.5% vs 24.2% of reported AEs in the respective group were of moderate intensity and 1 AE in each group was assessed as severe.

  Most AEs were assessed as possibly related to treatment (60.5% vs 59.3%). Five of reported AEs (3.4%) in the Dapa+Exe/Dapa+Exe group and 2 AEs (2.2%) in the Placebo/Dapa+Exe group, were assessed as related to the IP (all of mild intensity).

  Also between week 24 and week 52, the majority of the reported AEs were mild (63.9% vs 83.3%), while 31.1% vs 14.3% were of moderate intensity and 4 AEs were severe. The majority was assessed as possibly related to the IP in both groups (63.9% vs 66.6%). No AE reported during this period was assessed as related to the IP.

Withdrawals due to adverse events

- Four subjects (all in the Dapa+Exe/Dapa+Exe group) were withdrawn from the study during the 28-week open-label extension period due to the occurrence of AEs (1 subject due to eye allergy and 1 subject due to dizziness, fatigue and nausea) or SAEs (1 subject due to gastrointestinal haemorrhage and adenocarcinoma of colon and 1 subject due to angioedema). In addition, 1 subject (Dapa+Exe/Dapa+Exe group) reported SAE injury, during the initial 24-week study period, however completed the entire 52-week study.

Adverse events by system organ class and preferred term

- The most common SOCs, reported by >50% of subjects in any group, during the entire 52-week study, were general disorders and administration site conditions (76.2% vs 76.5% of all subjects in the Dapa+Exe/Dapa+Exe and placebo groups, respectively), gastrointestinal disorders (71.4% vs 76.5%) and infections and infestations (61.9% vs 52.9%).

  The most common PTs reported in the Dapa+Exe/Dapa+Exe group were nausea (42.9% vs 23.5% in Placebo/Dapa+Exe group), nasopharyngitis (38.1% vs 17.6%), dizziness (33.3% vs 17.6%) and decreased appetite (33.3% vs 11.8%).

  The most common PTs reported in the Placebo/Dapa+Exe group were pollakiuria (64.7% [23.8% in Dapa+Exe/Dapa+Exe group]), injection site mass (35.3% [28.6%]) and fatigue (35.3% [28.6%]).

Adverse events of special interest

- 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 entire study and there was no major difference in reporting frequency between treatment groups.
- During the entire study period, gastrointestinal AEs of special interest with regard to the mode of action of exenatide treatment were reported by a smaller proportion of subjects in the Dapa+Exe/Dapa+Exe group than in the Placebo/Dapa+Exe group: 61.9% vs 76.5% of all subjects in the two groups, respectively. Most AEs reported in the Placebo/Dapa+Exe group were reported during the initial 24weeks, i.e. the subjects were on placebo treatment. The most common gastrointestinal symptoms were nausea, upper abdominal pain and diarrhoea.
- Injection site-related AEs were similarly reported in both groups: 42.8% vs 41.2% of all subjects in the Dapa+Exe/Dapa+Exe and Placebo/Dapa+Exe groups, respectively. All reactions, except one, were reported during the initial 24-week main study period. The most common injection site-related AEs were injection site mass, injection site pruritus and injection site erythema.

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, non-diabetic subjects. The study was divided into two parts. The first part, referred to as the main study, used a randomized, double-blind and placebo-controlled design with 2 treatment arms, in which active treatment (dapagliflozin/exenatide) or placebo was administered in a 1:1 fashion for 24 weeks. The second part, referred to as the extension study, was a 28-week open-label study in which dapagliflozin/exenatide were administered to subjects who had completed the 24-week double-blind study and who were eligible and willing to continue treatment with study medication. This report describes the results obtained during the entire 52-week study period. The results from the 24-week double blind study are briefly described here and summarized separately in the clinical trial report for the 24-week short-term treatment period (version 1.1, dated 11 Jan 2017, provided in Appendix 16.5).

During the initial 24 week double-blind main study, a total of 50 subjects were treated with either dapagliflozin/exenatide (25 subjects) or matching placebo (25 subjects). In total, 43 subjects (86.0%) completed the main 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.

Of the 43 subjects who completed the main study, 38 subjects (21 from the previous dapagliflozin/exenatide group and 17 from the previous placebo group) continued in the 28-week open-label extension study. In total, 33 subjects (86.9%) completed the extension study; 16 subjects (76.2%) receiving dapagliflozin and exenatide for 24+28 weeks (the Dapa+Exe/Dapa+Exe group), and 17 subjects (100%) receiving placebo for 24 weeks and dapagliflozin and exenatide for 28 weeks (the Placebo/Dapa+Exe group).

All of the 38 subjects who participated both in the main study and in the extension study were included in the FAS (referred to as extension-FAS; 21 subjects in the Dapa+Exe/Dapa+Exe group and 17 subjects in the Placebo/Dapa+Exe group), while 30 subjects were included in the PPAS (referred to as extension-PPAS; 15 subjects in the Dapa+Exe/Dapa+Exe group and 15 subjects in the Placebo/Dapa+Exe group).

The treatment groups were well balanced at baseline with regard to demographics, prior medical history 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 Dapa+Exe/Dapa+Exe group compared to the Placebo/Dapa+Exe group. 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 variable was change in body weight (kg) from baseline to week 24 and the secondary variable was percent change in body weight from baseline to week 24. Exploratory variables included, measurements of body fat composition (total adipose tissue, abdominal subcutaneous adipose tissue, abdominal visceral adipose tissue and total lean tissue), HbA1, glucose tolerance, insulin, blood lipid profile, vital signs and other anthropometric measurements. Within-group analyses (baseline to 24 weeks/52 weeks and 24 weeks to 52 weeks) were performed on the extension study variables.

Following 24 weeks of treatment with dapagliflozin/exenatide, the 21 subjects in the Dapa+Exe/Dapa+Exe group had a mean body weight reduction of 4.3 kg ($p<0.0001$) compared to baseline, whereas no statistically significant weight reduction was observed for the 17 subjects who received placebo (Placebo/Dapa+Exe group) during the first 24 weeks.

During the following 28-week open-label extension study period, when all 38 subjects received active treatment, no further statistically significant weight reduction was observed in the Dapa+Exe/Dapa+Exe group, whereas a statistically significant mean weight reduction of 4.8 kg ($p<0.0001$) was observed in the Placebo/Dapa+Exe group.

Overall, from baseline to week 52, there were statistically significant reductions in body weight, within both groups (-5.3 kg, p=0.0013, Dapa+Exe/Dapa+Exe group; -5.4 kg, p=0.0023, Placebo/Dapa+Exe group). Most of the total weight loss occurred during the first 12 to 14 weeks of active treatment.

In a recent publication, data from 7 different studies evaluating dapagliflozin as mono- or combination therapy in T2DM were pooled.[5] The results showed a mean weight loss of 2 kg following 24 weeks of treatment with dapagliflozin. 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]

Besides body weight, additional anthropometric measurements including waist circumference, WHR and BMI were also assessed. Statistically significant reductions of the mean BMI were observed within the Dapa+Exe/Dapa+Exe group from baseline to week 24 ($p<0.0001$), from baseline to week 52 (p=0.0014) and within the Placebo/Dapa+Exe group from week 24 to week 52 ($p<0.0001$) and from baseline to week 52 (p=0.0026).

Similarly, statistically significant reductions in waist circumference were observed within the Dapa+Exe/Dapa+Exe group, from baseline to week 24 ($p<0.0001$), from baseline to week 52 ($p<0.0001$) and within the Placebo/Dapa+Exe group, from week 24 to week 52 (p=0.0020) and from baseline to week 52 (p=0.0003). Also, statistically significant reductions in WHR were observed within both groups from baseline to week 52 (p=0.0049 and p=0.0140).

Measurements of body fat composition by whole body MRI in subjects in the Dapa+Exe/Dapa+Exe group, revealed that the dapagliflozin/exenatide induced reduction of body weight was largely accounted for by a loss of adipose tissue. Statistically significant reductions of total adipose tissue were observed from baseline to week 24 (-3.9 L, p=0.0008) and from baseline to week 52 (-5.1 L, p=0.0149). Abdominal subcutaneous adipose tissue, but not abdominal visceral adipose tissue, was significantly reduced from baseline to week 52 (-1.6 L, p=0.0053). In addition, there were statistically significant reductions of total lean tissue, from baseline to week 24 (-0.93 L, p=0.0111) and from baseline to week 52 (-1.3 L, p=0.0051) and of total liver fat, from week 24 to week 52 (-0.043 L, p=0.0265), within the Dapa+Exe/Dapa+Exe group. 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 abdominal subcutaneous and abdominal visceral adipose depots.[5]

In contrast, no statistically significant difference in percentage body fat as measured by bioimpedance was observed at any time point. Whole body MRI is however regarded as a more precise and accurate method for measuring total body fat compared to bioimpedance.[14]

Dapagliflozin, an SGLT-2 inhibitor, lowers plasma glucose by inhibiting the renal reabsorption of glucose and thereby promotes its urinary excretion. Thus, dapagliflozin is also associated with body weight reduction via a continuous loss of energy (up to 300 kcal/day) via the urine. Following the initial 24 weeks of treatment, mean urinary glucose during the 3h-OGTT was 52.3 mmol in the Dapa+Exe/Dapa+Exe group versus 0.08 mmol in the Placebo/Dapa+Exe group. The glucose excretion rate was maintained at week 52 (45.7 mmol/3h-OGTT) for the Dapa+Exe/Dapa+Exe group.

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, 15] The mechanisms of weight loss with exenatide may include decreased energy intake (loss of appetite).[16] Preclinical studies suggest that exenatide may reduce appetite by promoting satiety via GLP1 receptors in the hypothalamus as well as in other brain regions.[17] Nausea, the most common adverse effect of exenatide, may also contribute to an exenatide mediated weight loss.

Being developed for T2DM, both dapagliflozin and exenatide have demonstrated robust glucose-lowering effects, albeit via different mechanisms, and lead to reduction in FPG, post-challenge plasma glucose and HbA1c with no clear signs of hypoglycaemia.[4, 5, 6, 9] Improved glycaemic control was anticipated following treatment with dapagliflozin and exenatide via glucosuria and increased glucose-dependent insulin secretion, respectively. Exenatide has been shown to enhance insulin secretion (β-cell function) and reduce glucagon secretion in diabetic subjects.[9]

In agreement with this, both 24 weeks and 52 weeks of treatment with dapagliflozin/exenatide, significantly reduced HbA1c ($p<0.0001$, at week 24 and week 52), FPG ($p<0.0001$ and $p=0.0006$, respectively) and post-challenge glucose ($p=0.0002$ and $p<0.0001$, respectively) within the Dapa+Exe/Dapa+Exe group. Also, within the Placebo/Dapa+Exe group, HbA1c and FPG were significantly reduced between week 24 and week 52 ($p=0.0038$ and $p=0.0046$, respectively) and at week 52 compared to baseline ($p<0.0001$ and $p=0.0012$, respectively) (post-challenge glucose was not analysed for the Placebo/Dapa+Exe group in the extension study). There were no clear signs of hypoglycaemia reported during any parts of the study.

Impaired fasting glucose; IFG (defined as FPG≥5.6 mmol/L) is considered a pre-diabetic state and is associated with insulin resistance. At week 24, a statistically significant reduction in the proportion of subjects with IFG ($p=0.0082$) was observed within the Dapa+Exe/Dapa+Exe group compared to baseline (IFG was not analysed for the Placebo/Dapa+Exe group in the extension study). There were also statistically significant reductions observed in the proportion of subjects with IGT within the Dapa+Exe/Dapa+Exe group, between baseline and week 24 ($p=0.0196$) and week 52 ($p=0.0253$). A proportion of 33.3% of subjects in the Dapa+Exe/Dapa+Exe group shifted from raised IGT status to normal post-challenge glucose levels between baseline and week 52.

A statistically significant reduction in mean fasting insulin was observed within the Dapa+Exe/Dapa+Exe group between week 24 and week 52 ($p=0.0006$), which could be indicative of long-term treatment effects of dapagliflozin/exenatide on pre-challenge insulin levels.

Statistically significant reductions in mean systolic blood pressure were observed within the Dapa+Exe/Dapa+Exe group following both 24 and 52 weeks of treatment (-8.8 mmHg, $p=0.0004$, and -13.0 mmHg, $p<0.0001$, respectively). A corresponding reduction compared to baseline was observed within the Placebo/Dapa+Exe group at week 52 (-8.6 mmHg, $p=0.0045$) but not at week 24 (following placebo treatment). In addition, a statistically significant increase in mean pulse was observed within the Placebo/Dapa+Exe group between week 24 and week 52 (5.6 beats/min, $p=0.0107$). 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, 18] The blood pressure reduction can partly be explained by decreased adiposity and by a SGLT2i-mediated diuresis.

In summary, 52 weeks of combined treatment with dapagliflozin and exenatide resulted in a statistically significant mean weight loss of 5.3 kg compared to baseline in the Dapa+Exe/Dapa+Exe group. Correspondingly, 28 weeks of treatment with dapagliflozin/exenatide gave rise to a mean weight loss of 5.4 kg in the Placebo/Dapa+Exe group. The weight lowering effect of dapagliflozin/exenatide was most evident during the first 12 to 14 weeks of treatment and the weight loss was largely accounted for by a loss of adipose tissue. In addition to its weight-reducing effect, the combined treatment with dapagliflozin and exenatide significantly lowered HbA1c and FPG without any clear signs of hypoglycaemia. Fasting insulin was significantly reduced between

week 24 and week 52 in the Dapa+Exe/Dapa+Exe group indicating a long term treatment effect on pre-challenge insulin levels. Finally, treatment with dapagliflozin and exenatide led to a statistically significant reduction of systolic blood pressure.

In the main study, in which the active treatment group was compared to the placebo group, there was a statistically significant difference in mean body weight loss of 4.1 kg observed in the group treated with dapagliflozin/exenatide for 24 weeks, compared to the group treated with placebo. Similarly, statistically significant reductions of the mean BMI, body fat composition, HbA1c, FPG and post-challenge plasma glucose levels were shown in the dapagliflozin/exenatide group compared to the placebo group. Also, in line with the extension study, the mean systolic blood pressure was significantly lowered in the active group compared to the group that received placebo for 24 weeks.

13.1.2 Safety

The safety results of the 24-week double-blind main study and the 28-week open-label extension study indicated no new or unexpected safety or tolerability concerns for combined treatment with dapagliflozin and exenatide in obese subjects.

There were no major changes in mean laboratory values and no apparent differences between treatment groups except a numerical decrease in the creatinine clearance rate observed in the Dapa+Exe/Dapa+Exe group at week 24 and week 52 and in the Placebo/Dapa+Exe group at week 52. The reduction in estimated creatinine clearance rate observed after receiving active treatment is probably at least partly attributable to the reduced mean body weight observed. 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[11] 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, in the main study, 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. During the extension study part, the same trend was observed, the total number of reported AEs was higher (approximately 20 percentage points) in the Dapa+Exe/Dapa+Exe group, even though both groups received active treatment.

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. A total of 10 subjects were withdrawn from the study due to AEs; 2 subjects in the dapagliflozin/exenatide group and 4 subjects in the placebo group were withdrawn from the main study and 4 subjects (all in the Dapa+Exe/Dapa+Exe group) were withdrawn due to AEs during the extension study. Importantly, there were no reported AEs of confirmed 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.[19] 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.[12] 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 low frequency (9 events, reported by 5 subjects during the entire study, all except one subject was on active treatment at the time for the event). 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.

AEs of special interest with regard to the mode of action of exenatide include gastrointestinal symptoms and injection site-related AEs.[13, 20] During the entire 52-week study the pre-defined

gastrointestinal AE were reported by a smaller proportion of subjects in the Dapa+Exe/Dapa+Exe group than in the Placebo/Dapa+Exe group (61.9% vs 76.5%). The most common symptoms were nausea, upper abdominal pain and diarrhoea. The most AEs in the Placebo/Dapa+Exe group were reported when the subjects were on placebo treatment.

During the entire 52-week study, injection site-related AEs, were reported to a similar extent in the respective groups (42.8% vs 41.2%). All reactions, except one, were reported during the initial 24-week main study period. The most frequently reported injection site-related events were injection site mass, injection site pruritus and injection site erythema.

Reduced appetite is an expected and mainly positive effect as it is promoting weight loss. It was observed that AEs referring to appetite changes differed somewhat between the groups. During the entire 52-week study, AEs related to appetite regulation were reported by 42.8% in the Dapa+Exe/Dapa+Exe group and by 17.6% in the Placebo/Dapa+Exe group (4 of 6 events reported when the subjects were on placebo treatment).

In conclusion, no safety issues were raised with regard to the combined dapagliflozin/exenatide treatment in obese subjects without diabetes, based on laboratory measurements, creatinine clearance, vital signs and reported AEs, following either short-term (24 weeks) or long term (52 weeks) treatment.

13.2 OVERALL CONCLUSIONS

13.2.1 Efficacy

- Combined treatment with dapagliflozin (10 mg once daily) and exenatide (2 mg weekly injections) in obese, non-diabetic subjects resulted in a statistically significant weight loss of approximately 5.3 kg over 52 weeks. The weight reduction was most prominent during the first 12 to 14 weeks after start of treatment and was largely accounted for by a loss of adipose tissue.
  In addition to the weight-reducing effect, the combined dapagliflozin/exenatide treatment significantly lowered plasma levels of HbA1c and FPG with no clear signs of hypoglycaemia.

- In response to a glucose challenge, both post-challenge plasma glucose levels and $AUC_{0\text{-}3h}$ as well as the fasting glucose were significantly reduced following 24 and 52 weeks treatment with dapagliflozin and exenatide. Fasting insulin was significantly reduced between 24 and 52 weeks in the group that was on active treatment for 24 +28 weeks.

- Combined treatment with dapagliflozin and exenatide led to a statistically significant reduction of mean systolic blood pressure of 13.0 mmHg over 52 weeks.

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) in obese, non-diabetic, subjects during 52 weeks of treatment, based on clinical laboratory tests, creatinine clearance, vital signs and AEs/SAEs.

- The AE reporting did not reveal any sign of new safety or tolerability issues 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 subjects 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 84 Disposition of subjects (24-week double-blind main study)

	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

Source: Clinical trial report for the 24-week short-term treatment period (version 1.1, dated 11 Jan 2017), Appendix 16.5.

Table 85 Disposition of subjects (28-week open-label extension study)

	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg	Placebo/ Dapa 10mg+Exe 2mg	Total
Enrolled			39
Eligible			38
Not eligible			1
Screening failures			1
Completed trial	16 (76.2%)	17 (94.4%)	33 (84.6%)
Prematurely withdrawn	5 (23.8%)	0	5 (12.8%)
Analysis datasets			
Extension safety analysis set	21 (100.0%)	17 (94.4%)	38 (97.4%)
Extension full analysis set	21 (100.0%)	17 (94.4%)	38 (97.4%)
Extension per-protocol analysis set	15 (71.4%)	15 (83.3%)	30 (76.9%)

Percentages are based on the number of enrolled subjects.

Table 86 Attended visits. Enrolled subjects (28-week open-label extension study)

	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=18)	Total (N=39)
Visit 1	21 (100.0%)	18 (100.0%)	39 (100.0%)
Visit 2	21 (100.0%)	18 (100.0%)	39 (100.0%)
Visit 3[1]	21 (100.0%)	18 (100.0%)	39 (100.0%)
Visit 4	21 (100.0%)	18 (100.0%)	39 (100.0%)
Visit 5	21 (100.0%)	18 (100.0%)	39 (100.0%)
Visit 6	21 (100.0%)	18 (100.0%)	39 (100.0%)
Visit 7	21 (100.0%)	18 (100.0%)	39 (100.0%)
Visit 8	21 (100.0%)	18 (100.0%)	39 (100.0%)
Visit 9[1]	21 (100.0%)	17 (94.4%)	38 (97.4%)
Visit 10	19 (90.5%)	17 (94.4%)	36 (92.3%)
Visit 11/End of study	20 (95.2%)	17 (94.4%)	37 (94.9%)

[1]Visit is a telephone contact or site visit.
Percentages are based on the number of enrolled subjects.

14.1.2 Demographics

Table 87 Demographics. Extension safety analysis set

	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)	Total (N=38)
Age (years)[1]			
n/nmiss	21/0	17/0	38/0
Mean (SD)	53.4 (14.2)	49.8 (12.9)	51.8 (13.6)
Median	58.0	52.0	53.5
Q1, Q3	42.0, 65.0	43.0, 57.0	42.0, 65.0
Min, Max	20, 69	23, 68	20, 69
Gender[1]			
Female	13 (61.9%)	11 (64.7%)	24 (63.2%)
Male	8 (38.1%)	6 (35.3%)	14 (36.8%)
Race[1]			
American Indian or Alaska Native	0	0	0
Asian	1 (4.8%)	0	1 (2.6%)
Black or African American	0	0	0
Native Hawaiian of other Pacific Islander	0	0	0
White	19 (90.5%)	17 (100.0%)	36 (94.7%)
Other	1 (4.8%)	0	1 (2.6%)
Childbearing potential[1]			
Yes	4 (19.0%)	4 (23.5%)	8 (21.1%)
No	9 (42.9%)	7 (41.2%)	16 (42.1%)
Reason[2]			
Postmenopausal	7 (77.8%)	6 (85.7%)	13 (81.3%)
Surgically sterile	0	1 (14.3%)	1 (6.3%)
Premenarcheal	1 (11.1%)	0	1 (6.3%)
Other	1 (11.1%)	0	1 (6.3%)

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles.
[1]Percentages are based on the number of subjects in the applicable analysis set.
[2]Percentages are based on the number of females without childbearing potential.

14.1.3 Medical History

Table 88 Medical history. Extension safety analysis set

System organ class/Preferred term	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Any medical history	10 (47.6%)	5 (29.4%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (9.5%)	0
Choriocarcinoma	1 (4.8%)	0
Seborrhoeic keratosis	1 (4.8%)	0
Nervous system disorders	1 (4.8%)	0
Cerebral haemorrhage	1 (4.8%)	0
Muscle spasticity	1 (4.8%)	0
Ear and labyrinth disorders	1 (4.8%)	0
Vertigo positional	1 (4.8%)	0
Musculoskeletal and connective tissue disorders	1 (4.8%)	2 (11.8%)
Intervertebral disc protrusion	0	2 (11.8%)
Osteoarthritis	1 (4.8%)	0
Renal and urinary disorders	0	1 (5.9%)
Nephrolithiasis	0	1 (5.9%)
General disorders and administration site conditions	1 (4.8%)	0
Inflammation	1 (4.8%)	0
Investigations	1 (4.8%)	0
Biopsy breast normal	1 (4.8%)	0
Injury, poisoning and procedural complications	3 (14.3%)	1 (5.9%)
Ankle fracture	1 (4.8%)	0
Concussion	1 (4.8%)	0
Ligament rupture	0	1 (5.9%)
Tendon rupture	1 (4.8%)	0
Wrist fracture	1 (4.8%)	0
Social circumstances	1 (4.8%)	2 (11.8%)
Clinical trial participant	1 (4.8%)	1 (5.9%)
Joint prosthesis user	0	1 (5.9%)

Medical history is coded according to MedDRA version 18.0E.
Percentages are based on the number of subjects in the applicable analysis set

Table 89 Medical History. Extension full analysis set

System organ class/Preferred term	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Any medical history	10 (47.6%)	5 (29.4%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (9.5%)	0
Choriocarcinoma	1 (4.8%)	0
Seborrhoeic keratosis	1 (4.8%)	0
Nervous system disorders	1 (4.8%)	0
Cerebral haemorrhage	1 (4.8%)	0
Muscle spasticity	1 (4.8%)	0
Ear and labyrinth disorders	1 (4.8%)	0
Vertigo positional	1 (4.8%)	0
Musculoskeletal and connective tissue disorders	1 (4.8%)	2 (11.8%)
Intervertebral disc protrusion	0	2 (11.8%)
Osteoarthritis	1 (4.8%)	0
Renal and urinary disorders	0	1 (5.9%)
Nephrolithiasis	0	1 (5.9%)
General disorders and administration site conditions	1 (4.8%)	0
Inflammation	1 (4.8%)	0
Investigations	1 (4.8%)	0
Biopsy breast normal	1 (4.8%)	0
Injury, poisoning and procedural complications	3 (14.3%)	1 (5.9%)
Ankle fracture	1 (4.8%)	0
Concussion	1 (4.8%)	0
Ligament rupture	0	1 (5.9%)
Tendon rupture	1 (4.8%)	0
Wrist fracture	1 (4.8%)	0
Social circumstances	1 (4.8%)	2 (11.8%)
Clinical trial participant	1 (4.8%)	1 (5.9%)
Joint prosthesis user	0	1 (5.9%)

Medical history is coded according to MedDRA version 18.0E.
Percentages are based on the number of subjects in the applicable analysis set

14.1.4 Concurrent Diseases

Table 90 Concurrent diseases. Extension safety analysis set

System organ class/Preferred term	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Any concurrent disease	16 (76.2%)	12 (70.6%)
Infections and infestations	1 (4.8%)	1 (5.9%)
Chronic sinusitis	1 (4.8%)	0
Herpes simplex	0	1 (5.9%)
Blood and lymphatic system disorders	1 (4.8%)	0
Anaemia macrocytic	1 (4.8%)	0
Immune system disorders	1 (4.8%)	2 (11.8%)
Seasonal allergy	1 (4.8%)	2 (11.8%)
Endocrine disorders	3 (14.3%)	2 (11.8%)
Goitre	0	1 (5.9%)
Hypothyroidism	3 (14.3%)	1 (5.9%)
Metabolism and nutrition disorders	1 (4.8%)	1 (5.9%)
Vitamin B12 deficiency	1 (4.8%)	0
Vitamin D deficiency	0	1 (5.9%)
Psychiatric disorders	3 (14.3%)	1 (5.9%)
Depression	2 (9.5%)	1 (5.9%)
Sleep disorder	1 (4.8%)	0
Nervous system disorders	3 (14.3%)	1 (5.9%)
Hemianopia homonymous	1 (4.8%)	0
Hemiparesis	1 (4.8%)	0
Migraine	1 (4.8%)	0
Restless legs syndrome	1 (4.8%)	0
Sciatica	0	1 (5.9%)
Eye disorders	0	1 (5.9%)
Ocular hypertension	0	1 (5.9%)
Cardiac disorders	0	1 (5.9%)
Palpitations	0	1 (5.9%)
Vascular disorders	4 (19.0%)	1 (5.9%)
Hypertension	4 (19.0%)	1 (5.9%)
Respiratory, thoracic and mediastinal disorders	4 (19.0%)	3 (17.6%)
Asthma	2 (9.5%)	3 (17.6%)
Sleep apnoea syndrome	2 (9.5%)	0

System organ class/Preferred term	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Gastrointestinal disorders	6 (28.6%)	2 (11.8%)
Constipation	2 (9.5%)	0
Duodenal ulcer	0	1 (5.9%)
Flatulence	0	1 (5.9%)
Gastrooesophageal reflux disease	1 (4.8%)	0
Haemorrhoids	1 (4.8%)	0
Hiatus hernia	2 (9.5%)	0
Irritable bowel syndrome	1 (4.8%)	0
Hepatobiliary disorders	1 (4.8%)	0
Hepatic steatosis	1 (4.8%)	0
Skin and subcutaneous tissue disorders	2 (9.5%)	1 (5.9%)
Psoriasis	1 (4.8%)	1 (5.9%)
Rash	1 (4.8%)	0
Musculoskeletal and connective tissue disorders	4 (19.0%)	5 (29.4%)
Arthralgia	1 (4.8%)	2 (11.8%)
Osteoarthritis	3 (14.3%)	1 (5.9%)
Rheumatic disorder	0	1 (5.9%)
Spondyloarthropathy	0	1 (5.9%)
Synovial cyst	0	1 (5.9%)
Reproductive system and breast disorders	2 (9.5%)	0
Benign prostatic hyperplasia	1 (4.8%)	0
Menorrhagia	1 (4.8%)	0
Congenital, familial and genetic disorders	1 (4.8%)	0
Thalassaemia beta	1 (4.8%)	0
General disorders and administration site conditions	0	1 (5.9%)
Peripheral swelling	0	1 (5.9%)
Injury, poisoning and procedural complications	0	2 (11.8%)
Injury	0	1 (5.9%)
Meniscus injury	0	1 (5.9%)

Concurrent diseases are coded according to MedDRA version 18.0E.
Percentages are based on the number of subjects in the applicable analysis set.

Table 91 Concurrent Diseases. Extension full analysis set

System organ class/Preferred term	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Any concurrent disease	16 (76.2%)	12 (70.6%)
Infections and infestations	1 (4.8%)	1 (5.9%)
Chronic sinusitis	1 (4.8%)	0
Herpes simplex	0	1 (5.9%)
Blood and lymphatic system disorders	1 (4.8%)	0
Anaemia macrocytic	1 (4.8%)	0
Immune system disorders	1 (4.8%)	2 (11.8%)
Seasonal allergy	1 (4.8%)	2 (11.8%)
Endocrine disorders	3 (14.3%)	2 (11.8%)
Goitre	0	1 (5.9%)
Hypothyroidism	3 (14.3%)	1 (5.9%)
Metabolism and nutrition disorders	1 (4.8%)	1 (5.9%)
Vitamin B12 deficiency	1 (4.8%)	0
Vitamin D deficiency	0	1 (5.9%)
Psychiatric disorders	3 (14.3%)	1 (5.9%)
Depression	2 (9.5%)	1 (5.9%)
Sleep disorder	1 (4.8%)	0
Nervous system disorders	3 (14.3%)	1 (5.9%)
Hemianopia homonymous	1 (4.8%)	0
Hemiparesis	1 (4.8%)	0
Migraine	1 (4.8%)	0
Restless legs syndrome	1 (4.8%)	0
Sciatica	0	1 (5.9%)
Eye disorders	0	1 (5.9%)
Ocular hypertension	0	1 (5.9%)
Cardiac disorders	0	1 (5.9%)
Palpitations	0	1 (5.9%)
Vascular disorders	4 (19.0%)	1 (5.9%)
Hypertension	4 (19.0%)	1 (5.9%)
Respiratory, thoracic and mediastinal disorders	4 (19.0%)	3 (17.6%)
Asthma	2 (9.5%)	3 (17.6%)
Sleep apnoea syndrome	2 (9.5%)	0
Gastrointestinal disorders	6 (28.6%)	2 (11.8%)

System organ class/Preferred term	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Constipation	2 (9.5%)	0
Duodenal ulcer	0	1 (5.9%)
Flatulence	0	1 (5.9%)
Gastrooesophageal reflux disease	1 (4.8%)	0
Haemorrhoids	1 (4.8%)	0
Hiatus hernia	2 (9.5%)	0
Irritable bowel syndrome	1 (4.8%)	0
Hepatobiliary disorders	1 (4.8%)	0
Hepatic steatosis	1 (4.8%)	0
Skin and subcutaneous tissue disorders	2 (9.5%)	1 (5.9%)
Psoriasis	1 (4.8%)	1 (5.9%)
Rash	1 (4.8%)	0
Musculoskeletal and connective tissue disorders	4 (19.0%)	5 (29.4%)
Arthralgia	1 (4.8%)	2 (11.8%)
Osteoarthritis	3 (14.3%)	1 (5.9%)
Rheumatic disorder	0	1 (5.9%)
Spondyloarthropathy	0	1 (5.9%)
Synovial cyst	0	1 (5.9%)
Reproductive system and breast disorders	2 (9.5%)	0
Benign prostatic hyperplasia	1 (4.8%)	0
Menorrhagia	1 (4.8%)	0
Congenital, familial and genetic disorders	1 (4.8%)	0
Thalassaemia beta	1 (4.8%)	0
General disorders and administration site conditions	0	1 (5.9%)
Peripheral swelling	0	1 (5.9%)
Injury, poisoning and procedural complications	0	2 (11.8%)
Injury	0	1 (5.9%)
Meniscus injury	0	1 (5.9%)

Concurrent diseases are coded according to MedDRA version 18.0E.
Percentages are based on the number of subjects in the applicable analysis set.

14.1.5 Prior Procedures

Table 92 Prior procedures. Extension safety analysis set

System organ class/Preferred term	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Any surgical/medical history	12 (57.1%)	7 (41.2%)
Surgical and medical procedures	12 (57.1%)	7 (41.2%)
Appendicectomy	5 (23.8%)	2 (11.8%)
Chemotherapy	0	1 (5.9%)
Cholecystectomy	1 (4.8%)	2 (11.8%)
Hip arthroplasty	0	1 (5.9%)
Hysterectomy	1 (4.8%)	0
Inguinal hernia repair	1 (4.8%)	0
Knee arthroplasty	2 (9.5%)	1 (5.9%)
Knee operation	1 (4.8%)	2 (11.8%)
Lymphoma operation	0	1 (5.9%)
Neck surgery	0	1 (5.9%)
Renal stone removal	0	1 (5.9%)
Shoulder operation	1 (4.8%)	0
Surgery	1 (4.8%)	1 (5.9%)
Tendon operation	2 (9.5%)	0
Thrombosis prophylaxis	1 (4.8%)	0
Thyroidectomy	2 (9.5%)	0
Varicose vein operation	1 (4.8%)	0

Surgical/medical history is coded according to MedDRA version 18.0E.
Percentages are based on the number of subjects in the applicable analysis set.

Table 93 Prior procedures. Extension full analysis set

System organ class/Preferred term	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Any surgical/medical history	12 (57.1%)	7 (41.2%)
Surgical and medical procedures	12 (57.1%)	7 (41.2%)
Appendicectomy	5 (23.8%)	2 (11.8%)
Chemotherapy	0	1 (5.9%)
Cholecystectomy	1 (4.8%)	2 (11.8%)
Hip arthroplasty	0	1 (5.9%)
Hysterectomy	1 (4.8%)	0
Inguinal hernia repair	1 (4.8%)	0
Knee arthroplasty	2 (9.5%)	1 (5.9%)
Knee operation	1 (4.8%)	2 (11.8%)
Lymphoma operation	0	1 (5.9%)
Neck surgery	0	1 (5.9%)
Renal stone removal	0	1 (5.9%)
Shoulder operation	1 (4.8%)	0
Surgery	1 (4.8%)	1 (5.9%)
Tendon operation	2 (9.5%)	0
Thrombosis prophylaxis	1 (4.8%)	0
Thyroidectomy	2 (9.5%)	0
Varicose vein operation	1 (4.8%)	0

Surgical/medical history is coded according to MedDRA version 18.0E.
Percentages are based on the number of subjects in the applicable analysis set.

14.1.6 Concomitant Procedures

Table 94 Concomitant procedures. Extension safety analysis set

System organ class/Preferred term	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Any concurrent surgical/medical procedure	4 (19.0%)	4 (23.5%)
Surgical and medical procedures	4 (19.0%)	4 (23.5%)
Continuous positive airway pressure	1 (4.8%)	0
Contraception	0	1 (5.9%)
Contraceptive implant	0	1 (5.9%)
Hip surgery	1 (4.8%)	0
Hormone replacement therapy	1 (4.8%)	0
Hysterectomy	0	1 (5.9%)
Knee arthroplasty	1 (4.8%)	0
Oral contraception	0	1 (5.9%)

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 95 Concomitant procedures. Extension full analysis set

System organ class/Preferred term	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Any concurrent surgical/medical procedure	4 (19.0%)	4 (23.5%)
Surgical and medical procedures	4 (19.0%)	4 (23.5%)
Continuous positive airway pressure	1 (4.8%)	0
Contraception	0	1 (5.9%)
Contraceptive implant	0	1 (5.9%)
Hip surgery	1 (4.8%)	0
Hormone replacement therapy	1 (4.8%)	0
Hysterectomy	0	1 (5.9%)
Knee arthroplasty	1 (4.8%)	0
Oral contraception	0	1 (5.9%)

Concurrent surgical procedures are coded according to MedDRA version 18.0E.
Percentages are based on the number of subjects in the applicable analysis set.

14.1.7 Prior Medication

Table 96 Prior medication. Extension safety analysis set

Therapeutic main group/Preferred term	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Any prior medication	7 (33.3%)	3 (17.6%)
ANALGESICS	1 (4.8%)	1 (5.9%)
PARACETAMOL	1 (4.8%)	1 (5.9%)
TRAMADOL	0	1 (5.9%)
ANTIANEMIC PREPARATIONS	1 (4.8%)	0
CALCIUM PHOSPHATE+FOLIC ACID	1 (4.8%)	0
ANTIBACTERIALS FOR SYSTEMIC USE	1 (4.8%)	0
DOXYCYCLINE	1 (4.8%)	0
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	1 (4.8%)	1 (5.9%)
DICLOFENAC	0	1 (5.9%)
IBUPROFEN	1 (4.8%)	1 (5.9%)
ANTINEOPLASTIC AGENTS	1 (4.8%)	0
* ANTINEOPLASTIC AGENTS	1 (4.8%)	0
ANTIOBESITY PREPARATIONS, EXCL. DIET PRODUCTS	4 (19.0%)	1 (5.9%)
ORLISTAT	2 (9.5%)	1 (5.9%)
SIBUTRAMINE HYDROCHLORIDE	3 (14.3%)	0
ANTITHROMBOTIC AGENTS	1 (4.8%)	0
ACETYLSALICYLIC ACID	1 (4.8%)	0
DRUGS FOR ACID RELATED DISORDERS	0	1 (5.9%)
OMEPRAZOLE	0	1 (5.9%)
NO MATCH	1 (4.8%)	0
RIMONABANT	1 (4.8%)	0
PSYCHOANALEPTICS	1 (4.8%)	0
CITALOPRAM	1 (4.8%)	0
PSYCHOLEPTICS	0	1 (5.9%)
PREGABALIN	0	1 (5.9%)

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.

Table 97 Prior medication. Extension full analysis set

Therapeutic main group/Preferred term	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Any prior medication	7 (33.3%)	3 (17.6%)
ANALGESICS	1 (4.8%)	1 (5.9%)
PARACETAMOL	1 (4.8%)	1 (5.9%)
TRAMADOL	0	1 (5.9%)
ANTIANEMIC PREPARATIONS	1 (4.8%)	0
CALCIUM PHOSPHATE+FOLIC ACID	1 (4.8%)	0
ANTIBACTERIALS FOR SYSTEMIC USE	1 (4.8%)	0
DOXYCYCLINE	1 (4.8%)	0
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	1 (4.8%)	1 (5.9%)
DICLOFENAC	0	1 (5.9%)
IBUPROFEN	1 (4.8%)	1 (5.9%)
ANTINEOPLASTIC AGENTS	1 (4.8%)	0
* ANTINEOPLASTIC AGENTS	1 (4.8%)	0
ANTIOBESITY PREPARATIONS, EXCL. DIET PRODUCTS	4 (19.0%)	1 (5.9%)
ORLISTAT	2 (9.5%)	1 (5.9%)
SIBUTRAMINE HYDROCHLORIDE	3 (14.3%)	0
ANTITHROMBOTIC AGENTS	1 (4.8%)	0
ACETYLSALICYLIC ACID	1 (4.8%)	0
DRUGS FOR ACID RELATED DISORDERS	0	1 (5.9%)
OMEPRAZOLE	0	1 (5.9%)
NO MATCH	1 (4.8%)	0
RIMONABANT	1 (4.8%)	0
PSYCHOANALEPTICS	1 (4.8%)	0
CITALOPRAM	1 (4.8%)	0
PSYCHOLEPTICS	0	1 (5.9%)
PREGABALIN	0	1 (5.9%)

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.

14.1.8 Concomitant Medication

Table 98 Concomitant medication - Baseline to 24 weeks. Extension safety analysis set

Therapeutic main group/Preferred term	Baseline to 24 weeks Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Any concomitant medication	20 (95.2%)	15 (88.2%)
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	2 (9.5%)	1 (5.9%)
ENALAPRIL	0	1 (5.9%)
LOSARTAN	1 (4.8%)	0
RAMIPRIL	1 (4.8%)	0
ANALGESICS	10 (47.6%)	6 (35.3%)
ACETYLSALICYLIC ACID	3 (14.3%)	0
BUPRENORPHINE	0	1 (5.9%)
MORPHINE	0	2 (11.8%)
MORPHINE SULFATE	0	1 (5.9%)
OXYCODONE HYDROCHLORIDE	0	1 (5.9%)
PARACETAMOL	9 (42.9%)	4 (23.5%)
PARACETAMOL+PHENYLEPHRINE	1 (4.8%)	0
SUMATRIPTAN	0	1 (5.9%)
TRAMADOL	0	1 (5.9%)
TRAMADOL HYDROCHLORIDE	0	1 (5.9%)
ANESTHETICS	1 (4.8%)	0
LIDOCAINE	1 (4.8%)	0
ANTIANEMIC PREPARATIONS	4 (19.0%)	0
CALCIUM PHOSPHATE+FOLIC ACID	1 (4.8%)	0
CYANOCOBALAMIN	4 (19.0%)	0
FERROUS SULFATE	1 (4.8%)	0
ANTIBACTERIALS FOR SYSTEMIC USE	4 (19.0%)	2 (11.8%)
* ANTIBACTERIALS FOR SYSTEMIC USE	1 (4.8%)	0
AMOXICILLIN	1 (4.8%)	0
BENZYLPENICILLIN	0	1 (5.9%)
DOXYCYCLINE MONOHYDRATE	0	1 (5.9%)
FLUCLOXACILLIN SODIUM	2 (9.5%)	0
PHENOXYMETHYLPENICILLIN POTASSIUM	2 (9.5%)	0
ANTIFUNGALS FOR DERMATOLOGICAL USE	1 (4.8%)	0
ECONAZOLE NITRATE	1 (4.8%)	0
ANTIHISTAMINES FOR SYSTEMIC USE	3 (14.3%)	2 (11.8%)
CETIRIZINE HYDROCHLORIDE	0	1 (5.9%)
EBASTINE	1 (4.8%)	1 (5.9%)
LORATADINE	2 (9.5%)	0
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	6 (28.6%)	6 (35.3%)
DICLOFENAC	1 (4.8%)	1 (5.9%)
IBUPROFEN	4 (19.0%)	2 (11.8%)

Therapeutic main group/Preferred term	Baseline to 24 weeks Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
KETOPROFEN	0	2 (11.8%)
NAPROXEN	1 (4.8%)	1 (5.9%)
ANTITHROMBOTIC AGENTS	0	1 (5.9%)
* ANTITHROMBOTIC AGENTS	0	1 (5.9%)
ANTIVIRALS FOR SYSTEMIC USE	0	1 (5.9%)
VALACICLOVIR	0	1 (5.9%)
BETA BLOCKING AGENTS	0	1 (5.9%)
METOPROLOL TARTRATE	0	1 (5.9%)
CALCIUM CHANNEL BLOCKERS	0	1 (5.9%)
FELODIPINE	0	1 (5.9%)
CORTICOSTEROIDS FOR SYSTEMIC USE	0	2 (11.8%)
BETAMETHASONE	0	1 (5.9%)
BUDESONIDE	0	1 (5.9%)
CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS	2 (9.5%)	0
* CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS	1 (4.8%)	0
CLOBETASOL PROPIONATE	1 (4.8%)	0
DIURETICS	2 (9.5%)	1 (5.9%)
AMILORIDE	1 (4.8%)	0
AMILORIDE+HYDROCHLOROTHIAZIDE	1 (4.8%)	0
BENDROFLUMETHIAZIDE	1 (4.8%)	0
FUROSEMIDE	0	1 (5.9%)
DRUGS FOR ACID RELATED DISORDERS	7 (33.3%)	2 (11.8%)
CALCIUM CARBONATE+MAGNESIUM HYDROXIDE	1 (4.8%)	0
FAMOTIDINE	1 (4.8%)	0
GAVISCON /OLD FORM/	1 (4.8%)	0
OMEPRAZOLE	4 (19.0%)	2 (11.8%)
PANTOPRAZOLE	1 (4.8%)	0
DRUGS FOR CONSTIPATION	1 (4.8%)	0
PLANTAGO AFRA SEED+SODIUM CHLORIDE+THIAMINE	1 (4.8%)	0
DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS	0	1 (5.9%)
DIMETICONE	0	1 (5.9%)
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	2 (9.5%)	3 (17.6%)
BUDESONIDE+FORMOTEROL	1 (4.8%)	1 (5.9%)
MONTELUKAST	1 (4.8%)	1 (5.9%)
TERBUTALINE	1 (4.8%)	0
TERBUTALINE SULFATE	0	2 (11.8%)

Therapeutic main group/Preferred term	Baseline to 24 weeks Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
GYNECOLOGICAL ANTIINFECTIVES AND ANTISEPTICS	2 (9.5%)	0
CLINDAMYCIN HYDROCHLORIDE	1 (4.8%)	0
FLUCONAZOLE	1 (4.8%)	0
IMMUNOSTIMULANTS	1 (4.8%)	0
ECHINACEA PURPUREA	1 (4.8%)	0
IMMUNOSUPPRESSANTS	1 (4.8%)	0
ETANERCEPT	1 (4.8%)	0
MINERAL SUPPLEMENTS	0	1 (5.9%)
CALCIUM CARBONATE+COLECALCIFEROL	0	1 (5.9%)
NASAL PREPARATIONS	1 (4.8%)	2 (11.8%)
MOMETASONE FUROATE	1 (4.8%)	1 (5.9%)
PHENYLPROPANOLAMINE HYDROCHLORIDE	0	1 (5.9%)
NO MATCH	2 (9.5%)	1 (5.9%)
AL DIACETATE+HYDROCORTISONE+LIDOCAINE+ZN OXID	1 (4.8%)	0
BETAMETHASONE+CALCIPOTRIOL	0	1 (5.9%)
MACROGOL+K CHLORIDE+NA BICARBONATE+NA CHLORID	1 (4.8%)	0
PSYCHOANALEPTICS	2 (9.5%)	2 (11.8%)
CITALOPRAM	0	2 (11.8%)
FLUOXETINE	1 (4.8%)	0
MIANSERIN	1 (4.8%)	0
PSYCHOLEPTICS	1 (4.8%)	1 (5.9%)
ZOLPIDEM TARTRATE	0	1 (5.9%)
ZOPICLONE	1 (4.8%)	0
SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM	1 (4.8%)	4 (23.5%)
DESOGESTREL	1 (4.8%)	1 (5.9%)
ESTRIOL	0	1 (5.9%)
ETONOGESTREL	0	1 (5.9%)
PROGESTERONE	0	1 (5.9%)
THROAT PREPARATIONS	1 (4.8%)	0
BAFUCIN	1 (4.8%)	0
THYROID THERAPY	4 (19.0%)	1 (5.9%)
LEVOTHYROXINE SODIUM	4 (19.0%)	1 (5.9%)
LIOTHYRONINE	1 (4.8%)	0
TOPICAL PRODUCTS FOR JOINT AND MUSCULAR PAIN	2 (9.5%)	0

Therapeutic main group/Preferred term	Baseline to 24 weeks Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
ACETYLSALICYLIC ACID	1 (4.8%)	0
DICLOFENAC	1 (4.8%)	0
UROLOGICALS	1 (4.8%)	0
ALFUZOSIN	1 (4.8%)	0
FINASTERIDE	1 (4.8%)	0
VITAMINS	0	2 (11.8%)
* VITAMIN D AND ANALOGUES	0	1 (5.9%)
COLECALCIFEROL	0	1 (5.9%)

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.

Table 99 Concomitant medication - 24 to 52 weeks. Extension safety analysis set

Therapeutic main group/Preferred term	24 to 52 weeks Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Any concomitant medication	14 (66.7%)	11 (64.7%)
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	1 (4.8%)	0
RAMIPRIL	1 (4.8%)	0
ANALGESICS	2 (9.5%)	3 (17.6%)
OXYCODONE HYDROCHLORIDE	1 (4.8%)	0
PARACETAMOL	1 (4.8%)	3 (17.6%)
TRAMADOL	0	1 (5.9%)
ANTIBACTERIALS FOR SYSTEMIC USE	2 (9.5%)	1 (5.9%)
CLOXACILLIN SODIUM	1 (4.8%)	0
FLUCLOXACILLIN SODIUM	1 (4.8%)	1 (5.9%)
PHENOXYMETHYLPENICILLIN POTASSIUM	1 (4.8%)	0
ANTIFUNGALS FOR DERMATOLOGICAL USE	0	1 (5.9%)
HYDROCORTISONE+MICONAZOLE	0	1 (5.9%)
ANTIHEMORRHAGICS	3 (14.3%)	0
EPINEPHRINE	1 (4.8%)	0
TRANEXAMIC ACID	2 (9.5%)	0
ANTIHISTAMINES FOR SYSTEMIC USE	2 (9.5%)	1 (5.9%)
CETIRIZINE	0	1 (5.9%)
EBASTINE	1 (4.8%)	0
LORATADINE	1 (4.8%)	0
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	2 (9.5%)	3 (17.6%)
ETORICOXIB	0	1 (5.9%)
IBUPROFEN	1 (4.8%)	1 (5.9%)

Therapeutic main group/Preferred term	24 to 52 weeks Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	24 to 52 weeks Placebo/ Dapa 10mg+Exe 2mg (N=17)
KETOROLAC TROMETHAMINE	1 (4.8%)	0
NAPROXEN	0	1 (5.9%)
ANTIMYCOTICS FOR SYSTEMIC USE	0	1 (5.9%)
FLUCONAZOLE	0	1 (5.9%)
BETA BLOCKING AGENTS	0	1 (5.9%)
METOPROLOL	0	1 (5.9%)
CALCIUM CHANNEL BLOCKERS	0	1 (5.9%)
FELODIPINE	0	1 (5.9%)
CORTICOSTEROIDS FOR SYSTEMIC USE	1 (4.8%)	0
BETAMETHASONE SODIUM PHOSPHATE	1 (4.8%)	0
CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS	0	1 (5.9%)
MOMETASONE FUROATE	0	1 (5.9%)
COUGH AND COLD PREPARATIONS	2 (9.5%)	0
BROMHEXINE+EPHEDRINE+ETHANOL+POLYSORBATE 20	2 (9.5%)	0
DIURETICS	1 (4.8%)	1 (5.9%)
AMILORIDE+HYDROCHLOROTHIAZIDE	1 (4.8%)	0
FUROSEMIDE	0	1 (5.9%)
DRUGS FOR ACID RELATED DISORDERS	3 (14.3%)	2 (11.8%)
CALCIUM CARBONATE+MAGNESIUM HYDROXIDE	1 (4.8%)	0
OMEPRAZOLE	1 (4.8%)	1 (5.9%)
RANITIDINE HYDROCHLORIDE	1 (4.8%)	1 (5.9%)
DRUGS FOR CONSTIPATION	2 (9.5%)	0
LACTULOSE	1 (4.8%)	0
STERCULIA URENS	2 (9.5%)	0
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	1 (4.8%)	0
BUDESONIDE	1 (4.8%)	0
GYNECOLOGICAL ANTIINFECTIVES AND ANTISEPTICS	0	1 (5.9%)
ECONAZOLE NITRATE	0	1 (5.9%)
LIPID MODIFYING AGENTS	0	1 (5.9%)
ATORVASTATIN	0	1 (5.9%)
MINERAL SUPPLEMENTS	1 (4.8%)	0
POTASSIUM CHLORIDE	1 (4.8%)	0
NO MATCH	1 (4.8%)	0
INFLUENZA VIRUS VACCINE POLYVALENT	1 (4.8%)	0

Therapeutic main group/Preferred term	24 to 52 weeks Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
OPHTHALMOLOGICALS	1 (4.8%)	0
CROMOGLICATE SODIUM	1 (4.8%)	0
PSYCHOLEPTICS	1 (4.8%)	0
PROPIOMAZINE MALEATE	1 (4.8%)	0
THYROID THERAPY	1 (4.8%)	0
LIOTHYRONINE	1 (4.8%)	0
TOPICAL PRODUCTS FOR JOINT AND MUSCULAR PAIN	1 (4.8%)	0
DICLOFENAC	1 (4.8%)	0
UROLOGICALS	0	1 (5.9%)
ALFUZOSIN	0	1 (5.9%)
VITAMINS	1 (4.8%)	0
PYRIDOXINE HYDROCHLORIDE	1 (4.8%)	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.

Table 100 Concomitant medication - Baseline to 52 weeks. Extension safety analysis set

Therapeutic main group/Preferred term	Baseline to 52 weeks Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Any concomitant medication	20 (95.2%)	16 (94.1%)
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	2 (9.5%)	1 (5.9%)
ENALAPRIL	0	1 (5.9%)
LOSARTAN	1 (4.8%)	0
RAMIPRIL	1 (4.8%)	0
ANALGESICS	11 (52.4%)	8 (47.1%)
ACETYLSALICYLIC ACID	3 (14.3%)	0
BUPRENORPHINE	0	1 (5.9%)
MORPHINE	0	2 (11.8%)
MORPHINE SULFATE	0	1 (5.9%)
OXYCODONE HYDROCHLORIDE	1 (4.8%)	1 (5.9%)
PARACETAMOL	9 (42.9%)	7 (41.2%)
PARACETAMOL+PHENYLEPHRINE	1 (4.8%)	0
SUMATRIPTAN	0	1 (5.9%)
TRAMADOL	0	1 (5.9%)
TRAMADOL HYDROCHLORIDE	0	1 (5.9%)
ANESTHETICS	1 (4.8%)	0
LIDOCAINE	1 (4.8%)	0

Therapeutic main group/Preferred term	Baseline to 52 weeks Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
ANTIANEMIC PREPARATIONS	4 (19.0%)	0
CALCIUM PHOSPHATE+FOLIC ACID	1 (4.8%)	0
CYANOCOBALAMIN	4 (19.0%)	0
FERROUS SULFATE	1 (4.8%)	0
ANTIBACTERIALS FOR SYSTEMIC USE	6 (28.6%)	3 (17.6%)
* ANTIBACTERIALS FOR SYSTEMIC USE	1 (4.8%)	0
AMOXICILLIN	1 (4.8%)	0
BENZYLPENICILLIN	0	1 (5.9%)
CLOXACILLIN SODIUM	1 (4.8%)	0
DOXYCYCLINE MONOHYDRATE	0	1 (5.9%)
FLUCLOXACILLIN SODIUM	3 (14.3%)	1 (5.9%)
PHENOXYMETHYLPENICILLIN POTASSIUM	3 (14.3%)	0
ANTIFUNGALS FOR DERMATOLOGICAL USE	1 (4.8%)	1 (5.9%)
ECONAZOLE NITRATE	1 (4.8%)	0
HYDROCORTISONE+MICONAZOLE	0	1 (5.9%)
ANTIHEMORRHAGICS	3 (14.3%)	0
EPINEPHRINE	1 (4.8%)	0
TRANEXAMIC ACID	2 (9.5%)	0
ANTIHISTAMINES FOR SYSTEMIC USE	3 (14.3%)	3 (17.6%)
CETIRIZINE	0	1 (5.9%)
CETIRIZINE HYDROCHLORIDE	0	1 (5.9%)
EBASTINE	1 (4.8%)	1 (5.9%)
LORATADINE	2 (9.5%)	0
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	7 (33.3%)	8 (47.1%)
DICLOFENAC	1 (4.8%)	1 (5.9%)
ETORICOXIB	0	1 (5.9%)
IBUPROFEN	4 (19.0%)	3 (17.6%)
KETOPROFEN	0	2 (11.8%)
KETOROLAC TROMETHAMINE	1 (4.8%)	0
NAPROXEN	1 (4.8%)	2 (11.8%)
ANTIMYCOTICS FOR SYSTEMIC USE	0	1 (5.9%)
FLUCONAZOLE	0	1 (5.9%)
ANTITHROMBOTIC AGENTS	0	1 (5.9%)
* ANTITHROMBOTIC AGENTS	0	1 (5.9%)
ANTIVIRALS FOR SYSTEMIC USE	0	1 (5.9%)
VALACICLOVIR	0	1 (5.9%)
BETA BLOCKING AGENTS	0	1 (5.9%)
METOPROLOL	0	1 (5.9%)
METOPROLOL TARTRATE	0	1 (5.9%)
CALCIUM CHANNEL BLOCKERS	0	2 (11.8%)
FELODIPINE	0	2 (11.8%)

Therapeutic main group/Preferred term	Baseline to 52 weeks Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
CORTICOSTEROIDS FOR SYSTEMIC USE	1 (4.8%)	2 (11.8%)
BETAMETHASONE	0	1 (5.9%)
BETAMETHASONE SODIUM PHOSPHATE	1 (4.8%)	0
BUDESONIDE	0	1 (5.9%)
CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS	2 (9.5%)	1 (5.9%)
* CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS	1 (4.8%)	0
CLOBETASOL PROPIONATE	1 (4.8%)	0
MOMETASONE FUROATE	0	1 (5.9%)
COUGH AND COLD PREPARATIONS	2 (9.5%)	0
BROMHEXINE+EPHEDRINE+ETHANOL+POLYSORBATE 20	2 (9.5%)	0
DIURETICS	2 (9.5%)	1 (5.9%)
AMILORIDE	1 (4.8%)	0
AMILORIDE+HYDROCHLOROTHIAZIDE	1 (4.8%)	0
BENDROFLUMETHIAZIDE	1 (4.8%)	0
FUROSEMIDE	0	1 (5.9%)
DRUGS FOR ACID RELATED DISORDERS	7 (33.3%)	3 (17.6%)
CALCIUM CARBONATE+MAGNESIUM HYDROXIDE	1 (4.8%)	0
FAMOTIDINE	1 (4.8%)	0
GAVISCON /OLD FORM/	1 (4.8%)	0
OMEPRAZOLE	4 (19.0%)	2 (11.8%)
PANTOPRAZOLE	1 (4.8%)	0
RANITIDINE HYDROCHLORIDE	1 (4.8%)	1 (5.9%)
DRUGS FOR CONSTIPATION	3 (14.3%)	0
LACTULOSE	1 (4.8%)	0
PLANTAGO AFRA SEED+SODIUM CHLORIDE+THIAMINE	1 (4.8%)	0
STERCULIA URENS	2 (9.5%)	0
DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS	0	1 (5.9%)
DIMETICONE	0	1 (5.9%)
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	3 (14.3%)	3 (17.6%)
BUDESONIDE	1 (4.8%)	0
BUDESONIDE+FORMOTEROL	1 (4.8%)	1 (5.9%)
MONTELUKAST	1 (4.8%)	1 (5.9%)
TERBUTALINE	1 (4.8%)	0
TERBUTALINE SULFATE	0	2 (11.8%)
GYNECOLOGICAL ANTIINFECTIVES AND ANTISEPTICS	2 (9.5%)	1 (5.9%)
ECONAZOLE NITRATE	0	1 (5.9%)

Therapeutic main group/Preferred term	Baseline to 52 weeks Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
FLUCONAZOLE	1 (4.8%)	0
CLINDAMYCIN HYDROCHLORIDE	1 (4.8%)	0
IMMUNOSTIMULANTS	1 (4.8%)	0
ECHINACEA PURPUREA	1 (4.8%)	0
IMMUNOSUPPRESSANTS	1 (4.8%)	0
ETANERCEPT	1 (4.8%)	0
LIPID MODIFYING AGENTS	0	1 (5.9%)
ATORVASTATIN	0	1 (5.9%)
MINERAL SUPPLEMENTS	1 (4.8%)	1 (5.9%)
CALCIUM CARBONATE+COLECALCIFEROL	0	1 (5.9%)
POTASSIUM CHLORIDE	1 (4.8%)	0
NASAL PREPARATIONS	1 (4.8%)	2 (11.8%)
MOMETASONE FUROATE	1 (4.8%)	1 (5.9%)
PHENYLPROPANOLAMINE HYDROCHLORIDE	0	1 (5.9%)
NO MATCH	3 (14.3%)	1 (5.9%)
AL DIACETATE+HYDROCORTISONE+LIDOCAINE+ZN OXID	1 (4.8%)	0
BETAMETHASONE+CALCIPOTRIOL	0	1 (5.9%)
INFLUENZA VIRUS VACCINE POLYVALENT	1 (4.8%)	0
MACROGOL+K CHLORIDE+NA BICARBONATE+NA CHLORID	1 (4.8%)	0
OPHTHALMOLOGICALS	1 (4.8%)	0
CROMOGLICATE SODIUM	1 (4.8%)	0
PSYCHOANALEPTICS	2 (9.5%)	2 (11.8%)
CITALOPRAM	0	2 (11.8%)
FLUOXETINE	1 (4.8%)	0
MIANSERIN	1 (4.8%)	0
PSYCHOLEPTICS	2 (9.5%)	1 (5.9%)
PROPIOMAZINE MALEATE	1 (4.8%)	0
ZOLPIDEM TARTRATE	0	1 (5.9%)
ZOPICLONE	1 (4.8%)	0
SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM	1 (4.8%)	4 (23.5%)
DESOGESTREL	1 (4.8%)	1 (5.9%)
ESTRIOL	0	1 (5.9%)
ETONOGESTREL	0	1 (5.9%)
PROGESTERONE	0	1 (5.9%)
THROAT PREPARATIONS	1 (4.8%)	0
BAFUCIN	1 (4.8%)	0

Therapeutic main group/Preferred term	Baseline to 52 weeks Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
THYROID THERAPY	4 (19.0%)	1 (5.9%)
LEVOTHYROXINE SODIUM	4 (19.0%)	1 (5.9%)
LIOTHYRONINE	2 (9.5%)	0
TOPICAL PRODUCTS FOR JOINT AND MUSCULAR PAIN	3 (14.3%)	0
ACETYLSALICYLIC ACID	1 (4.8%)	0
DICLOFENAC	2 (9.5%)	0
UROLOGICALS	1 (4.8%)	1 (5.9%)
ALFUZOSIN	1 (4.8%)	1 (5.9%)
FINASTERIDE	1 (4.8%)	0
VITAMINS	1 (4.8%)	2 (11.8%)
* VITAMIN D AND ANALOGUES	0	1 (5.9%)
COLECALCIFEROL	0	1 (5.9%)
PYRIDOXINE HYDROCHLORIDE	1 (4.8%)	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.

Table 101 Concomitant medication - Baseline to 24 weeks. Extension full analysis set

Therapeutic main group/Preferred term	Baseline to 24 weeks Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Any concomitant medication	20 (95.2%)	15 (88.2%)
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	2 (9.5%)	1 (5.9%)
ENALAPRIL	0	1 (5.9%)
LOSARTAN	1 (4.8%)	0
RAMIPRIL	1 (4.8%)	0
ANALGESICS	10 (47.6%)	6 (35.3%)
ACETYLSALICYLIC ACID	3 (14.3%)	0
BUPRENORPHINE	0	1 (5.9%)
MORPHINE	0	2 (11.8%)
MORPHINE SULFATE	0	1 (5.9%)
OXYCODONE HYDROCHLORIDE	0	1 (5.9%)
PARACETAMOL	9 (42.9%)	4 (23.5%)
PARACETAMOL+PHENYLEPHRINE	1 (4.8%)	0
SUMATRIPTAN	0	1 (5.9%)
TRAMADOL	0	1 (5.9%)
TRAMADOL HYDROCHLORIDE	0	1 (5.9%)
ANESTHETICS	1 (4.8%)	0
LIDOCAINE	1 (4.8%)	0
ANTIANEMIC PREPARATIONS	4 (19.0%)	0
CALCIUM PHOSPHATE+FOLIC ACID	1 (4.8%)	0

Therapeutic main group/Preferred term	Baseline to 24 weeks Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
CYANOCOBALAMIN	4 (19.0%)	0
FERROUS SULFATE	1 (4.8%)	0
ANTIBACTERIALS FOR SYSTEMIC USE	4 (19.0%)	2 (11.8%)
* ANTIBACTERIALS FOR SYSTEMIC USE	1 (4.8%)	0
AMOXICILLIN	1 (4.8%)	0
BENZYLPENICILLIN	0	1 (5.9%)
DOXYCYCLINE MONOHYDRATE	0	1 (5.9%)
FLUCLOXACILLIN SODIUM	2 (9.5%)	0
PHENOXYMETHYLPENICILLIN POTASSIUM	2 (9.5%)	0
ANTIFUNGALS FOR DERMATOLOGICAL USE	1 (4.8%)	0
ECONAZOLE NITRATE	1 (4.8%)	0
ANTIHISTAMINES FOR SYSTEMIC USE	3 (14.3%)	2 (11.8%)
CETIRIZINE HYDROCHLORIDE	0	1 (5.9%)
EBASTINE	1 (4.8%)	1 (5.9%)
LORATADINE	2 (9.5%)	0
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	6 (28.6%)	6 (35.3%)
DICLOFENAC	1 (4.8%)	1 (5.9%)
IBUPROFEN	4 (19.0%)	2 (11.8%)
KETOPROFEN	0	2 (11.8%)
NAPROXEN	1 (4.8%)	1 (5.9%)
ANTITHROMBOTIC AGENTS	0	1 (5.9%)
* ANTITHROMBOTIC AGENTS	0	1 (5.9%)
ANTIVIRALS FOR SYSTEMIC USE	0	1 (5.9%)
VALACICLOVIR	0	1 (5.9%)
BETA BLOCKING AGENTS	0	1 (5.9%)
METOPROLOL TARTRATE	0	1 (5.9%)
CALCIUM CHANNEL BLOCKERS	0	1 (5.9%)
FELODIPINE	0	1 (5.9%)
CORTICOSTEROIDS FOR SYSTEMIC USE	0	2 (11.8%)
BETAMETHASONE	0	1 (5.9%)
BUDESONIDE	0	1 (5.9%)
CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS	2 (9.5%)	0
* CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS	1 (4.8%)	0
CLOBETASOL PROPIONATE	1 (4.8%)	0
DIURETICS	2 (9.5%)	1 (5.9%)
AMILORIDE	1 (4.8%)	0
AMILORIDE+HYDROCHLOROTHIAZIDE	1 (4.8%)	0
BENDROFLUMETHIAZIDE	1 (4.8%)	0

Therapeutic main group/Preferred term	Baseline to 24 weeks Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
FUROSEMIDE	0	1 (5.9%)
DRUGS FOR ACID RELATED DISORDERS	7 (33.3%)	2 (11.8%)
CALCIUM CARBONATE+MAGNESIUM HYDROXIDE	1 (4.8%)	0
FAMOTIDINE	1 (4.8%)	0
GAVISCON /OLD FORM/	1 (4.8%)	0
OMEPRAZOLE	4 (19.0%)	2 (11.8%)
PANTOPRAZOLE	1 (4.8%)	0
DRUGS FOR CONSTIPATION	1 (4.8%)	0
PLANTAGO AFRA SEED+SODIUM CHLORIDE+THIAMINE	1 (4.8%)	0
DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS	0	1 (5.9%)
DIMETICONE	0	1 (5.9%)
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	2 (9.5%)	3 (17.6%)
BUDESONIDE+FORMOTEROL	1 (4.8%)	1 (5.9%)
MONTELUKAST	1 (4.8%)	1 (5.9%)
TERBUTALINE	1 (4.8%)	0
TERBUTALINE SULFATE	0	2 (11.8%)
GYNECOLOGICAL ANTIINFECTIVES AND ANTISEPTICS	2 (9.5%)	0
CLINDAMYCIN HYDROCHLORIDE	1 (4.8%)	0
FLUCONAZOLE	1 (4.8%)	0
IMMUNOSTIMULANTS	1 (4.8%)	0
ECHINACEA PURPUREA	1 (4.8%)	0
IMMUNOSUPPRESSANTS	1 (4.8%)	0
ETANERCEPT	1 (4.8%)	0
MINERAL SUPPLEMENTS	0	1 (5.9%)
CALCIUM CARBONATE+COLECALCIFEROL	0	1 (5.9%)
NASAL PREPARATIONS	1 (4.8%)	2 (11.8%)
MOMETASONE FUROATE	1 (4.8%)	1 (5.9%)
PHENYLPROPANOLAMINE HYDROCHLORIDE	0	1 (5.9%)
NO MATCH	2 (9.5%)	1 (5.9%)
AL DIACETATE+HYDROCORTISONE+LIDOCAINE+ZN OXID	1 (4.8%)	0
BETAMETHASONE+CALCIPOTRIOL	0	1 (5.9%)
MACROGOL+K CHLORIDE+NA BICARBONATE+NA CHLORID	1 (4.8%)	0
PSYCHOANALEPTICS	2 (9.5%)	2 (11.8%)
CITALOPRAM	0	2 (11.8%)

Therapeutic main group/Preferred term	Baseline to 24 weeks Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
FLUOXETINE	1 (4.8%)	0
MIANSERIN	1 (4.8%)	0
PSYCHOLEPTICS	1 (4.8%)	1 (5.9%)
ZOLPIDEM TARTRATE	0	1 (5.9%)
ZOPICLONE	1 (4.8%)	0
SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM	1 (4.8%)	4 (23.5%)
DESOGESTREL	1 (4.8%)	1 (5.9%)
ESTRIOL	0	1 (5.9%)
ETONOGESTREL	0	1 (5.9%)
PROGESTERONE	0	1 (5.9%)
THROAT PREPARATIONS	1 (4.8%)	0
BAFUCIN	1 (4.8%)	0
THYROID THERAPY	4 (19.0%)	1 (5.9%)
LEVOTHYROXINE SODIUM	4 (19.0%)	1 (5.9%)
LIOTHYRONINE	1 (4.8%)	0
TOPICAL PRODUCTS FOR JOINT AND MUSCULAR PAIN	2 (9.5%)	0
ACETYLSALICYLIC ACID	1 (4.8%)	0
DICLOFENAC	1 (4.8%)	0
UROLOGICALS	1 (4.8%)	0
ALFUZOSIN	1 (4.8%)	0
FINASTERIDE	1 (4.8%)	0
VITAMINS	0	2 (11.8%)
* VITAMIN D AND ANALOGUES	0	1 (5.9%)
COLECALCIFEROL	0	1 (5.9%)

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.

Table 102 Concomitant medication - 24 to 52 weeks. Extension full analysis set

Therapeutic main group/Preferred term	24 to 52 weeks Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Any concomitant medication	14 (66.7%)	11 (64.7%)
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	1 (4.8%)	0
RAMIPRIL	1 (4.8%)	0
ANALGESICS	2 (9.5%)	3 (17.6%)
OXYCODONE HYDROCHLORIDE	1 (4.8%)	0
PARACETAMOL	1 (4.8%)	3 (17.6%)

Therapeutic main group/Preferred term	24 to 52 weeks Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
TRAMADOL	0	1 (5.9%)
ANTIBACTERIALS FOR SYSTEMIC USE	2 (9.5%)	1 (5.9%)
CLOXACILLIN SODIUM	1 (4.8%)	0
FLUCLOXACILLIN SODIUM	1 (4.8%)	1 (5.9%)
PHENOXYMETHYLPENICILLIN POTASSIUM	1 (4.8%)	0
ANTIFUNGALS FOR DERMATOLOGICAL USE	0	1 (5.9%)
HYDROCORTISONE+MICONAZOLE	0	1 (5.9%)
ANTIHEMORRHAGICS	3 (14.3%)	0
EPINEPHRINE	1 (4.8%)	0
TRANEXAMIC ACID	2 (9.5%)	0
ANTIHISTAMINES FOR SYSTEMIC USE	2 (9.5%)	1 (5.9%)
CETIRIZINE	0	1 (5.9%)
EBASTINE	1 (4.8%)	0
LORATADINE	1 (4.8%)	0
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	2 (9.5%)	3 (17.6%)
ETORICOXIB	0	1 (5.9%)
IBUPROFEN	1 (4.8%)	1 (5.9%)
KETOROLAC TROMETHAMINE	1 (4.8%)	0
NAPROXEN	0	1 (5.9%)
ANTIMYCOTICS FOR SYSTEMIC USE	0	1 (5.9%)
FLUCONAZOLE	0	1 (5.9%)
BETA BLOCKING AGENTS	0	1 (5.9%)
METOPROLOL	0	1 (5.9%)
CALCIUM CHANNEL BLOCKERS	0	1 (5.9%)
FELODIPINE	0	1 (5.9%)
CORTICOSTEROIDS FOR SYSTEMIC USE	1 (4.8%)	0
BETAMETHASONE SODIUM PHOSPHATE	1 (4.8%)	0
CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS	0	1 (5.9%)
MOMETASONE FUROATE	0	1 (5.9%)
COUGH AND COLD PREPARATIONS	2 (9.5%)	0
BROMHEXINE+EPHEDRINE+ETHANOL+POLYSORBATE 20	2 (9.5%)	0
DIURETICS	1 (4.8%)	1 (5.9%)
AMILORIDE+HYDROCHLOROTHIAZIDE	1 (4.8%)	0
FUROSEMIDE	0	1 (5.9%)
DRUGS FOR ACID RELATED DISORDERS	3 (14.3%)	2 (11.8%)

Therapeutic main group/Preferred term	24 to 52 weeks Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	24 to 52 weeks Placebo/ Dapa 10mg+Exe 2mg (N=17)
CALCIUM CARBONATE+MAGNESIUM HYDROXIDE	1 (4.8%)	0
OMEPRAZOLE	1 (4.8%)	1 (5.9%)
RANITIDINE HYDROCHLORIDE	1 (4.8%)	1 (5.9%)
DRUGS FOR CONSTIPATION	2 (9.5%)	0
LACTULOSE	1 (4.8%)	0
STERCULIA URENS	2 (9.5%)	0
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	1 (4.8%)	0
BUDESONIDE	1 (4.8%)	0
GYNECOLOGICAL ANTIINFECTIVES AND ANTISEPTICS	0	1 (5.9%)
ECONAZOLE NITRATE	0	1 (5.9%)
LIPID MODIFYING AGENTS	0	1 (5.9%)
ATORVASTATIN	0	1 (5.9%)
MINERAL SUPPLEMENTS	1 (4.8%)	0
POTASSIUM CHLORIDE	1 (4.8%)	0
NO MATCH	1 (4.8%)	0
INFLUENZA VIRUS VACCINE POLYVALENT	1 (4.8%)	0
OPHTHALMOLOGICALS	1 (4.8%)	0
CROMOGLICATE SODIUM	1 (4.8%)	0
PSYCHOLEPTICS	1 (4.8%)	0
PROPIOMAZINE MALEATE	1 (4.8%)	0
THYROID THERAPY	1 (4.8%)	0
LIOTHYRONINE	1 (4.8%)	0
TOPICAL PRODUCTS FOR JOINT AND MUSCULAR PAIN	1 (4.8%)	0
DICLOFENAC	1 (4.8%)	0
UROLOGICALS	0	1 (5.9%)
ALFUZOSIN	0	1 (5.9%)
VITAMINS	1 (4.8%)	0
PYRIDOXINE HYDROCHLORIDE	1 (4.8%)	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.

Table 103 Concomitant medication - Baseline to 52 weeks. Extension full analysis set

Therapeutic main group/Preferred term	Baseline to 52 weeks Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Any concomitant medication	20 (95.2%)	16 (94.1%)
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	2 (9.5%)	1 (5.9%)
ENALAPRIL	0	1 (5.9%)
LOSARTAN	1 (4.8%)	0
RAMIPRIL	1 (4.8%)	0
ANALGESICS	11 (52.4%)	8 (47.1%)
ACETYLSALICYLIC ACID	3 (14.3%)	0
BUPRENORPHINE	0	1 (5.9%)
MORPHINE	0	2 (11.8%)
MORPHINE SULFATE	0	1 (5.9%)
OXYCODONE HYDROCHLORIDE	1 (4.8%)	1 (5.9%)
PARACETAMOL	9 (42.9%)	7 (41.2%)
PARACETAMOL+PHENYLEPHRINE	1 (4.8%)	0
SUMATRIPTAN	0	1 (5.9%)
TRAMADOL	0	1 (5.9%)
TRAMADOL HYDROCHLORIDE	0	1 (5.9%)
ANESTHETICS	1 (4.8%)	0
LIDOCAINE	1 (4.8%)	0
ANTIANEMIC PREPARATIONS	4 (19.0%)	0
CALCIUM PHOSPHATE+FOLIC ACID	1 (4.8%)	0
CYANOCOBALAMIN	4 (19.0%)	0
FERROUS SULFATE	1 (4.8%)	0
ANTIBACTERIALS FOR SYSTEMIC USE	6 (28.6%)	3 (17.6%)
* ANTIBACTERIALS FOR SYSTEMIC USE	1 (4.8%)	0
AMOXICILLIN	1 (4.8%)	0
BENZYLPENICILLIN	0	1 (5.9%)
CLOXACILLIN SODIUM	1 (4.8%)	0
DOXYCYCLINE MONOHYDRATE	0	1 (5.9%)
FLUCLOXACILLIN SODIUM	3 (14.3%)	1 (5.9%)
PHENOXYMETHYLPENICILLIN POTASSIUM	3 (14.3%)	0
ANTIFUNGALS FOR DERMATOLOGICAL USE	1 (4.8%)	1 (5.9%)
ECONAZOLE NITRATE	1 (4.8%)	0
HYDROCORTISONE+MICONAZOLE	0	1 (5.9%)
ANTIHEMORRHAGICS	3 (14.3%)	0
EPINEPHRINE	1 (4.8%)	0
TRANEXAMIC ACID	2 (9.5%)	0
ANTIHISTAMINES FOR SYSTEMIC USE	3 (14.3%)	3 (17.6%)
CETIRIZINE	0	1 (5.9%)
CETIRIZINE HYDROCHLORIDE	0	1 (5.9%)
EBASTINE	1 (4.8%)	1 (5.9%)
LORATADINE	2 (9.5%)	0

Therapeutic main group/Preferred term	Baseline to 52 weeks Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	7 (33.3%)	8 (47.1%)
DICLOFENAC	1 (4.8%)	1 (5.9%)
ETORICOXIB	0	1 (5.9%)
IBUPROFEN	4 (19.0%)	3 (17.6%)
KETOPROFEN	0	2 (11.8%)
KETOROLAC TROMETHAMINE	1 (4.8%)	0
NAPROXEN	1 (4.8%)	2 (11.8%)
ANTIMYCOTICS FOR SYSTEMIC USE	0	1 (5.9%)
FLUCONAZOLE	0	1 (5.9%)
ANTITHROMBOTIC AGENTS	0	1 (5.9%)
* ANTITHROMBOTIC AGENTS	0	1 (5.9%)
ANTIVIRALS FOR SYSTEMIC USE	0	1 (5.9%)
VALACICLOVIR	0	1 (5.9%)
BETA BLOCKING AGENTS	0	1 (5.9%)
METOPROLOL	0	1 (5.9%)
METOPROLOL TARTRATE	0	1 (5.9%)
CALCIUM CHANNEL BLOCKERS	0	2 (11.8%)
FELODIPINE	0	2 (11.8%)
CORTICOSTEROIDS FOR SYSTEMIC USE	1 (4.8%)	2 (11.8%)
BETAMETHASONE	0	1 (5.9%)
BETAMETHASONE SODIUM PHOSPHATE	1 (4.8%)	0
BUDESONIDE	0	1 (5.9%)
CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS	2 (9.5%)	1 (5.9%)
* CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS	1 (4.8%)	0
CLOBETASOL PROPIONATE	1 (4.8%)	0
MOMETASONE FUROATE	0	1 (5.9%)
COUGH AND COLD PREPARATIONS	2 (9.5%)	0
BROMHEXINE+EPHEDRINE+ETHANOL+POLYSORBATE 20	2 (9.5%)	0
DIURETICS	2 (9.5%)	1 (5.9%)
AMILORIDE	1 (4.8%)	0
AMILORIDE+HYDROCHLOROTHIAZIDE	1 (4.8%)	0
BENDROFLUMETHIAZIDE	1 (4.8%)	0
FUROSEMIDE	0	1 (5.9%)
DRUGS FOR ACID RELATED DISORDERS	7 (33.3%)	3 (17.6%)
CALCIUM CARBONATE+MAGNESIUM HYDROXIDE	1 (4.8%)	0
FAMOTIDINE	1 (4.8%)	0

Therapeutic main group/Preferred term	Baseline to 52 weeks Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
GAVISCON /OLD FORM/	1 (4.8%)	0
OMEPRAZOLE	4 (19.0%)	2 (11.8%)
PANTOPRAZOLE	1 (4.8%)	0
RANITIDINE HYDROCHLORIDE	1 (4.8%)	1 (5.9%)
DRUGS FOR CONSTIPATION	3 (14.3%)	0
LACTULOSE	1 (4.8%)	0
PLANTAGO AFRA SEED+SODIUM CHLORIDE+THIAMINE	1 (4.8%)	0
STERCULIA URENS	2 (9.5%)	0
DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS	0	1 (5.9%)
DIMETICONE	0	1 (5.9%)
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	3 (14.3%)	3 (17.6%)
BUDESONIDE	1 (4.8%)	0
BUDESONIDE+FORMOTEROL	1 (4.8%)	1 (5.9%)
MONTELUKAST	1 (4.8%)	1 (5.9%)
TERBUTALINE	1 (4.8%)	0
TERBUTALINE SULFATE	0	2 (11.8%)
GYNECOLOGICAL ANTIINFECTIVES AND ANTISEPTICS	2 (9.5%)	1 (5.9%)
ECONAZOLE NITRATE	0	1 (5.9%)
FLUCONAZOLE	1 (4.8%)	0
CLINDAMYCIN HYDROCHLORIDE	1 (4.8%)	0
IMMUNOSTIMULANTS	1 (4.8%)	0
ECHINACEA PURPUREA	1 (4.8%)	0
IMMUNOSUPPRESSANTS	1 (4.8%)	0
ETANERCEPT	1 (4.8%)	0
LIPID MODIFYING AGENTS	0	1 (5.9%)
ATORVASTATIN	0	1 (5.9%)
MINERAL SUPPLEMENTS	1 (4.8%)	1 (5.9%)
CALCIUM CARBONATE+COLECALCIFEROL	0	1 (5.9%)
POTASSIUM CHLORIDE	1 (4.8%)	0
NASAL PREPARATIONS	1 (4.8%)	2 (11.8%)
MOMETASONE FUROATE	1 (4.8%)	1 (5.9%)
PHENYLPROPANOLAMINE HYDROCHLORIDE	0	1 (5.9%)
NO MATCH	3 (14.3%)	1 (5.9%)
AL DIACETATE+HYDROCORTISONE+LIDOCAINE+ZN OXID	1 (4.8%)	0
BETAMETHASONE+CALCIPOTRIOL	0	1 (5.9%)
INFLUENZA VIRUS VACCINE POLYVALENT	1 (4.8%)	0

Therapeutic main group/Preferred term	Baseline to 52 weeks Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
MACROGOL+K CHLORIDE+NA BICARBONATE+NA CHLORID	1 (4.8%)	0
OPHTHALMOLOGICALS	1 (4.8%)	0
CROMOGLICATE SODIUM	1 (4.8%)	0
PSYCHOANALEPTICS	2 (9.5%)	2 (11.8%)
CITALOPRAM	0	2 (11.8%)
FLUOXETINE	1 (4.8%)	0
MIANSERIN	1 (4.8%)	0
PSYCHOLEPTICS	2 (9.5%)	1 (5.9%)
PROPIOMAZINE MALEATE	1 (4.8%)	0
ZOLPIDEM TARTRATE	0	1 (5.9%)
ZOPICLONE	1 (4.8%)	0
SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM	1 (4.8%)	4 (23.5%)
DESOGESTREL	1 (4.8%)	1 (5.9%)
ESTRIOL	0	1 (5.9%)
ETONOGESTREL	0	1 (5.9%)
PROGESTERONE	0	1 (5.9%)
THROAT PREPARATIONS	1 (4.8%)	0
BAFUCIN	1 (4.8%)	0
THYROID THERAPY	4 (19.0%)	1 (5.9%)
LEVOTHYROXINE SODIUM	4 (19.0%)	1 (5.9%)
LIOTHYRONINE	2 (9.5%)	0
TOPICAL PRODUCTS FOR JOINT AND MUSCULAR PAIN	3 (14.3%)	0
ACETYLSALICYLIC ACID	1 (4.8%)	0
DICLOFENAC	2 (9.5%)	0
UROLOGICALS	1 (4.8%)	1 (5.9%)
ALFUZOSIN	1 (4.8%)	1 (5.9%)
FINASTERIDE	1 (4.8%)	0
VITAMINS	1 (4.8%)	2 (11.8%)
* VITAMIN D AND ANALOGUES	0	1 (5.9%)
COLECALCIFEROL	0	1 (5.9%)
PYRIDOXINE HYDROCHLORIDE	1 (4.8%)	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.

14.1.9 Treatment Compliance

Table 104 Compliance - Baseline to 24 weeks. Extension safety analysis set

	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Injection compliance (%)		
n/nmiss	21/0	17/0
Mean (SD)	100.8 (4.0)	100.0 (2.0)
Median	101.8	100.0
Q1, Q3	100.0, 102.9	99.4, 100.6
Min, Max	86, 104	96, 104
Tablet compliance (%)		
n/nmiss	21/0	17/0
Mean (SD)	98.9 (7.8)	99.1 (4.6)
Median	100.6	98.8
Q1, Q3	98.8, 101.2	97.7, 100.6
Min, Max	81, 116	90, 112

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

Table 105 Compliance - 24 to 52 weeks. Extension safety analysis set

	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Injection compliance (%)		
n/nmiss	21/0	17/0
Mean (SD)	94.7 (12.0)	97.0 (8.5)
Median	100.0	100.0
Q1, Q3	92.9, 100.5	99.5, 100.5
Min, Max	51, 104	75, 106
Tablet compliance (%)		
n/nmiss	21/0	17/0
Mean (SD)	93.3 (13.5)	98.6 (6.3)
Median	98.0	98.0
Q1, Q3	88.7, 100.5	96.4, 100.0
Min, Max	56, 113	83, 113

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 – Extension Data Sets

Table 106 Body weight (kg) and adjusted mean change from baseline to 24 weeks. Extension per-protocol analysis set

Body weight (kg)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=15)	Placebo/Dapa 10mg+Exe 2mg (N=15)
Baseline		
n/nmiss	15/0	15/0
Mean (SD)	103.05 (13.08)	101.13 (13.77)
Median	99.10	97.40
Q1, Q3	90.80, 112.10	92.50, 108.60
Min, Max	84.0, 127.1	82.3, 134.0
4 weeks		
n/nmiss	15/0	15/0
Mean (SD)	102.53 (13.39)	100.53 (14.27)
Median	99.70	96.60
Q1, Q3	92.20, 114.30	92.70, 109.40
Min, Max	83.8, 126.3	81.9, 133.6
Adjusted mean change (95% CI)	-0.71 (-1.63, 0.21)	-0.77 (-1.71, 0.17)
p-value	0.1251	0.1032
8 weeks		
n/nmiss	15/0	15/0
Mean (SD)	101.41 (13.11)	100.83 (14.49)
Median	98.90	95.30
Q1, Q3	92.00, 113.90	93.30, 109.90
Min, Max	83.0, 122.1	81.9, 134.8
Adjusted mean change (95% CI)	-1.84 (-3.11, -0.56)	-0.47 (-1.75, 0.81)
p-value	0.0062	0.4606
12 weeks		
n/nmiss	15/0	15/0
Mean (SD)	99.67 (13.96)	100.47 (14.40)
Median	97.60	95.50
Q1, Q3	87.90, 112.70	92.60, 109.60
Min, Max	80.1, 121.9	81.1, 134.8
Adjusted mean change (95% CI)	-3.57 (-5.21, -1.93)	-0.83 (-2.48, 0.82)
p-value	0.0001	0.3130
24 weeks		
n/nmiss	15/0	15/0
Mean (SD)	98.51 (15.16)	100.82 (14.24)
Median	96.00	95.50
Q1, Q3	83.00, 112.10	93.30, 109.70
Min, Max	77.4, 123.5	83.3, 134.6
Adjusted mean change (95% CI)	-4.73 (-6.93, -2.53)	-0.48 (-2.68, 1.73)
p-value	0.0001	0.6619

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 107 Body weight (kg) and adjusted mean change from 24 weeks to 52 weeks. Extension per-protocol analysis set

Body weight (kg)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=15)	Placebo/Dapa 10mg+Exe 2mg (N=15)
24 weeks		
n/nmiss	15/0	15/0
Mean (SD)	98.51 (15.16)	100.82 (14.24)
Median	96.00	95.50
Q1, Q3	83.00, 112.10	93.30, 109.70
Min, Max	77.4, 123.5	83.3, 134.6
38 weeks		
n/nmiss	15/0	15/0
Mean (SD)	98.26 (16.14)	97.39 (13.96)
Median	97.90	92.60
Q1, Q3	83.30, 113.60	89.00, 105.40
Min, Max	75.1, 121.8	80.9, 132.6
Adjusted mean change (95% CI)	-0.47 (-2.29, 1.34)	-3.82 (-5.78, -1.86)
p-value	0.5945	0.0005
52 weeks		
n/nmiss	15/0	15/0
Mean (SD)	97.36 (17.38)	96.09 (13.84)
Median	95.40	91.20
Q1, Q3	82.30, 109.90	87.40, 105.50
Min, Max	72.2, 126.0	80.5, 134.1
Adjusted mean change (95% CI)	-1.37 (-3.75, 1.00)	-5.13 (-7.61, -2.64)
p-value	0.2448	0.0002

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 108 Body weight (kg) and adjusted mean change from baseline to 52 weeks. Extension per-protocol analysis set

Body weight (kg)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=15)	Placebo/Dapa 10mg+Exe 2mg (N=15)
Baseline		
n/nmiss	15/0	15/0
Mean (SD)	103.05 (13.08)	101.13 (13.77)
Median	99.10	97.40
Q1, Q3	90.80, 112.10	92.50, 108.60
Min, Max	84.0, 127.1	82.3, 134.0
4 weeks		
n/nmiss	15/0	15/0
Mean (SD)	102.53 (13.39)	100.53 (14.27)
Median	99.70	96.60
Q1, Q3	92.20, 114.30	92.70, 109.40
Min, Max	83.8, 126.3	81.9, 133.6
Adjusted mean change (95% CI)	-0.69 (-1.61, 0.23)	-0.73 (-1.66, 0.20)
p-value	0.1360	0.1193
8 weeks		
n/nmiss	15/0	15/0
Mean (SD)	101.41 (13.11)	100.83 (14.49)
Median	98.90	95.30
Q1, Q3	92.00, 113.90	93.30, 109.90
Min, Max	83.0, 122.1	81.9, 134.8
Adjusted mean change (95% CI)	-1.81 (-3.09, -0.54)	-0.43 (-1.71, 0.85)
p-value	0.0067	0.4967
12 weeks		
n/nmiss	15/0	15/0
Mean (SD)	99.67 (13.96)	100.47 (14.40)
Median	97.60	95.50
Q1, Q3	87.90, 112.70	92.60, 109.60
Min, Max	80.1, 121.9	81.1, 134.8
Adjusted mean change (95% CI)	-3.55 (-5.19, -1.90)	-0.79 (-2.44, 0.86)
p-value	0.0001	0.3351
24 weeks		
n/nmiss	15/0	15/0
Mean (SD)	98.51 (15.16)	100.82 (14.24)
Median	96.00	95.50
Q1, Q3	83.00, 112.10	93.30, 109.70
Min, Max	77.4, 123.5	83.3, 134.6
Adjusted mean change (95% CI)	-4.71 (-6.90, -2.51)	-0.44 (-2.64, 1.76)
p-value	0.0001	0.6868
38 weeks		
n/nmiss	15/0	15/0
Mean (SD)	98.26 (16.14)	97.39 (13.96)
Median	97.90	92.60
Q1, Q3	83.30, 113.60	89.00, 105.40
Min, Max	75.1, 121.8	80.9, 132.6
Adjusted mean change (95% CI)	-4.96 (-8.16, -1.77)	-3.87 (-7.07, -0.67)

Body weight (kg)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=15)	Placebo/Dapa 10mg+Exe 2mg (N=15)
p-value	0.0036	0.0196
52 weeks		
n/nmiss	15/0	15/0
Mean (SD)	97.36 (17.38)	96.09 (13.84)
Median	95.40	91.20
Q1, Q3	82.30, 109.90	87.40, 105.50
Min, Max	72.2, 126.0	80.5, 134.1
Adjusted mean change (95% CI)	-5.86 (-9.69, -2.04)	-5.17 (-9.00, -1.34)
p-value	0.0040	0.0099

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

14.2.2 Primary Efficacy Variable – Full Data Sets

Table 109 Change from baseline in body weight (kg). Full FAS

	Adjusted LSmean (95% CI)	p-value
0-24w Dapa+Exe/Dapa+Exe	-4.48 (-6.09, -2.88)	<.0001
4-24w Dapa+Exe/Dapa+Exe	-3.51 (-4.88, -2.14)	<.0001
8-24w Dapa+Exe/Dapa+Exe	-2.33 (-3.53, -1.12)	0.0003
12-24w Dapa+Exe/Dapa+Exe	-0.53 (-1.55, 0.49)	0.3037
0-52w Dapa+Exe/Dapa+Exe	-5.69 (-8.63, -2.75)	0.0003
4-52w Dapa+Exe/Dapa+Exe	-4.72 (-7.43, -2.01)	0.0011
8-52w Dapa+Exe/Dapa+Exe	-3.53 (-6.08, -0.99)	0.0077
12-52w Dapa+Exe/Dapa+Exe	-1.73 (-3.95, 0.48)	0.1216
24-52w Dapa+Exe/Dapa+Exe	-1.21 (-3.19, 0.78)	0.2252
38-52w Dapa+Exe/Dapa+Exe	-0.87 (-2.13, 0.39)	0.1697
0-24w Placebo/Dapa+Exe	-0.34 (-2.02, 1.33)	0.6803
4-24w Placebo/Dapa+Exe	0.25 (-1.20, 1.69)	0.7320
8-24w Placebo/Dapa+Exe	0.12 (-1.17, 1.40)	0.8552
12-24w Placebo/Dapa+Exe	0.09 (-1.01, 1.19)	0.8746
0-52w Placebo/Dapa+Exe	-4.15 (-7.19, -1.10)	0.0088
4-52w Placebo/Dapa+Exe	-3.56 (-6.37, -0.74)	0.0146
8-52w Placebo/Dapa+Exe	-3.69 (-6.34, -1.03)	0.0077
12-52w Placebo/Dapa+Exe	-3.72 (-6.02, -1.41)	0.0023
24-52w Placebo/Dapa+Exe	-3.80 (-5.85, -1.75)	0.0006
38-52w Placebo/Dapa+Exe	-0.49 (-1.76, 0.78)	0.4346

LSmean = Least Square Mean, CI = Confidence interval.
p-value based on a mixed model for repeated measures (MMRM), adjusted for treatment group, sex, visit, the interaction between treatment group and visit, and the continuous covariate baseline value, estimated over the entire 52 week study period for the 'full FAS' population.

14.2.3 Secondary Efficacy Variable – Extension Data Sets

Table 110 Body weight (kg) and adjusted mean percentage change from baseline to 24 weeks. Extension per-protocol analysis set

Body weight (kg)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=15)	Placebo/ Dapa 10mg+Exe 2mg (N=15)
Baseline		
n/nmiss	15/0	15/0
Mean (SD)	103.05 (13.08)	101.13 (13.77)
Median	99.10	97.40
Q1, Q3	90.80, 112.10	92.50, 108.60
Min, Max	84.0, 127.1	82.3, 134.0
4 weeks		
n/nmiss	15/0	15/0
Mean (SD)	102.53 (13.39)	100.53 (14.27)
Median	99.70	96.60
Q1, Q3	92.20, 114.30	92.70, 109.40
Min, Max	83.8, 126.3	81.9, 133.6
Adjusted mean percentage change (95% CI)	-0.72 (-1.64, 0.19)	-0.84 (-1.77, 0.09)
p-value	0.1179	0.0735
8 weeks		
n/nmiss	15/0	15/0
Mean (SD)	101.41 (13.11)	100.83 (14.49)
Median	98.90	95.30
Q1, Q3	92.00, 113.90	93.30, 109.90
Min, Max	83.0, 122.1	81.9, 134.8
Adjusted mean percentage change (95% CI)	-1.80 (-3.03, -0.57)	-0.56 (-1.81, 0.68)
p-value	0.0056	0.3607
12 weeks		
n/nmiss	15/0	15/0
Mean (SD)	99.67 (13.96)	100.47 (14.40)
Median	97.60	95.50
Q1, Q3	87.90, 112.70	92.60, 109.60
Min, Max	80.1, 121.9	81.1, 134.8
Adjusted mean percentage change (95% CI)	-3.57 (-5.17, -1.97)	-0.90 (-2.51, 0.70)
p-value	<.0001	0.2600
24 weeks		
n/nmiss	15/0	15/0
Mean (SD)	98.51 (15.16)	100.82 (14.24)
Median	96.00	95.50
Q1, Q3	83.00, 112.10	93.30, 109.70
Min, Max	77.4, 123.5	83.3, 134.6
Adjusted mean percentage change (95% CI)	-4.79 (-6.97, -2.62)	-0.53 (-2.71, 1.65)
p-value	0.0001	0.6224

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 111 Body weight (kg) and adjusted mean percentage change from 24 weeks to 52 weeks. Extension per-protocol analysis set

Body weight (kg)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=15)	Placebo/ Dapa 10mg+Exe 2mg (N=15)
24 weeks		
n/nmiss	15/0	15/0
Mean (SD)	98.51 (15.16)	100.82 (14.24)
Median	96.00	95.50
Q1, Q3	83.00, 112.10	93.30, 109.70
Min, Max	77.4, 123.5	83.3, 134.6
38 weeks		
n/nmiss	15/0	15/0
Mean (SD)	98.26 (16.14)	97.39 (13.96)
Median	97.90	92.60
Q1, Q3	83.30, 113.60	89.00, 105.40
Min, Max	75.1, 121.8	80.9, 132.6
Adjusted mean percentage change (95% CI)	-0.57 (-2.41, 1.27)	-3.80 (-5.79, -1.80)
p-value	0.5270	0.0006
52 weeks		
n/nmiss	15/0	15/0
Mean (SD)	97.36 (17.38)	96.09 (13.84)
Median	95.40	91.20
Q1, Q3	82.30, 109.90	87.40, 105.50
Min, Max	72.2, 126.0	80.5, 134.1
Adjusted mean percentage change (95% CI)	-1.68 (-3.96, 0.59)	-5.02 (-7.41, -2.62)
p-value	0.1411	0.0002

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 112 Body weight (kg) and adjusted mean percentage change from baseline to 52 weeks. Extension per-protocol analysis set

Body weight (kg)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=15)	Placebo/ Dapa 10mg+Exe 2mg (N=15)
Baseline		
n/nmiss	15/0	15/0
Mean (SD)	103.05 (13.08)	101.13 (13.77)
Median	99.10	97.40
Q1, Q3	90.80, 112.10	92.50, 108.60
Min, Max	84.0, 127.1	82.3, 134.0
4 weeks		
n/nmiss	15/0	15/0
Mean (SD)	102.53 (13.39)	100.53 (14.27)
Median	99.70	96.60
Q1, Q3	92.20, 114.30	92.70, 109.40
Min, Max	83.8, 126.3	81.9, 133.6
Adjusted mean percentage change (95% CI)	-0.69 (-1.60, 0.22)	-0.80 (-1.73, 0.13)

Body weight (kg)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=15)	Placebo/ Dapa 10mg+Exe 2mg (N=15)
p-value	0.1325	0.0877
8 weeks		
n/nmiss	15/0	15/0
Mean (SD)	101.41 (13.11)	100.83 (14.49)
Median	98.90	95.30
Q1, Q3	92.00, 113.90	93.30, 109.90
Min, Max	83.0, 122.1	81.9, 134.8
Adjusted mean percentage change (95% CI)	-1.77 (-3.00, -0.54)	-0.52 (-1.76, 0.72)
p-value	0.0063	0.3984
12 weeks		
n/nmiss	15/0	15/0
Mean (SD)	99.67 (13.96)	100.47 (14.40)
Median	97.60	95.50
Q1, Q3	87.90, 112.70	92.60, 109.60
Min, Max	80.1, 121.9	81.1, 134.8
Adjusted mean percentage change (95% CI)	-3.54 (-5.13, -1.94)	-0.86 (-2.47, 0.75)
p-value	<.0001	0.2833
24 weeks		
n/nmiss	15/0	15/0
Mean (SD)	98.51 (15.16)	100.82 (14.24)
Median	96.00	95.50
Q1, Q3	83.00, 112.10	93.30, 109.70
Min, Max	77.4, 123.5	83.3, 134.6
Adjusted mean percentage change (95% CI)	-4.76 (-6.94, -2.59)	-0.49 (-2.67, 1.69)
p-value	0.0001	0.6516
38 weeks		
n/nmiss	15/0	15/0
Mean (SD)	98.26 (16.14)	97.39 (13.96)
Median	97.90	92.60
Q1, Q3	83.30, 113.60	89.00, 105.40
Min, Max	75.1, 121.8	80.9, 132.6
Adjusted mean percentage change (95% CI)	-5.02 (-8.13, -1.91)	-3.83 (-6.94, -0.71)
p-value	0.0026	0.0179
52 weeks		
n/nmiss	15/0	15/0
Mean (SD)	97.36 (17.38)	96.09 (13.84)
Median	95.40	91.20
Q1, Q3	82.30, 109.90	87.40, 105.50
Min, Max	72.2, 126.0	80.5, 134.1
Adjusted mean percentage change (95% CI)	-6.00 (-9.68, -2.32)	-5.07 (-8.75, -1.38)
p-value	0.0024	0.0087

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

14.2.4 Secondary Efficacy Variable – Full Data Sets

Table 113 Percent change from baseline in body weight (kg). Full FAS

	Adjusted LSmean (95% CI)	p-value
0-24w Dapa+Exe/Dapa+Exe	-4.47 (-6.05, -2.90)	<.0001
4-24w Dapa+Exe/Dapa+Exe	-3.52 (-4.86, -2.19)	<.0001
8-24w Dapa+Exe/Dapa+Exe	-2.41 (-3.59, -1.24)	0.0002
12-24w Dapa+Exe/Dapa+Exe	-0.64 (-1.62, 0.33)	0.1906
0-52w Dapa+Exe/Dapa+Exe	-5.66 (-8.43, -2.89)	0.0002
4-52w Dapa+Exe/Dapa+Exe	-4.71 (-7.24, -2.18)	0.0005
8-52w Dapa+Exe/Dapa+Exe	-3.60 (-5.97, -1.24)	0.0037
12-52w Dapa+Exe/Dapa+Exe	-1.83 (-3.90, 0.24)	0.0819
24-52w Dapa+Exe/Dapa+Exe	-1.19 (-3.00, 0.63)	0.1927
38-52w Dapa+Exe/Dapa+Exe	-0.89 (-1.99, 0.22)	0.1128
0-24w Placebo/Dapa+Exe	-0.27 (-1.91, 1.37)	0.7397
4-24w Placebo/Dapa+Exe	0.31 (-1.11, 1.72)	0.6637
8-24w Placebo/Dapa+Exe	0.18 (-1.07, 1.43)	0.7730
12-24w Placebo/Dapa+Exe	0.18 (-0.87, 1.23)	0.7369
0-52w Placebo/Dapa+Exe	-4.07 (-6.94, -1.21)	0.0064
4-52w Placebo/Dapa+Exe	-3.49 (-6.13, -0.86)	0.0105
8-52w Placebo/Dapa+Exe	-3.62 (-6.09, -1.15)	0.0051
12-52w Placebo/Dapa+Exe	-3.62 (-5.79, -1.46)	0.0016
24-52w Placebo/Dapa+Exe	-3.80 (-5.68, -1.92)	0.0002
38-52w Placebo/Dapa+Exe	-0.61 (-1.72, 0.50)	0.2691

LSmean = Least Square Mean, CI = Confidence interval.
P-value based on a mixed model for repeated measures (MMRM), adjusted for treatment group, sex, visit, the interaction between treatment group and visit, and the continuous covariate baseline value, estimated over the entire 52 week study period for the 'full FAS' population.

14.2.5 Exploratory Variables

14.2.5.1 Body Fat Composition

14.2.5.1.1 Total, abdominal subcutaneous and abdominal visceral adipose tissue and total lean tissue

Total adipose tissue

Table 114 Total adipose tissue (L) and adjusted mean change from 24 weeks to 52 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension full analysis set

Total adipose tissue (L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)
24 weeks	
n/nmiss	21/0
Mean (SD)	52.835 (12.944)
Median	51.340
Q1, Q3	42.640, 62.190
Min, Max	33.06, 75.98
52 weeks	
n/nmiss	15/6
Mean (SD)	50.571 (17.619)
Median	45.940
Q1, Q3	38.660, 67.140
Min, Max	25.95, 84.15
Adjusted mean change (95% CI)	-1.566 (-3.185, 0.053)
p-value	0.0567

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

Table 115 Total adipose tissue (L) and adjusted mean change from baseline to 24 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension per-protocol analysis set

Total adipose tissue (L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=15)
Baseline	
n/nmiss	14/1
Mean (SD)	54.258 (10.318)
Median	52.765
Q1, Q3	44.980, 57.250
Min, Max	42.27, 76.06
24 weeks	
n/nmiss	15/0
Mean (SD)	50.178 (13.062)
Median	47.150
Q1, Q3	38.650, 54.530
Min, Max	33.06, 75.98
Adjusted mean change (95% CI)	-4.148 (-7.244, -1.051)
p-value	0.0133

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

Table 116 Total adipose tissue (L) and adjusted mean change from 24 weeks to 52 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension per-protocol analysis set

Total adipose tissue (L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=15)
24 weeks	
n/nmiss	15/0
Mean (SD)	50.178 (13.062)
Median	47.150
Q1, Q3	38.650, 54.530
Min, Max	33.06, 75.98
52 weeks	
n/nmiss	14/1
Mean (SD)	49.101 (17.303)
Median	45.935
Q1, Q3	38.660, 54.190
Min, Max	25.95, 84.15
Adjusted mean change (95% CI)	-1.309 (-2.900, 0.282)
p-value	0.0975

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

Table 117 Total adipose tissue (L) and adjusted mean change from baseline to 52 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension per-protocol analysis set

Total adipose tissue (L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=15)
Baseline	
n/nmiss	14/1
Mean (SD)	54.258 (10.318)
Median	52.765
Q1, Q3	44.980, 57.250
Min, Max	42.27, 76.06
24 weeks	
n/nmiss	15/0
Mean (SD)	50.178 (13.062)
Median	47.150
Q1, Q3	38.650, 54.530
Min, Max	33.06, 75.98
Adjusted mean change (95% CI)	-3.889 (-7.496, -0.282)
p-value	0.0370
52 weeks	
n/nmiss	14/1
Mean (SD)	49.101 (17.303)
Median	45.935
Q1, Q3	38.660, 54.190
Min, Max	25.95, 84.15
Adjusted mean change (95% CI)	-5.354 (-11.238, 0.530)
p-value	0.0708

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Abdominal subcutaneous adipose tissue

Table 118 Abdominal subcutaneous adipose tissue (L) and adjusted mean change from 24 weeks to 52 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension full analysis set

Abdominal subcutaneous adipose tissue (L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)
24 weeks	
n/nmiss	21/0
Mean (SD)	12.690 (4.697)
Median	11.610
Q1, Q3	9.030, 16.600
Min, Max	7.19, 25.01
52 weeks	
n/nmiss	15/6
Mean (SD)	12.225 (5.525)
Median	11.350
Q1, Q3	7.480, 17.660
Min, Max	5.75, 23.52
Adjusted mean change (95% CI)	-0.362 (-0.971, 0.246)
p-value	0.2190

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

Table 119 Abdominal subcutaneous adipose tissue (L) and adjusted mean change from baseline to 24 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension per-protocol analysis set

Abdominal subcutaneous adipose tissue (L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=15)
Baseline	
n/nmiss	14/1
Mean (SD)	12.732 (2.840)
Median	11.790
Q1, Q3	11.130, 14.170
Min, Max	8.24, 17.39
24 weeks	
n/nmiss	15/0
Mean (SD)	11.443 (3.797)
Median	10.700
Q1, Q3	8.730, 12.990
Min, Max	7.19, 18.76
Adjusted mean change (95% CI)	-1.200 (-2.133, -0.266)
p-value	0.0164

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

Table 120 Abdominal subcutaneous adipose tissue (L) and adjusted mean change from 24 weeks to 52 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension per-protocol analysis set

Abdominal subcutaneous adipose tissue (L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=15)
24 weeks	
n/nmiss	15/0
Mean (SD)	11.443 (3.797)
Median	10.700
Q1, Q3	8.730, 12.990
Min, Max	7.19, 18.76
52 weeks	
n/nmiss	14/1
Mean (SD)	11.419 (4.729)
Median	10.640
Q1, Q3	7.480, 13.340
Min, Max	5.75, 20.64
Adjusted mean change (95% CI)	-0.078 (-0.566, 0.410)
p-value	0.7308

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

Table 121 A**bdominal subcutaneous adipose tissue (L) and adjusted mean change from baseline to 52 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension per-protocol analysis set**

Abdominal subcutaneous adipose tissue (L)	**Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=15)**
Baseline	
n/nmiss	14/1
Mean (SD)	12.732 (2.840)
Median	11.790
Q1, Q3	11.130, 14.170
Min, Max	8.24, 17.39
24 weeks	
n/nmiss	15/0
Mean (SD)	11.443 (3.797)
Median	10.700
Q1, Q3	8.730, 12.990
Min, Max	7.19, 18.76
Adjusted mean change (95% CI)	-1.279 (-2.265, -0.292)
p-value	0.0158
52 weeks	
n/nmiss	14/1
Mean (SD)	11.419 (4.729)
Median	10.640
Q1, Q3	7.480, 13.340
Min, Max	5.75, 20.64
Adjusted mean change (95% CI)	-1.539 (-3.009, -0.069)
p-value	0.0416

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Abdominal visceral adipose tissue

Table 122 Abdominal visceral adipose tissue (L) and adjusted mean change from 24 weeks to 52 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension full analysis set

Abdominal visceral adipose tissue (L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)
24 weeks	
n/nmiss	21/0
Mean (SD)	5.748 (3.118)
Median	4.430
Q1, Q3	3.540, 7.720
Min, Max	1.82, 11.90
52 weeks	
n/nmiss	15/6
Mean (SD)	5.153 (3.176)
Median	4.840
Q1, Q3	2.510, 6.790
Min, Max	1.28, 12.64
Adjusted mean change (95% CI)	-0.211 (-0.516, 0.094)
p-value	0.1573

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

Table 123 **Abdominal visceral adipose tissue (L) and adjusted mean change from baseline to 52 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension full analysis set**

Abdominal visceral adipose tissue (L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)
Baseline	
Mean (SD)	6.179 (3.242)
Median	5.050
Q1, Q3	3.685, 8.900
Min, Max	1.95, 12.50
24 weeks	
Mean (SD)	5.748 (3.118)
Median	4.430
Q1, Q3	3.540, 7.720
Min, Max	1.82, 11.90
n/nmiss	21/0
Adjusted mean change (95% CI)	-0.338 (-0.648, -0.029)
p-value	0.0340
52 weeks	
Mean (SD)	5.153 (3.176)
Median	4.840
Q1, Q3	2.510, 6.790
Min, Max	1.28, 12.64
n/nmiss	15/6
Adjusted mean change (95% CI)	-0.494 (-1.010, 0.022)
p-value	0.0596

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 124 Abdominal visceral adipose tissue (L) and adjusted mean change from baseline to 24 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension per-protocol analysis set

Abdominal visceral adipose tissue (L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=15)
Baseline	
n/nmiss	14/1
Mean (SD)	5.941 (3.272)
Median	4.800
Q1, Q3	3.340, 8.540
Min, Max	1.95, 12.50
24 weeks	
n/nmiss	15/0
Mean (SD)	5.472 (3.132)
Median	4.430
Q1, Q3	2.760, 7.720
Min, Max	1.82, 11.90
Adjusted mean change (95% CI)	-0.436 (-0.873, 0.002)
p-value	0.0508

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

Table 125 Abdominal visceral adipose tissue (L) and adjusted mean change from 24 weeks to 52 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension per-protocol analysis set

Abdominal visceral adipose tissue (L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=15)
24 weeks	
n/nmiss	15/0
Mean (SD)	5.472 (3.132)
Median	4.430
Q1, Q3	2.760, 7.720
Min, Max	1.82, 11.90
52 weeks	
n/nmiss	14/1
Mean (SD)	5.051 (3.270)
Median	4.335
Q1, Q3	2.510, 6.790
Min, Max	1.28, 12.64
Adjusted mean change (95% CI)	-0.248 (-0.598, 0.102)
p-value	0.1470

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

Table 126 Abdominal visceral adipose tissue (L) and adjusted mean change from baseline to 52 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension per-protocol analysis set

Abdominal visceral adipose tissue (L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=15)
Baseline	
n/nmiss	14/1
Mean (SD)	5.941 (3.272)
Median	4.800
Q1, Q3	3.340, 8.540
Min, Max	1.95, 12.50
24 weeks	
n/nmiss	15/0
Mean (SD)	5.472 (3.132)
Median	4.430
Q1, Q3	2.760, 7.720
Min, Max	1.82, 11.90
Adjusted mean change (95% CI)	-0.369 (-0.803, 0.065)
p-value	0.0885
52 weeks	
n/nmiss	14/1
Mean (SD)	5.051 (3.270)
Median	4.335
Q1, Q3	2.510, 6.790
Min, Max	1.28, 12.64
Adjusted mean change (95% CI)	-0.544 (-1.220, 0.132)
p-value	0.1057

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Total lean tissue

Table 127 Total lean tissue (L) and adjusted mean change from 24 weeks to 52 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension full analysis set

Total lean tissue (L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)
24 weeks	
n/nmiss	21/0
Mean (SD)	41.774 (9.342)
Median	38.700
Q1, Q3	35.360, 46.130
Min, Max	28.09, 60.68
52 weeks	
n/nmiss	15/6
Mean (SD)	40.219 (8.725)
Median	37.860
Q1, Q3	33.780, 43.540
Min, Max	28.45, 60.69
Adjusted mean change (95% CI)	-0.679 (-1.618, 0.259)
p-value	0.1408

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

Table 128 Total lean tissue (L) and adjusted mean change from baseline to 24 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension per-protocol analysis set

Total lean tissue (L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=15)
Baseline	
n/nmiss	14/1
Mean (SD)	41.337 (8.984)
Median	37.880
Q1, Q3	35.080, 46.980
Min, Max	30.17, 57.69
24 weeks	
n/nmiss	15/0
Mean (SD)	40.618 (8.653)
Median	38.640
Q1, Q3	35.350, 46.130
Min, Max	29.41, 59.98
Adjusted mean change (95% CI)	-0.688 (-1.732, 0.357)
p-value	0.1751

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

Table 129 Total lean tissue (L) and adjusted mean change from 24 weeks to 52 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension per-protocol analysis set

Total lean tissue (L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=15)
24 weeks	
n/nmiss	15/0
Mean (SD)	40.618 (8.653)
Median	38.640
Q1, Q3	35.350, 46.130
Min, Max	29.41, 59.98
52 weeks	
n/nmiss	14/1
Mean (SD)	38.757 (6.888)
Median	37.325
Q1, Q3	33.780, 43.360
Min, Max	28.45, 52.80
Adjusted mean change (95% CI)	-0.716 (-1.886, 0.454)
p-value	0.2049

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

Table 130 Total lean tissue (L) and adjusted mean change from baseline to 52 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension per-protocol analysis set

Total lean tissue (L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=15)
Baseline	
n/nmiss	14/1
Mean (SD)	41.337 (8.984)
Median	37.880
Q1, Q3	35.080, 46.980
Min, Max	30.17, 57.69
24 weeks	
n/nmiss	15/0
Mean (SD)	40.618 (8.653)
Median	38.640
Q1, Q3	35.350, 46.130
Min, Max	29.41, 59.98
Adjusted mean change (95% CI)	-0.810 (-1.989, 0.368)
p-value	0.1585
52 weeks	
n/nmiss	14/1
Mean (SD)	38.757 (6.888)
Median	37.325
Q1, Q3	33.780, 43.360
Min, Max	28.45, 52.80
Adjusted mean change (95% CI)	-1.185 (-2.514, 0.144)
p-value	0.0743

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

14.2.5.1.2 Total Liver Fat and Percentage Liver Fat

Total liver fat

Table 131 Total liver fat (L) and adjusted mean change from baseline to 24 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension full analysis set

Total liver fat (L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)
Baseline	
n/nmiss	21/0
Mean (SD)	0.237 (0.287)
Median	0.100
Q1, Q3	0.040, 0.390
Min, Max	0.01, 1.23
24 weeks	
Mean (SD)	0.235 (0.317)
Median	0.095
Q1, Q3	0.040, 0.315
Min, Max	0.02, 1.38
Adjusted mean change (95% CI)	-0.011 (-0.048, 0.026)
p-value	0.5374

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

Table 132 Total liver fat (L) and adjusted mean change from baseline to 52 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension full analysis set

Total liver fat (L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)
Baseline	
n/nmiss	21/0
Mean (SD)	0.237 (0.287)
Median	0.100
Q1, Q3	0.040, 0.390
Min, Max	0.01, 1.23
24 weeks	
Mean (SD)	0.235 (0.317)
Median	0.095
Q1, Q3	0.040, 0.315
Min, Max	0.02, 1.38
Adjusted mean change (95% CI)	-0.007 (-0.050, 0.036)
p-value	0.7311
52 weeks	
n/nmiss	14/7
Mean (SD)	0.202 (0.243)
Median	0.080
Q1, Q3	0.040, 0.310
Min, Max	0.00, 0.82
Adjusted mean change (95% CI)	-0.023 (-0.081, 0.035)
p-value	0.3864

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 133 Total liver fat (L) and adjusted mean change from baseline to 24 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension per-protocol analysis set

Total liver fat (L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=15)
Baseline	
n/nmiss	15/0
Mean (SD)	0.219 (0.318)
Median	0.070
Q1, Q3	0.040, 0.260
Min, Max	0.01, 1.23
24 weeks	
n/nmiss	14/1
Mean (SD)	0.237 (0.363)
Median	0.095
Q1, Q3	0.040, 0.260
Min, Max	0.02, 1.38
Adjusted mean change (95% CI)	0.003 (-0.022, 0.028)
p-value	0.7716

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

Table 134 Total liver fat (L) and adjusted mean change from 24 weeks to 52 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension per-protocol analysis set

Total liver fat (L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=15)
24 weeks	
n/nmiss	14/1
Mean (SD)	0.237 (0.363)
Median	0.095
Q1, Q3	0.040, 0.260
Min, Max	0.02, 1.38
52 weeks	
n/nmiss	13/2
Mean (SD)	0.186 (0.246)
Median	0.070
Q1, Q3	0.040, 0.260
Min, Max	0.00, 0.82
Adjusted mean change (95% CI)	-0.039 (-0.081, 0.003)
p-value	0.0627

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

Table 135 Total liver fat (L) and adjusted mean change from baseline to 52 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension per-protocol analysis set

Total liver fat (L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=15)
Baseline	
n/nmiss	15/0
Mean (SD)	0.219 (0.318)
Median	0.070
Q1, Q3	0.040, 0.260
Min, Max	0.01, 1.23
24 weeks	
n/nmiss	14/1
Mean (SD)	0.237 (0.363)
Median	0.095
Q1, Q3	0.040, 0.260
Min, Max	0.02, 1.38
Adjusted mean change (95% CI)	0.005 (-0.029, 0.039)
p-value	0.7054
52 weeks	
n/nmiss	13/2
Mean (SD)	0.186 (0.246)
Median	0.070
Q1, Q3	0.040, 0.260
Min, Max	0.00, 0.82
Adjusted mean change (95% CI)	-0.046 (-0.140, 0.049)
p-value	0.2822

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Percentage Liver fat

Table 136 Liver fat (%) and adjusted mean change from baseline to 24 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension full analysis set

Liver fat (%)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)
Baseline	
n/nmiss	21/0
Mean (SD)	11.16 (11.50)
Median	4.90
Q1, Q3	2.90, 16.50
Min, Max	0.9, 45.3
24 weeks	
Mean (SD)	10.29 (11.09)
Median	5.00
Q1, Q3	2.55, 16.45
Min, Max	1.2, 45.4
Adjusted mean change (95% CI)	-1.09 (-2.65, 0.46)
p-value	0.1554

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

Table 137 Liver fat (%) and adjusted mean change from 24 weeks to 52 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension full analysis set

Liver fat (%)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)
24 weeks	
Mean (SD)	10.29 (11.09)
Median	5.00
Q1, Q3	2.55, 16.45
Min, Max	1.2, 45.4
52 weeks	
Mean (SD)	9.46 (10.17)
Median	5.20
Q1, Q3	2.10, 14.50
Min, Max	0.0, 33.9
n/nmiss	14/7
Adjusted mean change (95% CI)	-0.89 (-2.22, 0.45)
p-value	0.1695

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

Table 138 Liver fat (%) and adjusted mean change from baseline to 52 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension full analysis set

Liver fat (%)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)
Baseline	
n/nmiss	21/0
Mean (SD)	11.16 (11.50)
Median	4.90
Q1, Q3	2.90, 16.50
Min, Max	0.9, 45.3
24 weeks	
Mean (SD)	10.29 (11.09)
Median	5.00
Q1, Q3	2.55, 16.45
Min, Max	1.2, 45.4
Adjusted mean change (95% CI)	-0.98 (-2.58, 0.61)
p-value	0.2114
52 weeks	
n/nmiss	14/7
Mean (SD)	9.46 (10.17)
Median	5.20
Q1, Q3	2.10, 14.50
Min, Max	0.0, 33.9
Adjusted mean change (95% CI)	-1.47 (-3.19, 0.25)
p-value	0.0867

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 139 Liver fat (%) and adjusted mean change from baseline to 24 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension per-protocol analysis set

Liver fat (%)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=15)
Baseline	
n/nmiss	15/0
Mean (SD)	10.07 (11.94)
Median	4.90
Q1, Q3	2.30, 14.70
Min, Max	0.9, 45.3
24 weeks	
n/nmiss	14/1
Mean (SD)	10.06 (12.28)
Median	5.00
Q1, Q3	2.30, 11.10
Min, Max	1.2, 45.4
Adjusted mean change (95% CI)	-0.44 (-1.62, 0.73)
p-value	0.4234

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

Table 140 Liver fat (%) and adjusted mean change from 24 weeks to 52 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension per-protocol analysis set

Liver fat (%)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=15)
24 weeks	
n/nmiss	14/1
Mean (SD)	10.06 (12.28)
Median	5.00
Q1, Q3	2.30, 11.10
Min, Max	1.2, 45.4
52 weeks	
n/nmiss	13/2
Mean (SD)	8.91 (10.37)
Median	5.10
Q1, Q3	2.10, 13.30
Min, Max	0.0, 33.9
Adjusted mean change (95% CI)	-0.77 (-2.31, 0.76)
p-value	0.2827

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

Table 141 Liver fat (%) and adjusted mean change from baseline to 52 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension per-protocol analysis set

Liver fat (%)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=15)
Baseline	
n/nmiss	15/0
Mean (SD)	10.07 (11.94)
Median	4.90
Q1, Q3	2.30, 14.70
Min, Max	0.9, 45.3
24 weeks	
n/nmiss	14/1
Mean (SD)	10.06 (12.28)
Median	5.00
Q1, Q3	2.30, 11.10
Min, Max	1.2, 45.4
Adjusted mean change (95% CI)	-0.45 (-1.63, 0.72)
p-value	0.4151
52 weeks	
n/nmiss	13/2
Mean (SD)	8.91 (10.37)
Median	5.10
Q1, Q3	2.10, 13.30
Min, Max	0.0, 33.9
Adjusted mean change (95% CI)	-1.65 (-4.16, 0.86)
p-value	0.1739

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

14.2.5.1.3 Body Fat as Measured by Bioimpedance

Table 142 Body fat (%) and adjusted mean change from baseline to 24 weeks. Extension full analysis set

Body fat (%)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)	Placebo/Dapa 10mg+Exe 2mg (N=17)
Baseline		
n/nmiss	21/0	17/0
Mean (SD)	41.81 (6.62)	39.34 (5.68)
Median	43.70	40.70
Q1, Q3	35.90, 46.50	37.40, 43.00
Min, Max	27.9, 50.3	27.9, 47.8
12 weeks		
n/nmiss	21/0	17/0
Mean (SD)	41.44 (7.22)	39.37 (5.53)
Median	42.30	41.50
Q1, Q3	36.00, 47.20	37.20, 43.00
Min, Max	25.9, 51.6	27.8, 46.3
Adjusted mean change (95% CI)	-0.39 (-1.03, 0.26)	0.13 (-0.71, 0.98)
p-value	0.2300	0.7484
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	40.99 (7.22)	39.41 (5.73)
Median	40.80	40.60
Q1, Q3	37.20, 46.80	36.60, 43.90
Min, Max	24.2, 51.4	28.0, 45.9
Adjusted mean change (95% CI)	-0.84 (-1.77, 0.08)	0.17 (-0.95, 1.29)
p-value	0.0732	0.7610

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 143 Body fat (%) and adjusted mean change from 24 weeks to 52 weeks. Extension full analysis set

Body fat (%)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)	Placebo/Dapa 10mg+Exe 2mg (N=17)
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	40.99 (7.22)	39.41 (5.73)
Median	40.80	40.60
Q1, Q3	37.20, 46.80	36.60, 43.90
Min, Max	24.2, 51.4	28.0, 45.9
38 weeks		
n/nmiss	19/2	17/0
Mean (SD)	39.97 (7.91)	38.32 (6.29)
Median	39.40	40.90
Q1, Q3	35.40, 45.70	35.00, 42.80
Min, Max	19.7, 51.2	24.8, 45.1
Adjusted mean change (95% CI)	-0.67 (-1.44, 0.10)	-1.01 (-1.88, -0.14)
p-value	0.0851	0.0236
52 weeks		
n/nmiss	17/4	17/0
Mean (SD)	39.96 (8.73)	38.36 (6.80)
Median	39.40	40.20
Q1, Q3	35.30, 44.60	36.10, 42.80
Min, Max	20.0, 53.2	24.2, 48.3
Adjusted mean change (95% CI)	-0.26 (-1.67, 1.14)	-0.97 (-2.44, 0.51)
p-value	0.7066	0.1909

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 144 Body fat (%) and adjusted mean change from baseline to 52 weeks. Extension full analysis set

Body fat (%)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)	Placebo/Dapa 10mg+Exe 2mg (N=17)
Baseline		
n/nmiss	21/0	17/0
Mean (SD)	41.81 (6.62)	39.34 (5.68)
Median	43.70	40.70
Q1, Q3	35.90, 46.50	37.40, 43.00
Min, Max	27.9, 50.3	27.9, 47.8
12 weeks		
n/nmiss	21/0	17/0
Mean (SD)	41.44 (7.22)	39.37 (5.53)
Median	42.30	41.50
Q1, Q3	36.00, 47.20	37.20, 43.00
Min, Max	25.9, 51.6	27.8, 46.3
Adjusted mean change (95% CI)	-0.39 (-1.03, 0.25)	0.19 (-0.66, 1.04)
p-value	0.2209	0.6509
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	40.99 (7.22)	39.41 (5.73)
Median	40.80	40.60
Q1, Q3	37.20, 46.80	36.60, 43.90
Min, Max	24.2, 51.4	28.0, 45.9
Adjusted mean change (95% CI)	-0.85 (-1.78, 0.07)	0.23 (-0.90, 1.35)
p-value	0.0704	0.6863
38 weeks		
n/nmiss	19/2	17/0
Mean (SD)	39.97 (7.91)	38.32 (6.29)
Median	39.40	40.90
Q1, Q3	35.40, 45.70	35.00, 42.80
Min, Max	19.7, 51.2	24.8, 45.1
Adjusted mean change (95% CI)	-1.53 (-2.62, -0.45)	-0.86 (-2.12, 0.40)
p-value	0.0070	0.1767
52 weeks		
n/nmiss	17/4	17/0
Mean (SD)	39.96 (8.73)	38.36 (6.80)
Median	39.40	40.20
Q1, Q3	35.30, 44.60	36.10, 42.80
Min, Max	20.0, 53.2	24.2, 48.3
Adjusted mean change (95% CI)	-1.15 (-2.77, 0.47)	-0.82 (-2.56, 0.93)
p-value	0.1590	0.3504

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 145 Body fat (%) and adjusted mean change from baseline to 24 weeks. Extension per-protocol analysis set

Body fat (%)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=15)	Placebo/Dapa 10mg+Exe 2mg (N=15)
Baseline		
n/nmiss	15/0	15/0
Mean (SD)	41.39 (6.98)	40.23 (5.14)
Median	43.70	42.10
Q1, Q3	34.70, 46.30	38.70, 44.00
Min, Max	27.9, 50.3	30.0, 47.8
12 weeks		
n/nmiss	15/0	15/0
Mean (SD)	40.84 (7.54)	40.29 (4.91)
Median	42.30	41.90
Q1, Q3	35.10, 47.20	39.30, 43.40
Min, Max	25.9, 51.6	29.1, 46.3
Adjusted mean change (95% CI)	-0.57 (-1.44, 0.29)	0.01 (-1.04, 1.06)
p-value	0.1823	0.9851
24 weeks		
n/nmiss	15/0	15/0
Mean (SD)	40.29 (7.74)	40.35 (5.18)
Median	40.30	40.90
Q1, Q3	33.00, 46.80	39.50, 44.10
Min, Max	24.2, 51.4	28.0, 45.9
Adjusted mean change (95% CI)	-1.12 (-2.34, 0.09)	0.07 (-1.28, 1.42)
p-value	0.0693	0.9170

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 146 Body fat (%) and adjusted mean change from 24 weeks to 52 weeks. Extension per-protocol analysis set

Body fat (%)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=15)	Placebo/Dapa 10mg+Exe 2mg (N=15)
24 weeks		
n/nmiss	15/0	15/0
Mean (SD)	40.29 (7.74)	40.35 (5.18)
Median	40.30	40.90
Q1, Q3	33.00, 46.80	39.50, 44.10
Min, Max	24.2, 51.4	28.0, 45.9
38 weeks		
n/nmiss	15/0	15/0
Mean (SD)	39.43 (8.24)	39.45 (5.48)
Median	39.40	40.90
Q1, Q3	33.90, 45.70	37.10, 43.00
Min, Max	19.7, 49.9	25.1, 45.1
Adjusted mean change (95% CI)	-0.84 (-1.83, 0.14)	-0.88 (-1.94, 0.18)
p-value	0.0907	0.0998
52 weeks		
n/nmiss	15/0	15/0
Mean (SD)	39.87 (9.25)	39.45 (6.08)
Median	39.40	40.20
Q1, Q3	34.60, 46.30	36.10, 44.50
Min, Max	20.0, 53.2	24.9, 48.3
Adjusted mean change (95% CI)	-0.41 (-2.10, 1.28)	-0.88 (-2.61, 0.85)
p-value	0.6236	0.3083

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 147 Body fat (%) and adjusted mean change from baseline to 52 weeks. Extension per-protocol analysis set

Body fat (%)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=15)	Placebo/Dapa 10mg+Exe 2mg (N=15)
Baseline		
n/nmiss	15/0	15/0
Mean (SD)	41.39 (6.98)	40.23 (5.14)
Median	43.70	42.10
Q1, Q3	34.70, 46.30	38.70, 44.00
Min, Max	27.9, 50.3	30.0, 47.8
12 weeks		
n/nmiss	15/0	15/0
Mean (SD)	40.84 (7.54)	40.29 (4.91)
Median	42.30	41.90
Q1, Q3	35.10, 47.20	39.30, 43.40
Min, Max	25.9, 51.6	29.1, 46.3
Adjusted mean change (95% CI)	-0.55 (-1.42, 0.32)	0.07 (-1.01, 1.15)
p-value	0.2028	0.8959
24 weeks		
n/nmiss	15/0	15/0
Mean (SD)	40.29 (7.74)	40.35 (5.18)
Median	40.30	40.90
Q1, Q3	33.00, 46.80	39.50, 44.10
Min, Max	24.2, 51.4	28.0, 45.9
Adjusted mean change (95% CI)	-1.10 (-2.32, 0.12)	0.13 (-1.24, 1.50)
p-value	0.0755	0.8487
38 weeks		
n/nmiss	15/0	15/0
Mean (SD)	39.43 (8.24)	39.45 (5.48)
Median	39.40	40.90
Q1, Q3	33.90, 45.70	37.10, 43.00
Min, Max	19.7, 49.9	25.1, 45.1
Adjusted mean change (95% CI)	-1.96 (-3.33, -0.59)	-0.77 (-2.27, 0.73)
p-value	0.0068	0.3051
52 weeks		
n/nmiss	15/0	15/0
Mean (SD)	39.87 (9.25)	39.45 (6.08)
Median	39.40	40.20
Q1, Q3	34.60, 46.30	36.10, 44.50
Min, Max	20.0, 53.2	24.9, 48.3
Adjusted mean change (95% CI)	-1.53 (-3.49, 0.44)	-0.77 (-2.83, 1.29)
p-value	0.1233	0.4511

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

14.2.5.2 Glucose Tolerance, Insulin Secretion, Insulin Sensitivity and Lipolysis Regulation

14.2.5.2.1 Haemoglobin A1c

Table 148 HbA1c (mmol/mol) and adjusted mean change from baseline to 24 weeks. Extension per-protocol analysis set

HbA1c (mmol/mol)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=15)	Placebo/Dapa 10mg+Exe 2mg (N=15)
Screening		
n/nmiss	15/0	15/0
Mean (SD)	36.3 (3.1)	36.7 (2.4)
Median	36.0	37.0
Q1, Q3	35.0, 39.0	35.0, 39.0
Min, Max	29, 42	33, 41
12 weeks		
n/nmiss	15/0	15/0
Mean (SD)	34.0 (3.2)	36.6 (2.8)
Median	34.0	37.0
Q1, Q3	32.0, 36.0	34.0, 38.0
Min, Max	28, 39	32, 41
Adjusted mean change (95% CI)	-2.2 (-3.5, -0.9)	0.0 (-1.3, 1.4)
p-value	0.0019	0.9694
24 weeks		
n/nmiss	14/1	15/0
Mean (SD)	32.4 (3.4)	35.1 (2.4)
Median	32.0	34.0
Q1, Q3	30.0, 36.0	33.0, 37.0
Min, Max	27, 38	32, 39
Adjusted mean change (95% CI)	-3.4 (-4.5, -2.3)	-1.4 (-2.5, -0.4)
p-value	<.0001	0.0095

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 149 HbA1c (mmol/mol) and adjusted mean change from 24 weeks to 52 weeks. Extension per-protocol analysis set

HbA1c (mmol/mol)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=15)	Placebo/Dapa 10mg+Exe 2mg (N=15)
24 weeks		
n/nmiss	14/1	15/0
Mean (SD)	32.4 (3.4)	35.1 (2.4)
Median	32.0	34.0
Q1, Q3	30.0, 36.0	33.0, 37.0
Min, Max	27, 38	32, 39
52 weeks		
n/nmiss	15/0	14/1
Mean (SD)	33.2 (3.1)	33.3 (1.8)
Median	32.0	33.5
Q1, Q3	31.0, 36.0	32.0, 35.0
Min, Max	27, 39	31, 36
Adjusted mean change (95% CI)	-0.2 (-1.1, 0.6)	-1.2 (-2.1, -0.4)
p-value	0.5788	0.0073

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

Table 150 HbA1c (mmol/mol) and adjusted mean change from baseline to 52 weeks. Extension per-protocol analysis set

HbA1c (mmol/mol)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=15)	Placebo/Dapa 10mg+Exe 2mg (N=15)
Screening		
n/nmiss	15/0	15/0
Mean (SD)	36.3 (3.1)	36.7 (2.4)
Median	36.0	37.0
Q1, Q3	35.0, 39.0	35.0, 39.0
Min, Max	29, 42	33, 41
12 weeks		
n/nmiss	15/0	15/0
Mean (SD)	34.0 (3.2)	36.6 (2.8)
Median	34.0	37.0
Q1, Q3	32.0, 36.0	34.0, 38.0
Min, Max	28, 39	32, 41
Adjusted mean change (95% CI)	-2.3 (-3.6, -1.0)	0.0 (-1.3, 1.3)
p-value	0.0014	0.9952
24 weeks		
n/nmiss	14/1	15/0
Mean (SD)	32.4 (3.4)	35.1 (2.4)
Median	32.0	34.0
Q1, Q3	30.0, 36.0	33.0, 37.0
Min, Max	27, 38	32, 39
Adjusted mean change (95% CI)	-3.5 (-4.5, -2.4)	-1.5 (-2.5, -0.4)

HbA1c (mmol/mol)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=15)	Placebo/Dapa 10mg+Exe 2mg (N=15)
p-value	<.0001	0.0082
52 weeks		
n/nmiss	15/0	14/1
Mean (SD)	33.2 (3.1)	33.3 (1.8)
Median	32.0	33.5
Q1, Q3	31.0, 36.0	32.0, 35.0
Min, Max	27, 39	31, 36
Adjusted mean change (95% CI)	-3.1 (-4.0, -2.1)	-3.1 (-4.1, -2.1)
p-value	<.0001	<.0001

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

14.2.5.2.2 Glucose

Fasting plasma glucose

Table 151 Fasting plasma glucose (mmol/L) and adjusted mean change from baseline to 24 weeks. Extension per-protocol analysis set

Glucose (mmol/L)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=15)	Placebo/ Dapa 10mg+Exe 2mg (N=15)
Screening		
n/nmiss	15/0	15/0
Mean (SD)	5.84 (0.62)	5.67 (0.33)
Median	5.70	5.60
Q1, Q3	5.30, 6.10	5.40, 5.90
Min, Max	5.0, 7.2	5.1, 6.3
12 weeks		
n/nmiss	15/0	15/0
Mean (SD)	5.61 (0.54)	5.91 (0.35)
Median	5.70	5.80
Q1, Q3	5.10, 6.00	5.60, 6.30
Min, Max	4.7, 6.5	5.6, 6.6
Adjusted mean change (95% CI)	-0.18 (-0.36, -0.01)	0.22 (0.04, 0.40)
p-value	0.0441	0.0171
24 weeks		
n/nmiss	15/0	15/0
Mean (SD)	5.33 (0.40)	5.87 (0.45)
Median	5.20	5.80
Q1, Q3	5.10, 5.60	5.60, 6.20
Min, Max	4.7, 6.1	5.1, 6.9
Adjusted mean change (95% CI)	-0.46 (-0.66, -0.26)	0.18 (-0.02, 0.38)
p-value	<.0001	0.0724

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 152 Fasting plasma glucose (mmol/L) and adjusted mean change from 24 weeks to 52 weeks. Extension per-protocol analysis set

Glucose (mmol/L)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=15)	Placebo/ Dapa 10mg+Exe 2mg (N=15)
24 weeks		
n/nmiss	15/0	15/0
Mean (SD)	5.33 (0.40)	5.87 (0.45)
Median	5.20	5.80
Q1, Q3	5.10, 5.60	5.60, 6.20
Min, Max	4.7, 6.1	5.1, 6.9
52 weeks		
n/nmiss	15/0	15/0
Mean (SD)	5.48 (0.50)	5.47 (0.32)
Median	5.40	5.40
Q1, Q3	5.10, 5.70	5.30, 5.70
Min, Max	4.8, 6.8	4.9, 6.2
Adjusted mean change (95% CI)	0.08 (-0.11, 0.26)	-0.24 (-0.44, -0.05)
p-value	0.4001	0.0176

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

Table 153 Fasting plasma glucose (mmol/L) and adjusted mean change from baseline to 52 weeks. Extension per-protocol analysis set

Glucose (mmol/L)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=15)	Placebo/ Dapa 10mg+Exe 2mg (N=15)
Screening		
n/nmiss	15/0	15/0
Mean (SD)	5.84 (0.62)	5.67 (0.33)
Median	5.70	5.60
Q1, Q3	5.30, 6.10	5.40, 5.90
Min, Max	5.0, 7.2	5.1, 6.3
12 weeks		
n/nmiss	15/0	15/0
Mean (SD)	5.61 (0.54)	5.91 (0.35)
Median	5.70	5.80
Q1, Q3	5.10, 6.00	5.60, 6.30
Min, Max	4.7, 6.5	5.6, 6.6
Adjusted mean change (95% CI)	-0.17 (-0.34, 0.01)	0.23 (0.06, 0.41)
p-value	0.0579	0.0112
24 weeks		
n/nmiss	15/0	15/0
Mean (SD)	5.33 (0.40)	5.87 (0.45)
Median	5.20	5.80
Q1, Q3	5.10, 5.60	5.60, 6.20
Min, Max	4.7, 6.1	5.1, 6.9
Adjusted mean change (95% CI)	-0.45 (-0.64, -0.25)	0.19 (-0.00, 0.39)

Glucose (mmol/L)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=15)	Placebo/ Dapa 10mg+Exe 2mg (N=15)
p-value	<.0001	0.0544
52 weeks		
n/nmiss	15/0	15/0
Mean (SD)	5.48 (0.50)	5.47 (0.32)
Median	5.40	5.40
Q1, Q3	5.10, 5.70	5.30, 5.70
Min, Max	4.8, 6.8	4.9, 6.2
Adjusted mean change (95% CI)	-0.30 (-0.48, -0.12)	-0.21 (-0.39, -0.03)
p-value	0.0017	0.0221

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Post-challenge Plasma Glucose

Table 154 Glucose (mmol/L) 120 min and adjusted mean change from 24 weeks to 52 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension full analysis set

Glucose (mmol/L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)
24 weeks	
n/nmiss	21/0
Mean (SD)	5.95 (1.75)
Median	5.50
Q1, Q3	4.70, 6.60
Min, Max	3.8, 10.8
52 weeks	
n/nmiss	15/6
Mean (SD)	5.59 (1.85)
Median	5.30
Q1, Q3	4.00, 6.80
Min, Max	2.8, 9.7
Adjusted mean change (95% CI)	-0.30 (-1.04, 0.43)
p-value	0.3883

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

Table 155 Glucose (mmol/L) 120 min and adjusted mean change from baseline to 24 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension per-protocol analysis set

Glucose (mmol/L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=15)
Screening	
n/nmiss	15/0
Mean (SD)	7.65 (2.54)
Median	7.10
Q1, Q3	5.80, 10.10
Min, Max	4.3, 12.8
24 weeks	
n/nmiss	15/0
Mean (SD)	5.93 (1.94)
Median	5.40
Q1, Q3	4.70, 6.50
Min, Max	3.8, 10.8
Adjusted mean change (95% CI)	-1.68 (-2.89, -0.47)
p-value	0.0107

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

Table 156 Glucose (mmol/L) 120 min and adjusted mean change from 24 weeks to 52 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension per-protocol analysis set

Glucose (mmol/L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=15)
24 weeks	
n/nmiss	15/0
Mean (SD)	5.93 (1.94)
Median	5.40
Q1, Q3	4.70, 6.50
Min, Max	3.8, 10.8
52 weeks	
n/nmiss	14/1
Mean (SD)	5.55 (1.91)
Median	5.15
Q1, Q3	4.00, 6.80
Min, Max	2.8, 9.7
Adjusted mean change (95% CI)	-0.43 (-1.22, 0.37)
p-value	0.2625

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

Table 157 Glucose (mmol/L) 120 min and adjusted mean change from baseline to 52 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension per-protocol analysis set

Glucose (mmol/L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=15)
Screening	
n/nmiss	15/0
Mean (SD)	7.65 (2.54)
Median	7.10
Q1, Q3	5.80, 10.10
Min, Max	4.3, 12.8
24 weeks	
n/nmiss	15/0
Mean (SD)	5.93 (1.94)
Median	5.40
Q1, Q3	4.70, 6.50
Min, Max	3.8, 10.8
Adjusted mean change (95% CI)	-1.76 (-2.96, -0.56)
p-value	0.0077
52 weeks	
n/nmiss	14/1
Mean (SD)	5.55 (1.91)
Median	5.15
Q1, Q3	4.00, 6.80
Min, Max	2.8, 9.7
Adjusted mean change (95% CI)	-2.17 (-3.22, -1.12)
p-value	0.0007

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Area under the Curve (0-3h) Plasma Glucose

Table 158 Glucose area under the curve (180 min*mmol/L) and adjusted mean change from 24 weeks to 52 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension full analysis set

Glucose AUC (180 min*mmol/L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)
24 weeks	
Mean (SD)	1170.675 (225.907)
Median	1121.250
Q1, Q3	1003.500, 1307.625
Min, Max	899.25, 1674.75
52 weeks	
Mean (SD)	1166.946 (257.917)
Median	1104.000
Q1, Q3	1013.250, 1291.500
Min, Max	800.25, 1631.25
n/nmiss	14/7
Adjusted mean change (95% CI)	0.579 (-77.507, 78.665)
p-value	0.9871

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

Table 159 Glucose area under the curve (180 min*mmol/L) and adjusted mean change from baseline to 24 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension per-protocol analysis set

Glucose AUC (180 min*mmol/L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=15)
Screening	
n/nmiss	14/1
Mean (SD)	1371.321 (331.306)
Median	1284.750
Q1, Q3	1102.500, 1638.750
Min, Max	851.25, 1936.50
24 weeks	
n/nmiss	14/1
Mean (SD)	1148.411 (251.313)
Median	1055.625
Q1, Q3	978.000, 1215.000
Min, Max	899.25, 1674.75
Adjusted mean change (95% CI)	-180.355 (-332.635, -28.074)
p-value	0.0248

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

Table 160 **Glucose area under the curve (180 min*mmol/L) and adjusted mean change from 24 weeks to 52 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension per-protocol analysis set**

Glucose AUC (180 min*mmol/L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=15)
24 weeks	
n/nmiss	14/1
Mean (SD)	1148.411 (251.313)
Median	1055.625
Q1, Q3	978.000, 1215.000
Min, Max	899.25, 1674.75
52 weeks	
n/nmiss	13/2
Mean (SD)	1143.231 (252.060)
Median	1092.000
Q1, Q3	1013.250, 1236.750
Min, Max	800.25, 1631.25
Adjusted mean change (95% CI)	-5.667 (-93.658, 82.323)
p-value	0.8874

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

Table 161 **Glucose area under the curve (180 min*mmol/L) and adjusted mean change from baseline to 52 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension per-protocol analysis set**

Glucose AUC (180 min*mmol/L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=15)
Screening	
n/nmiss	14/1
Mean (SD)	1371.321 (331.306)
Median	1284.750
Q1, Q3	1102.500, 1638.750
Min, Max	851.25, 1936.50
24 weeks	
n/nmiss	14/1
Mean (SD)	1148.411 (251.313)
Median	1055.625
Q1, Q3	978.000, 1215.000
Min, Max	899.25, 1674.75
Adjusted mean change (95% CI)	-214.327 (-362.386, -66.268)
p-value	0.0090
52 weeks	
n/nmiss	13/2
Mean (SD)	1143.231 (252.060)
Median	1092.000
Q1, Q3	1013.250, 1236.750
Min, Max	800.25, 1631.25
Adjusted mean change (95% CI)	-232.754 (-349.649, -115.859)

Glucose AUC (180 min*mmol/L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=15)
p-value	0.0011

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

14.2.5.2.3 Impaired Fasting Glucose

Table 162 Impaired fasting glucose. Extension per-protocol analysis set

	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=15)
Screening	
Normal	5 (33.3%)
Raised	10 (66.7%)
24 weeks	
Normal	11 (73.3%)
Raised	4 (26.7%)
Shift in categories	
Normal to normal	5 (33.3%)
Normal to raised	0
Raised to normal	6 (40.0%)
Raised to raised	4 (26.7%)
p-value[1], change from baseline	0.0143
52 weeks	
Normal	11 (73.3%)
Raised	4 (26.7%)
Shift in categories	
From baseline, Normal to normal	5 (33.3%)
From baseline, Normal to raised	0
From baseline, Raised to normal	6 (40.0%)
From baseline, Raised to raised	4 (26.7%)
From 24 weeks, Normal to normal	9 (60.0%)
From 24 weeks, Normal to raised	2 (13.3%)
From 24 weeks, Raised to normal	2 (13.3%)
From 24 weeks, Raised to raised	2 (13.3%)
p-value[1], change from baseline	0.0143
p-value[1], change from 24 weeks	1.0000

[1]P-value based on a paired McNemar test.
Percentages are based on the number of subjects in the applicable analysis set with non-missing values.

14.2.5.2.4 Impaired Glucose Tolerance

Table 163 Impaired glucose tolerance. Extension per-protocol analysis set

	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=15)
Screening	
Normal	9 (60.0%)
Raised	6 (40.0%)
24 weeks	
Normal	12 (80.0%)
Raised	3 (20.0%)
Shift in categories	
Normal to normal	8 (53.3%)
Normal to raised	1 (6.7%)
Raised to normal	4 (26.7%)
Raised to raised	2 (13.3%)
p-value[1], change from baseline	0.1797
52 weeks	
Normal	12 (85.7%)
Raised	2 (14.3%)
Shift in categories	
From baseline, Normal to normal	8 (57.1%)
From baseline, Normal to raised	0
From baseline, Raised to normal	4 (28.6%)
From baseline, Raised to raised	2 (14.3%)
From 24 weeks, Normal to normal	11 (78.6%)
From 24 weeks, Normal to raised	0
From 24 weeks, Raised to normal	1 (7.1%)
From 24 weeks, Raised to raised	2 (14.3%)
p-value[1], change from baseline	0.0455
p-value[1], change from 24 weeks	0.3173

[1]P-value based on a paired McNemar test.
Percentages are based on the number of subjects in the applicable analysis set with non-missing values.

14.2.5.2.5 Impaired Fasting Glucose/Impaired Glucose Tolerance

Table 164 Any IFG/IGT category change from baseline. Extension full analysis set

Any IFG/IGT	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Screening		
Normal	6 (28.6%)	3 (17.6%)
Raised	15 (71.4%)	14 (82.4%)
Missing	0	0
24 weeks		
Normal	14 (66.7%)	3 (17.6%)
Raised	7 (33.3%)	14 (82.4%)
Missing	0	0
Shift from screening to 24 weeks		
Normal, no change	6 (28.6%)	2 (11.8%)
Normal to raised	0	1 (5.9%)
Raised to normal	8 (38.1%)	1 (5.9%)
Raised, no change	7 (33.3%)	13 (76.5%)
Missing	0	0
p-value[1]	0.0047	1.0000
p-value[2]	0.0031	
52 weeks		
Normal	11 (52.4%)	0
Raised	6 (28.6%)	9 (52.9%)
Missing	4 (19.0%)	8 (47.1%)
Shift from screening to 52 weeks		
Normal, no change	5 (23.8%)	0
Normal to raised	0	0
Raised to normal	6 (28.6%)	0
Raised, no change	6 (28.6%)	9 (52.9%)
Missing	4 (19.0%)	8 (47.1%)
p-value[1]	0.0143	N/A
p-value[2]	0.0143	
Shift from week 24 to 52 weeks		
Normal, no change	9 (42.9%)	0
Normal to raised	3 (14.3%)	0
Raised to normal	2 (9.5%)	0
Raised, no change	3 (14.3%)	9 (52.9%)
Missing	4 (19.0%)	8 (47.1%)
p-value[1]	0.6547	N/A
p-value[2]	0.0483	

[1]A two-sided McNemar's test was used to test a null hypothesis that the proportion of subjects with raised values is equal to the proportion at the reference visit.
[2]A two-sided Cochran–Mantel–Haenszel test adjusted for the value at the reference visit was used to test a null hypothesis of no difference between the treatment groups.

Table 165 Any IFG/IGT category change from baseline. Extension per-protocol analysis set

Any IFG/IGT	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=15)	Placebo/ Dapa 10mg+Exe 2mg (N=15)
Screening		
Normal	5 (33.3%)	3 (20.0%)
Raised	10 (66.7%)	12 (80.0%)
Missing	0	0
24 weeks		
Normal	11 (73.3%)	3 (20.0%)
Raised	4 (26.7%)	12 (80.0%)
Missing	0	0
Shift from screening to 24 weeks		
Normal, no change	5 (33.3%)	2 (13.3%)
Normal to raised	0	1 (6.7%)
Raised to normal	6 (40.0%)	1 (6.7%)
Raised, no change	4 (26.7%)	11 (73.3%)
Missing	0	0
p-value[1]	0.0143	1.0000
p-value[2]	0.0046	
52 weeks		
Normal	11 (73.3%)	0
Raised	4 (26.7%)	7 (46.7%)
Missing	0	8 (53.3%)
Shift from screening to 52 weeks		
Normal, no change	5 (33.3%)	0
Normal to raised	0	0
Raised to normal	6 (40.0%)	0
Raised, no change	4 (26.7%)	7 (46.7%)
Missing	0	8 (53.3%)
p-value[1]	0.0143	N/A
p-value[2]	0.0134	
Shift from week 24 to 52 weeks		
Normal, no change	9 (60.0%)	0
Normal to raised	2 (13.3%)	0
Raised to normal	2 (13.3%)	0
Raised, no change	2 (13.3%)	7 (46.7%)
Missing	0	8 (53.3%)
p-value[1]	1.0000	N/A
p-value[2]	0.0486	

[1]A two-sided McNemar's test was used to test a null hypothesis that the proportion of subjects with raised values is equal to the proportion at the reference visit.
[2]A two-sided Cochran–Mantel–Haenszel test adjusted for the value at the reference visit was used to test a null hypothesis of no difference between the treatment groups.

14.2.5.2.6 Insulin

Fasting insulin

Table 166 Fasting insulin (mU/L) and adjusted mean change from baseline to 24 weeks. Extension full analysis set

Insulin (mU/L)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Screening		
n/nmiss	21/0	17/0
Mean (SD)	12.99 (5.94)	14.18 (9.04)
Median	10.80	11.40
Q1, Q3	9.20, 17.80	9.80, 13.40
Min, Max	4.2, 25.0	6.5, 41.0
12 weeks		
n/nmiss	21/0	17/0
Mean (SD)	14.48 (8.04)	16.95 (8.61)
Median	10.80	15.90
Q1, Q3	9.00, 18.60	10.20, 19.90
Min, Max	5.1, 40.0	5.9, 38.0
Adjusted mean change (95% CI)	1.76 (-1.02, 4.53)	3.67 (0.55, 6.79)
p-value	0.2069	0.0225
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	14.99 (14.57)	15.49 (11.45)
Median	12.60	13.00
Q1, Q3	7.60, 14.40	7.90, 18.80
Min, Max	3.1, 72.0	4.0, 50.0
Adjusted mean change (95% CI)	2.27 (-2.43, 6.96)	2.20 (-3.03, 7.44)
p-value	0.3329	0.3978

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 167 Fasting insulin (mU/L) and adjusted mean change from baseline to 52 weeks. Extension full analysis set

Insulin (mU/L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)	Placebo/Dapa 10mg+Exe 2mg (N=17)
Screening		
n/nmiss	21/0	17/0
Mean (SD)	12.99 (5.94)	14.18 (9.04)
Median	10.80	11.40
Q1, Q3	9.20, 17.80	9.80, 13.40
Min, Max	4.2, 25.0	6.5, 41.0
12 weeks		
n/nmiss	21/0	17/0
Mean (SD)	14.48 (8.04)	16.95 (8.61)
Median	10.80	15.90
Q1, Q3	9.00, 18.60	10.20, 19.90
Min, Max	5.1, 40.0	5.9, 38.0
Adjusted mean change (95% CI)	1.79 (-1.01, 4.59)	3.86 (0.72, 7.00)
p-value	0.2033	0.0176
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	14.99 (14.57)	15.49 (11.45)
Median	12.60	13.00
Q1, Q3	7.60, 14.40	7.90, 18.80
Min, Max	3.1, 72.0	4.0, 50.0
Adjusted mean change (95% CI)	2.30 (-2.50, 7.10)	2.39 (-2.96, 7.74)
p-value	0.3375	0.3695
52 weeks		
n/nmiss	16/5	14/3
Mean (SD)	9.96 (6.11)	16.85 (9.31)
Median	10.15	13.35
Q1, Q3	4.90, 12.80	11.30, 19.40
Min, Max	0.2, 25.0	7.7, 41.0
Adjusted mean change (95% CI)	-2.53 (-5.39, 0.33)	3.05 (-0.08, 6.17)
p-value	0.0813	0.0555

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 168 Fasting insulin (mU/L) and adjusted mean change from baseline to 24 weeks. Extension per-protocol analysis set

Insulin (mU/L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=15)	Placebo/Dapa 10mg+Exe 2mg (N=15)
Screening		
n/nmiss	15/0	15/0
Mean (SD)	11.34 (5.16)	14.45 (9.63)
Median	10.10	11.40
Q1, Q3	7.00, 15.60	7.80, 13.60
Min, Max	4.2, 22.0	6.5, 41.0
12 weeks		
n/nmiss	15/0	15/0
Mean (SD)	12.84 (6.00)	16.35 (8.27)
Median	10.40	15.90
Q1, Q3	8.80, 17.50	10.00, 19.90
Min, Max	5.1, 25.0	5.9, 38.0
Adjusted mean change (95% CI)	1.35 (-1.64, 4.33)	3.15 (0.01, 6.29)
p-value	0.3618	0.0495
24 weeks		
n/nmiss	15/0	15/0
Mean (SD)	10.74 (5.24)	15.17 (12.10)
Median	11.80	11.40
Q1, Q3	6.80, 14.40	6.90, 18.80
Min, Max	3.1, 21.0	4.0, 50.0
Adjusted mean change (95% CI)	-0.75 (-4.57, 3.07)	1.97 (-1.96, 5.90)
p-value	0.6893	0.3138

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 169 Fasting insulin (mU/L) and adjusted mean change from 24 weeks to 52 weeks. Extension per-protocol analysis set

Insulin (mU/L)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=15)	Placebo/ Dapa 10mg+Exe 2mg (N=15)
24 weeks		
n/nmiss	15/0	15/0
Mean (SD)	10.74 (5.24)	15.17 (12.10)
Median	11.80	11.40
Q1, Q3	6.80, 14.40	6.90, 18.80
Min, Max	3.1, 21.0	4.0, 50.0
52 weeks		
n/nmiss	15/0	12/3
Mean (SD)	8.95 (4.77)	16.43 (8.98)
Median	10.00	13.35
Q1, Q3	4.80, 12.00	11.60, 17.95
Min, Max	0.2, 16.6	7.7, 41.0
Adjusted mean change (95% CI)	-2.40 (-4.49, -0.31)	1.92 (-0.59, 4.43)
p-value	0.0262	0.1274

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

Table 170 Fasting insulin (mU/L) and adjusted mean change from baseline to 52 weeks. Extension per-protocol analysis set

Insulin (mU/L)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=15)	Placebo/ Dapa 10mg+Exe 2mg (N=15)
Screening		
n/nmiss	15/0	15/0
Mean (SD)	11.34 (5.16)	14.45 (9.63)
Median	10.10	11.40
Q1, Q3	7.00, 15.60	7.80, 13.60
Min, Max	4.2, 22.0	6.5, 41.0
12 weeks		
n/nmiss	15/0	15/0
Mean (SD)	12.84 (6.00)	16.35 (8.27)
Median	10.40	15.90
Q1, Q3	8.80, 17.50	10.00, 19.90
Min, Max	5.1, 25.0	5.9, 38.0
Adjusted mean change (95% CI)	1.31 (-1.69, 4.31)	3.75 (0.64, 6.85)
p-value	0.3784	0.0200
24 weeks		
n/nmiss	15/0	15/0
Mean (SD)	10.74 (5.24)	15.17 (12.10)
Median	11.80	11.40
Q1, Q3	6.80, 14.40	6.90, 18.80
Min, Max	3.1, 21.0	4.0, 50.0
Adjusted mean change (95% CI)	-0.79 (-4.77, 3.18)	2.57 (-1.49, 6.62)

Insulin (mU/L)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=15)	Placebo/ Dapa 10mg+Exe 2mg (N=15)
p-value	0.6851	0.2046
52 weeks		
n/nmiss	15/0	12/3
Mean (SD)	8.95 (4.77)	16.43 (8.98)
Median	10.00	13.35
Q1, Q3	4.80, 12.00	11.60, 17.95
Min, Max	0.2, 16.6	7.7, 41.0
Adjusted mean change (95% CI)	-2.58 (-5.47, 0.31)	2.76 (-0.45, 5.98)
p-value	0.0777	0.0896

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Area under the curve – Insulin

Table 171 Insulin area under the curve (180 min*mU/L) and adjusted mean change from baseline to 24 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension full analysis set

Insulin AUC (180 min*mU/L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)
Screening	
Mean (SD)	12078.113 (7109.927)
Median	8680.875
Q1, Q3	6671.625, 16946.625
Min, Max	3792.75, 27447.00
24 weeks	
Mean (SD)	10802.605 (5918.380)
Median	9574.500
Q1, Q3	6594.000, 14212.500
Min, Max	3267.75, 24796.50
n/nmiss	19/2
Adjusted mean change (95% CI)	-590.161 (-2328.55, 1148.232)
p-value	0.4804

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

Table 172 Insulin area under the curve (180 min*mU/L) and adjusted mean change from 24 weeks to 52 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension full analysis set

Insulin AUC (180 min*mU/L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)
24 weeks	
n/nmiss	19/2
Mean (SD)	10802.605 (5918.380)
Median	9574.500
Q1, Q3	6594.000, 14212.500
Min, Max	3267.75, 24796.50
52 weeks	
n/nmiss	14/7
Mean (SD)	9300.857 (4271.123)
Median	7239.375
Q1, Q3	6408.750, 12042.000
Min, Max	3612.75, 18026.25
Adjusted mean change (95% CI)	-985.668 (-3175.79, 1204.455)
p-value	0.3352

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

Table 173 Insulin area under the curve (180 min*mU/L) and adjusted mean change from baseline to 52 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension full analysis set

Insulin AUC (180 min*mU/L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)
Screening	
Mean (SD)	12078.113 (7109.927)
Median	8680.875
Q1, Q3	6671.625, 16946.625
Min, Max	3792.75, 27447.00
24 weeks	
Mean (SD)	10802.605 (5918.380)
Median	9574.500
Q1, Q3	6594.000, 14212.500
Min, Max	3267.75, 24796.50
n/nmiss	19/2
Adjusted mean change (95% CI)	-627.144 (-2423.07, 1168.785)
p-value	0.4677
52 weeks	
Mean (SD)	9300.857 (4271.123)
Median	7239.375
Q1, Q3	6408.750, 12042.000
Min, Max	3612.75, 18026.25

Insulin AUC (180 min*mU/L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)
n/nmiss	14/7
Adjusted mean change (95% CI)	-1544.88 (-3924.18, 834.411)
p-value	0.1753

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 174 Insulin area under the curve (180 min*mU/L) and adjusted mean change from baseline to 24 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension per-protocol analysis set

Insulin AUC (180 min*mU/L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=15)
Screening	
n/nmiss	14/1
Mean (SD)	9720.750 (5125.481)
Median	8379.375
Q1, Q3	5925.000, 13657.500
Min, Max	3792.75, 22042.50
24 weeks	
n/nmiss	13/2
Mean (SD)	9128.827 (3634.798)
Median	9351.750
Q1, Q3	7114.500, 10749.000
Min, Max	3267.75, 14652.00
Adjusted mean change (95% CI)	97.375 (-1250.32, 1445.069)
p-value	0.8738

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

Table 175 Insulin area under the curve (180 min*mU/L) and adjusted mean change from 24 weeks to 52 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension per-protocol analysis set

Insulin AUC (180 min*mU/L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=15)
24 weeks	
n/nmiss	13/2
Mean (SD)	9128.827 (3634.798)
Median	9351.750
Q1, Q3	7114.500, 10749.000
Min, Max	3267.75, 14652.00
52 weeks	
n/nmiss	13/2
Mean (SD)	8732.654 (3855.654)
Median	6928.500
Q1, Q3	6408.750, 10758.750
Min, Max	3612.75, 18026.25
Adjusted mean change (95% CI)	-658.568 (-3187.82, 1870.683)
p-value	0.5648

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

Table 176 Insulin area under the curve (180 min*mU/L) and adjusted mean change from baseline to 52 weeks - Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension per-protocol analysis set

Insulin AUC (180 min*mU/L)	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=15)
Screening	
n/nmiss	14/1
Mean (SD)	9720.750 (5125.481)
Median	8379.375
Q1, Q3	5925.000, 13657.500
Min, Max	3792.75, 22042.50
24 weeks	
n/nmiss	13/2
Mean (SD)	9128.827 (3634.798)
Median	9351.750
Q1, Q3	7114.500, 10749.000
Min, Max	3267.75, 14652.00
Adjusted mean change (95% CI)	-138.447 (-1533.37, 1256.479)
p-value	0.8274
52 weeks	
n/nmiss	13/2
Mean (SD)	8732.654 (3855.654)
Median	6928.500
Q1, Q3	6408.750, 10758.750
Min, Max	3612.75, 18026.25
Adjusted mean change (95% CI)	-971.093 (-3207.64, 1265.451)
p-value	0.3550

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

14.2.5.2.7 Plasma Glucose (Descriptive Statistics only)

Table 177 Fasting plasma glucose (mmol/L) and mean change from baseline. Extension full analysis set

Fasting plasma glucose (mmol/L)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Screening		
n/nmiss	21/0	17/0
Mean (SD)	5.91 (0.64)	5.78 (0.42)
Median	5.80	5.70
Q1, Q3	5.40, 6.10	5.50, 6.00
Min, Max	5.0, 7.2	5.1, 6.6
Mean change (95% CI)		
12 weeks		
n/nmiss	21/0	17/0
Mean (SD)	5.65 (0.54)	5.97 (0.38)
Median	5.70	5.80
Q1, Q3	5.20, 5.90	5.70, 6.30
Min, Max	4.7, 6.8	5.6, 6.7
Mean change (95% CI)	-0.26 (-0.41, -0.11)	0.19 (-0.01, 0.40)
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	5.47 (0.54)	5.94 (0.47)
Median	5.40	5.80
Q1, Q3	5.20, 5.70	5.70, 6.20
Min, Max	4.7, 7.1	5.1, 6.9
Mean change (95% CI)	-0.45 (-0.64, -0.25)	0.16 (-0.04, 0.37)
52 weeks		
n/nmiss	17/4	17/0
Mean (SD)	5.54 (0.50)	5.51 (0.33)
Median	5.50	5.60
Q1, Q3	5.10, 5.80	5.30, 5.70
Min, Max	4.8, 6.8	4.9, 6.2
Mean change (95% CI)	-0.34 (-0.56, -0.13)	-0.27 (-0.50, -0.04)

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
Percentages are based on the number of subjects in the applicable analysis set.

Table 178 Fasting plasma glucose (mmol/L) and mean change from baseline. Extension per-protocol analysis set

Fasting plasma glucose (mmol/L)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=15)	Placebo/ Dapa 10mg+Exe 2mg (N=15)
Screening		
n/nmiss	15/0	15/0
Mean (SD)	5.84 (0.62)	5.67 (0.33)
Median	5.70	5.60
Q1, Q3	5.30, 6.10	5.40, 5.90
Min, Max	5.0, 7.2	5.1, 6.3
Mean change (95% CI)		
12 weeks		
n/nmiss	15/0	15/0
Mean (SD)	5.61 (0.54)	5.91 (0.35)
Median	5.70	5.80
Q1, Q3	5.10, 6.00	5.60, 6.30
Min, Max	4.7, 6.5	5.6, 6.6
Mean change (95% CI)	-0.23 (-0.41, -0.05)	0.24 (0.03, 0.45)
24 weeks		
n/nmiss	15/0	15/0
Mean (SD)	5.33 (0.40)	5.87 (0.45)
Median	5.20	5.80
Q1, Q3	5.10, 5.60	5.60, 6.20
Min, Max	4.7, 6.1	5.1, 6.9
Mean change (95% CI)	-0.51 (-0.75, -0.26)	0.20 (-0.03, 0.43)
52 weeks		
n/nmiss	15/0	15/0
Mean (SD)	5.48 (0.50)	5.47 (0.32)
Median	5.40	5.40
Q1, Q3	5.10, 5.70	5.30, 5.70
Min, Max	4.8, 6.8	4.9, 6.2
Mean change (95% CI)	-0.36 (-0.57, -0.15)	-0.21 (-0.45, 0.03)

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
Percentages are based on the number of subjects in the applicable analysis set.

14.2.5.2.8 Insulin (Descriptive Statistics only)

Table 179 Fasting insulin (mU/L) and mean change from baseline. Extension full analysis set

Insulin (mU/L)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Screening		
n/nmiss	21/0	17/0
Mean (SD)	12.99 (5.94)	14.18 (9.04)
Median	10.80	11.40
Q1, Q3	9.20, 17.80	9.80, 13.40
Min, Max	4.2, 25.0	6.5, 41.0
Mean change (95% CI)		
12 weeks		
n/nmiss	21/0	17/0
Mean (SD)	14.48 (8.04)	16.95 (8.61)
Median	10.80	15.90
Q1, Q3	9.00, 18.60	10.20, 19.90
Min, Max	5.1, 40.0	5.9, 38.0
Mean change (95% CI)	1.49 (-0.77, 3.75)	2.77 (-1.50, 7.04)
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	14.99 (14.57)	15.49 (11.45)
Median	12.60	13.00
Q1, Q3	7.60, 14.40	7.90, 18.80
Min, Max	3.1, 72.0	4.0, 50.0
Mean change (95% CI)	2.00 (-3.19, 7.19)	1.31 (-2.96, 5.57)
52 weeks		
n/nmiss	16/5	14/3
Mean (SD)	9.96 (6.11)	16.85 (9.31)
Median	10.15	13.35
Q1, Q3	4.90, 12.80	11.30, 19.40
Min, Max	0.2, 25.0	7.7, 41.0
Mean change (95% CI)	-2.24 (-4.10, -0.38)	1.95 (-3.96, 7.86)

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
Percentages are based on the number of subjects in the applicable analysis set.

Table 180 Fasting insulin (mU/L) and mean change from baseline. Extension per-protocol analysis set

Insulin (mU/L)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=15)	Placebo/ Dapa 10mg+Exe 2mg (N=15)
Screening		
n/nmiss	15/0	15/0
Mean (SD)	11.34 (5.16)	14.45 (9.63)
Median	10.10	11.40
Q1, Q3	7.00, 15.60	7.80, 13.60
Min, Max	4.2, 22.0	6.5, 41.0
Mean change (95% CI)		
12 weeks		
n/nmiss	15/0	15/0
Mean (SD)	12.84 (6.00)	16.35 (8.27)
Median	10.40	15.90
Q1, Q3	8.80, 17.50	10.00, 19.90
Min, Max	5.1, 25.0	5.9, 38.0
Mean change (95% CI)	1.50 (-0.90, 3.90)	1.90 (-2.23, 6.03)
24 weeks		
n/nmiss	15/0	15/0
Mean (SD)	10.74 (5.24)	15.17 (12.10)
Median	11.80	11.40
Q1, Q3	6.80, 14.40	6.90, 18.80
Min, Max	3.1, 21.0	4.0, 50.0
Mean change (95% CI)	-0.60 (-3.42, 2.22)	0.72 (-3.96, 5.40)
52 weeks		
n/nmiss	15/0	12/3
Mean (SD)	8.95 (4.77)	16.43 (8.98)
Median	10.00	13.35
Q1, Q3	4.80, 12.00	11.60, 17.95
Min, Max	0.2, 16.6	7.7, 41.0
Mean change (95% CI)	-2.39 (-4.36, -0.42)	1.08 (-5.04, 7.20)

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
Percentages are based on the number of subjects in the applicable analysis set.

14.2.5.2.9 C-Peptide

Table 181 Fasting c-peptide (nmol/L) and mean change from baseline. Extension full analysis set

C-peptide (nmol/L)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Screening		
n/nmiss	21/0	17/0
Mean (SD)	1.032 (0.327)	0.972 (0.296)
Median	0.910	0.870
Q1, Q3	0.800, 1.250	0.780, 1.100
Min, Max	0.54, 1.71	0.54, 1.47
Mean change (95% CI)		
12 weeks		
n/nmiss	21/0	17/0
Mean (SD)	1.193 (0.400)	1.094 (0.363)
Median	1.020	0.990
Q1, Q3	0.890, 1.420	0.830, 1.140
Min, Max	0.72, 2.20	0.70, 1.90
Mean change (95% CI)	0.161 (0.079, 0.244)	0.122 (0.005, 0.238)
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	1.152 (0.504)	1.043 (0.389)
Median	1.030	0.950
Q1, Q3	0.840, 1.370	0.790, 1.280
Min, Max	0.58, 2.70	0.54, 2.00
Mean change (95% CI)	0.120 (-0.023, 0.263)	0.071 (-0.026, 0.167)
52 weeks		
n/nmiss	16/5	15/2
Mean (SD)	1.008 (0.371)	1.085 (0.355)
Median	0.955	1.030
Q1, Q3	0.680, 1.265	0.770, 1.340
Min, Max	0.62, 1.81	0.73, 1.84
Mean change (95% CI)	0.006 (-0.106, 0.118)	0.095 (-0.048, 0.239)

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
Percentages are based on the number of subjects in the applicable analysis set.

Table 182 Fasting c-peptide (nmol/L) and mean change from baseline. Extension per-protocol analysis set

C-peptide (nmol/L)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=15)	Placebo/ Dapa 10mg+Exe 2mg (N=15)
Screening		
n/nmiss	15/0	15/0
Mean (SD)	0.972 (0.300)	0.931 (0.282)
Median	0.880	0.860
Q1, Q3	0.800, 1.160	0.750, 1.080
Min, Max	0.54, 1.66	0.54, 1.47
Mean change (95% CI)		
12 weeks		
n/nmiss	15/0	15/0
Mean (SD)	1.108 (0.333)	1.057 (0.338)
Median	1.020	0.990
Q1, Q3	0.840, 1.260	0.770, 1.140
Min, Max	0.72, 1.85	0.70, 1.90
Mean change (95% CI)	0.136 (0.056, 0.216)	0.127 (0.001, 0.252)
24 weeks		
n/nmiss	15/0	15/0
Mean (SD)	1.021 (0.298)	1.003 (0.380)
Median	0.990	0.910
Q1, Q3	0.790, 1.330	0.760, 1.280
Min, Max	0.60, 1.52	0.54, 2.00
Mean change (95% CI)	0.049 (-0.043, 0.142)	0.073 (-0.035, 0.180)
52 weeks		
n/nmiss	15/0	13/2
Mean (SD)	0.955 (0.314)	1.059 (0.310)
Median	0.930	1.030
Q1, Q3	0.670, 1.180	0.800, 1.070
Min, Max	0.62, 1.64	0.74, 1.84
Mean change (95% CI)	-0.017 (-0.125, 0.090)	0.115 (-0.028, 0.257)

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
Percentages are based on the number of subjects in the applicable analysis set.

14.2.5.2.10 Ketones

Table 183 Fasting ketones (mmol/L) and mean change from baseline. Extension full analysis set

Ketones (mmol/L)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Screening		
n/nmiss	21/0	17/0
Mean (SD)	0.22 (0.10)	0.18 (0.04)
Median	0.20	0.20
Q1, Q3	0.20, 0.20	0.20, 0.20
Min, Max	0.1, 0.6	0.1, 0.2
Mean change (95% CI)		
12 weeks		
n/nmiss	21/0	17/0
Mean (SD)	0.19 (0.08)	0.19 (0.09)
Median	0.20	0.20
Q1, Q3	0.10, 0.20	0.10, 0.20
Min, Max	0.1, 0.3	0.1, 0.4
Mean change (95% CI)	-0.04 (-0.08, 0.00)	0.01 (-0.03, 0.06)
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	0.22 (0.09)	0.19 (0.11)
Median	0.20	0.20
Q1, Q3	0.20, 0.30	0.10, 0.30
Min, Max	0.1, 0.4	0.1, 0.4
Mean change (95% CI)	-0.00 (-0.07, 0.07)	0.01 (-0.04, 0.06)
52 weeks		
n/nmiss	16/5	15/2
Mean (SD)	0.23 (0.16)	0.27 (0.31)
Median	0.20	0.10
Q1, Q3	0.10, 0.30	0.10, 0.20
Min, Max	0.0, 0.7	0.1, 1.1
Mean change (95% CI)	-0.01 (-0.11, 0.09)	0.09 (-0.07, 0.26)

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
Percentages are based on the number of subjects in the applicable analysis set.

Table 184 Fasting ketones (mmol/L) and mean change from baseline. Extension per-protocol analysis set

Ketones (mmol/L)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=15)	Placebo/ Dapa 10mg+Exe 2mg (N=15)
Screening		
n/nmiss	15/0	15/0
Mean (SD)	0.24 (0.12)	0.19 (0.04)
Median	0.20	0.20
Q1, Q3	0.20, 0.30	0.20, 0.20
Min, Max	0.1, 0.6	0.1, 0.2
Mean change (95% CI)		
12 weeks		
n/nmiss	15/0	15/0
Mean (SD)	0.19 (0.08)	0.19 (0.07)
Median	0.20	0.20
Q1, Q3	0.10, 0.30	0.10, 0.20
Min, Max	0.1, 0.3	0.1, 0.3
Mean change (95% CI)	-0.05 (-0.10, -0.00)	-0.00 (-0.04, 0.04)
24 weeks		
n/nmiss	15/0	15/0
Mean (SD)	0.23 (0.10)	0.19 (0.10)
Median	0.20	0.20
Q1, Q3	0.10, 0.30	0.10, 0.30
Min, Max	0.1, 0.4	0.1, 0.4
Mean change (95% CI)	-0.01 (-0.10, 0.08)	-0.00 (-0.05, 0.05)
52 weeks		
n/nmiss	15/0	13/2
Mean (SD)	0.23 (0.16)	0.22 (0.22)
Median	0.20	0.10
Q1, Q3	0.10, 0.30	0.10, 0.20
Min, Max	0.0, 0.7	0.1, 0.7
Mean change (95% CI)	-0.01 (-0.12, 0.10)	0.04 (-0.09, 0.17)

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
Percentages are based on the number of subjects in the applicable analysis set.

14.2.5.2.11 U-glucose

Table 185 U-glucose (mmol/3h-OGTT) and mean change from baseline. Extension safety analysis set

U-glucose (mmol)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
24 weeks		
n/nmiss	20/1	17/0
Mean (SD)	52.257 (31.837)	0.082 (0.056)
Median	45.245	0.060
Q1, Q3	28.930, 64.965	0.050, 0.110
Min, Max	12.00, 143.42	0.02, 0.25
Mean change (95% CI)		
52 weeks		
n/nmiss	16/5	
Mean (SD)	45.738 (29.279)	
Median	36.385	
Q1, Q3	30.040, 66.465	
Min, Max	4.86, 112.41	
Mean change (95% CI)		

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
Percentages are based on the number of subjects in the applicable analysis set.

14.2.5.3 Blood Lipid Profile

14.2.5.3.1 Total Cholesterol

Table 186 Fasting total cholesterol (mmol/L) and mean change from baseline. Extension full analysis set

Total cholesterol (TC) (mmol/L)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Screening		
n/nmiss	21/0	17/0
Mean (SD)	5.33 (1.08)	5.26 (0.94)
Median	5.20	5.30
Q1, Q3	4.70, 5.90	4.80, 5.70
Min, Max	3.1, 7.4	3.6, 7.9
Mean change (95% CI)		
12 weeks		
n/nmiss	21/0	17/0
Mean (SD)	5.00 (0.91)	5.19 (1.26)
Median	4.90	5.30
Q1, Q3	4.60, 5.50	4.10, 5.80
Min, Max	3.1, 7.4	3.5, 8.4
Mean change (95% CI)	-0.33 (-0.61, -0.05)	-0.07 (-0.41, 0.27)
24 weeks		
n/nmiss	20/1	17/0
Mean (SD)	5.25 (1.11)	4.98 (1.21)
Median	5.15	4.70
Q1, Q3	4.65, 5.65	4.30, 5.30
Min, Max	3.1, 7.8	3.5, 8.6
Mean change (95% CI)	-0.11 (-0.34, 0.12)	-0.28 (-0.62, 0.06)
52 weeks		
n/nmiss	16/5	17/0
Mean (SD)	5.06 (0.93)	4.91 (0.97)
Median	5.00	4.80
Q1, Q3	4.60, 5.45	4.00, 5.60
Min, Max	3.1, 7.5	3.5, 6.5
Mean change (95% CI)	-0.28 (-0.56, 0.01)	-0.35 (-0.69, -0.02)

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
Percentages are based on the number of subjects in the applicable analysis set.

Table 187 Fasting total cholesterol (mmol/L) and mean change from baseline. Extension per-protocol analysis set

Total cholesterol (TC) (mmol/L)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=15)	Placebo/ Dapa 10mg+Exe 2mg (N=15)
Screening		
n/nmiss	15/0	15/0
Mean (SD)	5.40 (0.98)	5.24 (1.00)
Median	5.40	5.10
Q1, Q3	4.80, 5.90	4.80, 5.70
Min, Max	3.1, 7.4	3.6, 7.9
Mean change (95% CI)		
12 weeks		
n/nmiss	15/0	15/0
Mean (SD)	5.01 (0.96)	5.15 (1.34)
Median	4.90	5.00
Q1, Q3	4.50, 5.50	4.10, 6.10
Min, Max	3.1, 7.4	3.5, 8.4
Mean change (95% CI)	-0.39 (-0.73, -0.04)	-0.09 (-0.48, 0.30)
24 weeks		
n/nmiss	14/1	15/0
Mean (SD)	5.25 (1.14)	4.93 (1.28)
Median	5.15	4.60
Q1, Q3	4.80, 5.50	4.10, 5.60
Min, Max	3.1, 7.8	3.5, 8.6
Mean change (95% CI)	-0.20 (-0.51, 0.11)	-0.31 (-0.70, 0.08)
52 weeks		
n/nmiss	14/1	15/0
Mean (SD)	5.12 (0.98)	4.81 (0.99)
Median	5.20	4.70
Q1, Q3	4.80, 5.50	3.90, 5.60
Min, Max	3.1, 7.5	3.5, 6.5
Mean change (95% CI)	-0.33 (-0.64, -0.02)	-0.43 (-0.79, -0.07)

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
Percentages are based on the number of subjects in the applicable analysis set.

14.2.5.3.2 Low-Density Lipoprotein Cholesterol

Table 188 Fasting low-density lipoprotein cholesterol (mmol/L) and mean change from baseline. Extension full analysis set

Low-density lipoprotein cholesterol (LDL-C) (mmol/L)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Screening		
n/nmiss	21/0	17/0
Mean (SD)	3.54 (0.95)	3.29 (0.86)
Median	3.30	3.40
Q1, Q3	3.10, 4.00	2.70, 3.70
Min, Max	1.9, 5.6	2.2, 5.7
Mean change (95% CI)		
12 weeks		
n/nmiss	21/0	17/0
Mean (SD)	3.22 (0.71)	3.25 (1.06)
Median	3.10	3.20
Q1, Q3	2.90, 3.40	2.60, 3.80
Min, Max	2.0, 5.2	1.4, 5.7
Mean change (95% CI)	-0.32 (-0.58, -0.07)	-0.04 (-0.28, 0.21)
24 weeks		
n/nmiss	20/1	17/0
Mean (SD)	3.37 (0.80)	3.07 (1.09)
Median	3.25	2.90
Q1, Q3	2.80, 3.75	2.30, 3.70
Min, Max	2.0, 5.2	1.6, 6.3
Mean change (95% CI)	-0.12 (-0.33, 0.09)	-0.22 (-0.50, 0.06)
52 weeks		
n/nmiss	16/5	17/0
Mean (SD)	3.16 (0.77)	2.96 (0.89)
Median	3.15	3.00
Q1, Q3	2.85, 3.35	2.10, 3.70
Min, Max	1.8, 5.4	1.6, 4.3
Mean change (95% CI)	-0.34 (-0.55, -0.13)	-0.33 (-0.64, -0.02)

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
Percentages are based on the number of subjects in the applicable analysis set.

Table 189 Fasting low-density lipoprotein cholesterol (mmol/L) and mean change from baseline. Extension per-protocol analysis set

Low-density lipoprotein cholesterol (LDL-C) (mmol/L)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=15)	Placebo/ Dapa 10mg+Exe 2mg (N=15)
Screening		
n/nmiss	15/0	15/0
Mean (SD)	3.56 (0.83)	3.25 (0.90)
Median	3.40	3.30
Q1, Q3	3.10, 4.00	2.40, 3.70
Min, Max	2.2, 5.6	2.2, 5.7
Mean change (95% CI)		
12 weeks		
n/nmiss	15/0	15/0
Mean (SD)	3.15 (0.72)	3.19 (1.11)
Median	3.00	3.20
Q1, Q3	2.70, 3.40	2.20, 4.00
Min, Max	2.0, 5.2	1.4, 5.7
Mean change (95% CI)	-0.41 (-0.69, -0.12)	-0.05 (-0.33, 0.23)
24 weeks		
n/nmiss	15/0	15/0
Mean (SD)	3.35 (0.79)	2.99 (1.14)
Median	3.40	2.70
Q1, Q3	2.70, 3.80	2.20, 3.50
Min, Max	2.0, 5.2	1.6, 6.3
Mean change (95% CI)	-0.21 (-0.46, 0.03)	-0.26 (-0.57, 0.05)
52 weeks		
n/nmiss	14/1	15/0
Mean (SD)	3.19 (0.82)	2.85 (0.89)
Median	3.20	2.90
Q1, Q3	2.90, 3.40	2.10, 3.40
Min, Max	1.8, 5.4	1.6, 4.3
Mean change (95% CI)	-0.39 (-0.61, -0.17)	-0.40 (-0.74, -0.06)

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
Percentages are based on the number of subjects in the applicable analysis set.

14.2.5.3.3 High-Density Lipoprotein Cholesterol

Table 190 Fasting high-density lipoprotein cholesterol (mmol/L) and mean change from baseline. Extension full analysis set

High-density lipoprotein cholesterol (HDL-C) (mmol/L)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Screening		
n/nmiss	21/0	17/0
Mean (SD)	1.255 (0.272)	1.332 (0.305)
Median	1.200	1.300
Q1, Q3	1.100, 1.500	1.100, 1.600
Min, Max	0.88, 1.90	0.88, 2.00
Mean change (95% CI)		
12 weeks		
n/nmiss	21/0	17/0
Mean (SD)	1.226 (0.283)	1.291 (0.334)
Median	1.200	1.200
Q1, Q3	1.000, 1.400	0.990, 1.500
Min, Max	0.76, 1.80	0.79, 2.10
Mean change (95% CI)	-0.029 (-0.150, 0.092)	-0.041 (-0.116, 0.034)
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	1.288 (0.252)	1.247 (0.304)
Median	1.300	1.200
Q1, Q3	1.100, 1.500	1.000, 1.400
Min, Max	0.78, 1.60	0.83, 1.90
Mean change (95% CI)	0.033 (-0.062, 0.128)	-0.085 (-0.170, 0.000)
52 weeks		
n/nmiss	16/5	17/0
Mean (SD)	1.292 (0.281)	1.344 (0.370)
Median	1.300	1.200
Q1, Q3	1.050, 1.500	1.100, 1.600
Min, Max	0.92, 1.80	0.87, 2.20
Mean change (95% CI)	-0.006 (-0.160, 0.149)	0.012 (-0.074, 0.099)

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
Percentages are based on the number of subjects in the applicable analysis set.

Table 191 Fasting high-density lipoprotein cholesterol (mmol/L) and mean change from baseline. Extension per-protocol analysis set

High-density lipoprotein cholesterol (HDL-C) (mmol/L)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=15)	Placebo/ Dapa 10mg+Exe 2mg (N=15)
Screening		
n/nmiss	15/0	15/0
Mean (SD)	1.304 (0.307)	1.364 (0.300)
Median	1.300	1.300
Q1, Q3	1.000, 1.500	1.100, 1.600
Min, Max	0.88, 1.90	0.96, 2.00
Mean change (95% CI)		
12 weeks		
n/nmiss	15/0	15/0
Mean (SD)	1.283 (0.314)	1.310 (0.326)
Median	1.400	1.200
Q1, Q3	1.000, 1.500	0.990, 1.600
Min, Max	0.76, 1.80	0.94, 2.10
Mean change (95% CI)	-0.021 (-0.193, 0.151)	-0.054 (-0.132, 0.024)
24 weeks		
n/nmiss	15/0	15/0
Mean (SD)	1.336 (0.271)	1.269 (0.308)
Median	1.500	1.200
Q1, Q3	1.100, 1.600	1.000, 1.400
Min, Max	0.78, 1.60	0.83, 1.90
Mean change (95% CI)	0.032 (-0.093, 0.157)	-0.095 (-0.192, 0.001)
52 weeks		
n/nmiss	14/1	15/0
Mean (SD)	1.326 (0.284)	1.365 (0.372)
Median	1.400	1.200
Q1, Q3	1.100, 1.500	1.100, 1.600
Min, Max	0.92, 1.80	0.88, 2.20
Mean change (95% CI)	0.001 (-0.178, 0.180)	0.001 (-0.094, 0.097)

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
Percentages are based on the number of subjects in the applicable analysis set.

14.2.5.3.4 Triglycerides

Table 192 Fasting triglycerides (mmol/L) and mean change from baseline. Extension full analysis set

Triglycerides (TG) (mmol/L)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Screening		
n/nmiss	21/0	17/0
Mean (SD)	1.351 (0.452)	1.449 (0.586)
Median	1.330	1.400
Q1, Q3	1.020, 1.620	1.090, 1.960
Min, Max	0.53, 2.26	0.54, 2.49
Mean change (95% CI)		
12 weeks		
n/nmiss	21/0	17/0
Mean (SD)	1.148 (0.344)	1.421 (0.627)
Median	1.180	1.330
Q1, Q3	0.860, 1.420	0.970, 1.760
Min, Max	0.56, 1.69	0.55, 2.89
Mean change (95% CI)	-0.203 (-0.328, -0.078)	-0.028 (-0.250, 0.194)
24 weeks		
n/nmiss	20/1	17/0
Mean (SD)	1.259 (0.517)	1.389 (0.597)
Median	1.130	1.320
Q1, Q3	0.910, 1.560	0.800, 1.910
Min, Max	0.51, 2.49	0.62, 2.36
Mean change (95% CI)	-0.114 (-0.337, 0.109)	-0.060 (-0.294, 0.174)
52 weeks		
n/nmiss	16/5	17/0
Mean (SD)	1.098 (0.428)	1.308 (0.616)
Median	0.955	1.120
Q1, Q3	0.780, 1.485	0.850, 1.980
Min, Max	0.45, 1.94	0.48, 2.41
Mean change (95% CI)	-0.261 (-0.464, -0.057)	-0.141 (-0.372, 0.090)

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
Percentages are based on the number of subjects in the applicable analysis set.

Table 193 Fasting triglycerides (mmol/L) and mean change from baseline. Extension per-protocol analysis set

Triglycerides (TG) (mmol/L)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=15)	Placebo/ Dapa 10mg+Exe 2mg (N=15)
Screening		
n/nmiss	15/0	15/0
Mean (SD)	1.290 (0.453)	1.374 (0.583)
Median	1.310	1.250
Q1, Q3	0.920, 1.560	1.030, 1.650
Min, Max	0.53, 2.26	0.54, 2.49
Mean change (95% CI)		
12 weeks		
n/nmiss	15/0	15/0
Mean (SD)	1.128 (0.343)	1.367 (0.627)
Median	1.180	1.120
Q1, Q3	0.810, 1.420	0.950, 1.760
Min, Max	0.56, 1.69	0.55, 2.89
Mean change (95% CI)	-0.162 (-0.305, -0.019)	-0.007 (-0.246, 0.232)
24 weeks		
n/nmiss	14/1	15/0
Mean (SD)	1.121 (0.357)	1.319 (0.602)
Median	1.095	1.150
Q1, Q3	0.830, 1.450	0.780, 1.880
Min, Max	0.51, 1.73	0.62, 2.36
Mean change (95% CI)	-0.195 (-0.446, 0.056)	-0.055 (-0.323, 0.214)
52 weeks		
n/nmiss	14/1	15/0
Mean (SD)	1.005 (0.364)	1.257 (0.611)
Median	0.935	1.070
Q1, Q3	0.780, 1.250	0.750, 1.980
Min, Max	0.45, 1.64	0.48, 2.41
Mean change (95% CI)	-0.286 (-0.516, -0.055)	-0.117 (-0.363, 0.129)

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
Percentages are based on the number of subjects in the applicable analysis set.

14.2.5.4 Vital Signs

14.2.5.4.1 Systolic Blood Pressure

Table 194 Systolic blood pressure (mmHg) and adjusted mean change from 24 weeks to 52 weeks. Extension full analysis set

Systolic blood pressure (mmHg)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	124.45 (11.39)	133.71 (11.43)
Median	121.00	135.00
Q1, Q3	117.00, 133.00	127.00, 141.00
Min, Max	97.0, 142.5	111.0, 151.0
38 weeks		
n/nmiss	19/2	17/0
Mean (SD)	122.45 (16.05)	127.29 (8.63)
Median	121.00	125.00
Q1, Q3	107.00, 136.50	121.00, 135.00
Min, Max	95.5, 150.0	112.5, 144.0
Adjusted mean change (95% CI)	-1.86 (-6.80, 3.07)	-4.51 (-9.56, 0.55)
p-value	0.4480	0.0789
52 weeks		
n/nmiss	17/4	17/0
Mean (SD)	121.44 (15.55)	127.68 (7.95)
Median	123.00	127.50
Q1, Q3	110.50, 128.00	120.50, 135.00
Min, Max	98.5, 160.0	114.0, 138.5
Adjusted mean change (95% CI)	-4.36 (-9.37, 0.64)	-4.12 (-9.10, 0.85)
p-value	0.0853	0.1009

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 195 Systolic blood pressure (mmHg) and adjusted mean change from baseline to 24 weeks. Extension per-protocol analysis set

Systolic blood pressure (mmHg)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=15)	Placebo/ Dapa 10mg+Exe 2mg (N=15)
Baseline		
n/nmiss	15/0	15/0
Mean (SD)	134.13 (13.42)	139.30 (12.97)
Median	129.50	138.00
Q1, Q3	122.50, 146.50	132.50, 153.00
Min, Max	119.5, 162.5	119.0, 161.0
4 weeks		
n/nmiss	15/0	15/0
Mean (SD)	129.63 (17.28)	137.50 (12.51)
Median	128.00	139.00
Q1, Q3	118.50, 144.00	127.00, 143.00
Min, Max	102.5, 159.0	118.0, 161.5
Adjusted mean change (95% CI)	-4.38 (-11.74, 2.97)	0.02 (-7.40, 7.44)
p-value	0.2317	0.9953
8 weeks		
n/nmiss	15/0	15/0
Mean (SD)	123.40 (14.26)	133.53 (12.85)
Median	124.00	132.00
Q1, Q3	114.00, 131.50	122.00, 145.00
Min, Max	100.0, 150.0	112.5, 157.5
Adjusted mean change (95% CI)	-10.62 (-15.37, -5.86)	-3.95 (-8.80, 0.91)
p-value	<.0001	0.1071
12 weeks		
n/nmiss	15/0	15/0
Mean (SD)	121.60 (12.05)	132.57 (12.69)
Median	123.50	134.00
Q1, Q3	109.50, 133.00	128.50, 142.00
Min, Max	105.0, 142.0	100.0, 147.5
Adjusted mean change (95% CI)	-12.42 (-17.36, -7.47)	-4.91 (-9.95, 0.12)
p-value	<.0001	0.0555
24 weeks		
n/nmiss	15/0	15/0
Mean (SD)	123.33 (11.76)	134.80 (11.20)
Median	121.00	136.00
Q1, Q3	116.00, 133.00	127.00, 144.00
Min, Max	97.0, 141.5	111.0, 151.0
Adjusted mean change (95% CI)	-10.68 (-17.02, -4.34)	-2.68 (-9.09, 3.73)
p-value	0.0021	0.3949

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 196 Systolic blood pressure (mmHg) and adjusted mean change from 24 weeks to 52 weeks. Extension per-protocol analysis set

Systolic blood pressure (mmHg)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=15)	Placebo/ Dapa 10mg+Exe 2mg (N=15)
24 weeks		
n/nmiss	15/0	15/0
Mean (SD)	123.33 (11.76)	134.80 (11.20)
Median	121.00	136.00
Q1, Q3	116.00, 133.00	127.00, 144.00
Min, Max	97.0, 141.5	111.0, 151.0
38 weeks		
n/nmiss	15/0	15/0
Mean (SD)	123.03 (14.86)	128.20 (8.81)
Median	121.00	126.00
Q1, Q3	113.00, 136.50	122.00, 136.00
Min, Max	95.5, 145.0	112.5, 144.0
Adjusted mean change (95% CI)	-0.90 (-6.20, 4.39)	-2.68 (-7.90, 2.54)
p-value	0.7291	0.3018
52 weeks		
n/nmiss	15/0	15/0
Mean (SD)	118.77 (12.74)	127.60 (7.57)
Median	122.00	127.50
Q1, Q3	109.00, 128.00	120.50, 135.00
Min, Max	98.5, 140.0	114.0, 137.5
Adjusted mean change (95% CI)	-5.17 (-9.85, -0.49)	-3.28 (-7.87, 1.31)
p-value	0.0316	0.1537

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 197 Systolic blood pressure (mmHg) and adjusted mean change from baseline to 52 weeks. Extension per-protocol analysis set

Systolic blood pressure (mmHg)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=15)	Placebo/ Dapa 10mg+Exe 2mg (N=15)
Baseline		
n/nmiss	15/0	15/0
Mean (SD)	134.13 (13.42)	139.30 (12.97)
Median	129.50	138.00
Q1, Q3	122.50, 146.50	132.50, 153.00
Min, Max	119.5, 162.5	119.0, 161.0
4 weeks		
n/nmiss	15/0	15/0
Mean (SD)	129.63 (17.28)	137.50 (12.51)
Median	128.00	139.00
Q1, Q3	118.50, 144.00	127.00, 143.00
Min, Max	102.5, 159.0	118.0, 161.5
Adjusted mean change (95% CI)	-4.37 (-11.76, 3.01)	0.31 (-7.13, 7.76)

Systolic blood pressure (mmHg)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=15)	Placebo/ Dapa 10mg+Exe 2mg (N=15)
p-value	0.2346	0.9317
8 weeks		
n/nmiss	15/0	15/0
Mean (SD)	123.40 (14.26)	133.53 (12.85)
Median	124.00	132.00
Q1, Q3	114.00, 131.50	122.00, 145.00
Min, Max	100.0, 150.0	112.5, 157.5
Adjusted mean change (95% CI)	-10.60 (-15.41, -5.80)	-3.65 (-8.56, 1.25)
p-value	0.0001	0.1383
12 weeks		
n/nmiss	15/0	15/0
Mean (SD)	121.60 (12.05)	132.57 (12.69)
Median	123.50	134.00
Q1, Q3	109.50, 133.00	128.50, 142.00
Min, Max	105.0, 142.0	100.0, 147.5
Adjusted mean change (95% CI)	-12.40 (-17.35, -7.46)	-4.62 (-9.66, 0.42)
p-value	<.0001	0.0711
24 weeks		
n/nmiss	15/0	15/0
Mean (SD)	123.33 (11.76)	134.80 (11.20)
Median	121.00	136.00
Q1, Q3	116.00, 133.00	127.00, 144.00
Min, Max	97.0, 141.5	111.0, 151.0
Adjusted mean change (95% CI)	-10.67 (-16.99, -4.35)	-2.39 (-8.78, 4.00)
p-value	0.0021	0.4467
38 weeks		
n/nmiss	15/0	15/0
Mean (SD)	123.03 (14.86)	128.20 (8.81)
Median	121.00	126.00
Q1, Q3	113.00, 136.50	122.00, 136.00
Min, Max	95.5, 145.0	112.5, 144.0
Adjusted mean change (95% CI)	-10.97 (-16.56, -5.39)	-8.99 (-14.66, -3.32)
p-value	0.0004	0.0031
52 weeks		
n/nmiss	15/0	15/0
Mean (SD)	118.77 (12.74)	127.60 (7.57)
Median	122.00	127.50
Q1, Q3	109.00, 128.00	120.50, 135.00
Min, Max	98.5, 140.0	114.0, 137.5
Adjusted mean change (95% CI)	-15.24 (-20.55, -9.93)	-9.59 (-14.99, -4.19)
p-value	<.0001	0.0012

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

14.2.5.4.2 Diastolic Blood Pressure

Table 198 Diastolic blood pressure (mmHg) and adjusted mean change from baseline to 24 weeks. Extension full analysis set

Diastolic blood pressure (mmHg)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Baseline		
n/nmiss	21/0	17/0
Mean (SD)	74.79 (10.34)	79.94 (12.05)
Median	75.00	77.00
Q1, Q3	70.50, 80.50	73.00, 91.00
Min, Max	45.0, 95.5	55.0, 97.5
4 weeks		
n/nmiss	21/0	17/0
Mean (SD)	72.19 (9.73)	76.65 (10.41)
Median	75.00	78.00
Q1, Q3	64.00, 80.00	71.50, 80.00
Min, Max	54.0, 89.0	55.0, 98.5
Adjusted mean change (95% CI)	-4.25 (-8.41, -0.09)	-1.92 (-6.59, 2.74)
p-value	0.0454	0.4085
8 weeks		
n/nmiss	21/0	17/0
Mean (SD)	71.81 (10.11)	81.53 (10.43)
Median	72.50	80.00
Q1, Q3	64.00, 80.00	79.00, 90.50
Min, Max	55.0, 91.0	52.0, 96.5
Adjusted mean change (95% CI)	-4.63 (-8.55, -0.71)	2.96 (-1.45, 7.36)
p-value	0.0219	0.1817
12 weeks		
n/nmiss	21/0	17/0
Mean (SD)	75.62 (11.25)	76.91 (9.30)
Median	76.00	76.50
Q1, Q3	70.00, 82.00	75.00, 83.50
Min, Max	55.0, 93.5	56.0, 91.0
Adjusted mean change (95% CI)	-0.82 (-5.17, 3.52)	-1.66 (-6.54, 3.22)
p-value	0.7031	0.4941
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	77.95 (11.04)	80.62 (10.44)
Median	78.00	79.00
Q1, Q3	70.00, 83.00	74.00, 88.00
Min, Max	57.0, 97.0	66.0, 107.0
Adjusted mean change (95% CI)	1.51 (-3.29, 6.31)	2.05 (-3.32, 7.42)
p-value	0.5270	0.4449

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 199 Diastolic blood pressure (mmHg) and adjusted mean change from 24 weeks to 52 weeks. Extension full analysis set

Diastolic blood pressure (mmHg)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	77.95 (11.04)	80.62 (10.44)
Median	78.00	79.00
Q1, Q3	70.00, 83.00	74.00, 88.00
Min, Max	57.0, 97.0	66.0, 107.0
38 weeks		
n/nmiss	19/2	17/0
Mean (SD)	76.84 (7.72)	78.44 (8.10)
Median	77.00	79.50
Q1, Q3	70.00, 84.00	73.00, 84.00
Min, Max	63.0, 90.0	63.5, 95.0
Adjusted mean change (95% CI)	-0.58 (-4.20, 3.04)	-0.71 (-4.52, 3.11)
p-value	0.7461	0.7089
52 weeks		
n/nmiss	17/4	17/0
Mean (SD)	76.00 (10.19)	79.41 (8.88)
Median	80.00	80.00
Q1, Q3	69.00, 81.50	79.00, 85.00
Min, Max	57.5, 96.5	59.0, 92.0
Adjusted mean change (95% CI)	-1.42 (-5.43, 2.60)	0.26 (-3.73, 4.26)
p-value	0.4781	0.8933

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 200 Diastolic blood pressure (mmHg) and adjusted mean change from baseline to 52 weeks. Extension full analysis set

Diastolic blood pressure (mmHg)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Baseline		
n/nmiss	21/0	17/0
Mean (SD)	74.79 (10.34)	79.94 (12.05)
Median	75.00	77.00
Q1, Q3	70.50, 80.50	73.00, 91.00
Min, Max	45.0, 95.5	55.0, 97.5
4 weeks		
n/nmiss	21/0	17/0
Mean (SD)	72.19 (9.73)	76.65 (10.41)
Median	75.00	78.00
Q1, Q3	64.00, 80.00	71.50, 80.00
Min, Max	54.0, 89.0	55.0, 98.5
Adjusted mean change (95% CI)	-4.45 (-8.53, -0.37)	-1.80 (-6.37, 2.76)

Diastolic blood pressure (mmHg)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
p-value	0.0336	0.4289
8 weeks		
n/nmiss	21/0	17/0
Mean (SD)	71.81 (10.11)	81.53 (10.43)
Median	72.50	80.00
Q1, Q3	64.00, 80.00	79.00, 90.50
Min, Max	55.0, 91.0	52.0, 96.5
Adjusted mean change (95% CI)	-4.83 (-8.77, -0.89)	3.08 (-1.33, 7.49)
p-value	0.0177	0.1651
12 weeks		
n/nmiss	21/0	17/0
Mean (SD)	75.62 (11.25)	76.91 (9.30)
Median	76.00	76.50
Q1, Q3	70.00, 82.00	75.00, 83.50
Min, Max	55.0, 93.5	56.0, 91.0
Adjusted mean change (95% CI)	-1.02 (-5.36, 3.32)	-1.54 (-6.39, 3.31)
p-value	0.6357	0.5241
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	77.95 (11.04)	80.62 (10.44)
Median	78.00	79.00
Q1, Q3	70.00, 83.00	74.00, 88.00
Min, Max	57.0, 97.0	66.0, 107.0
Adjusted mean change (95% CI)	1.31 (-3.39, 6.02)	2.17 (-3.09, 7.42)
p-value	0.5754	0.4083
38 weeks		
n/nmiss	19/2	17/0
Mean (SD)	76.84 (7.72)	78.44 (8.10)
Median	77.00	79.50
Q1, Q3	70.00, 84.00	73.00, 84.00
Min, Max	63.0, 90.0	63.5, 95.0
Adjusted mean change (95% CI)	0.61 (-2.91, 4.14)	-0.01 (-3.77, 3.75)
p-value	0.7262	0.9965
52 weeks		
n/nmiss	17/4	17/0
Mean (SD)	76.00 (10.19)	79.41 (8.88)
Median	80.00	80.00
Q1, Q3	69.00, 81.50	79.00, 85.00
Min, Max	57.5, 96.5	59.0, 92.0
Adjusted mean change (95% CI)	0.41 (-3.65, 4.47)	0.96 (-3.42, 5.35)
p-value	0.8376	0.6585

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 201 Diastolic blood pressure (mmHg) and adjusted mean change from baseline to 24 weeks. Extension per-protocol analysis set

Diastolic blood pressure (mmHg)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=15)	Placebo/ Dapa 10mg+Exe 2mg (N=15)
Baseline		
n/nmiss	15/0	15/0
Mean (SD)	73.20 (10.59)	81.30 (11.90)
Median	75.00	82.00
Q1, Q3	69.00, 80.50	73.00, 91.50
Min, Max	45.0, 90.0	55.0, 97.5
4 weeks		
n/nmiss	15/0	15/0
Mean (SD)	70.60 (10.83)	76.27 (11.07)
Median	67.50	78.00
Q1, Q3	62.50, 80.00	71.00, 82.00
Min, Max	54.0, 89.0	55.0, 98.5
Adjusted mean change (95% CI)	-5.37 (-10.74, -0.00)	-3.68 (-9.24, 1.87)
p-value	0.0498	0.1854
8 weeks		
n/nmiss	15/0	15/0
Mean (SD)	70.10 (10.76)	81.63 (11.13)
Median	70.00	80.00
Q1, Q3	61.00, 78.00	78.00, 91.00
Min, Max	55.0, 91.0	52.0, 96.5
Adjusted mean change (95% CI)	-5.87 (-10.84, -0.90)	1.68 (-3.49, 6.86)
p-value	0.0224	0.5117
12 weeks		
n/nmiss	15/0	15/0
Mean (SD)	72.50 (11.18)	76.77 (9.87)
Median	73.00	76.50
Q1, Q3	62.00, 80.00	71.00, 86.00
Min, Max	55.0, 93.5	56.0, 91.0
Adjusted mean change (95% CI)	-3.47 (-8.70, 1.77)	-3.18 (-8.61, 2.24)
p-value	0.1854	0.2402
24 weeks		
n/nmiss	15/0	15/0
Mean (SD)	75.13 (9.95)	80.87 (11.14)
Median	74.00	81.00
Q1, Q3	68.00, 82.50	72.50, 89.00
Min, Max	57.0, 91.0	66.0, 107.0
Adjusted mean change (95% CI)	-0.84 (-6.34, 4.67)	0.92 (-4.77, 6.60)
p-value	0.7581	0.7446

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 202 Diastolic blood pressure (mmHg) and adjusted mean change from 24 weeks to 52 weeks. Extension per-protocol analysis set

Diastolic blood pressure (mmHg)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=15)	Placebo/ Dapa 10mg+Exe 2mg (N=15)
24 weeks		
n/nmiss	15/0	15/0
Mean (SD)	75.13 (9.95)	80.87 (11.14)
Median	74.00	81.00
Q1, Q3	68.00, 82.50	72.50, 89.00
Min, Max	57.0, 91.0	66.0, 107.0
38 weeks		
n/nmiss	15/0	15/0
Mean (SD)	76.60 (7.02)	78.00 (8.51)
Median	76.00	79.00
Q1, Q3	70.00, 84.00	73.00, 84.50
Min, Max	63.5, 86.0	63.5, 95.0
Adjusted mean change (95% CI)	-0.08 (-4.22, 4.05)	-0.67 (-4.86, 3.53)
p-value	0.9670	0.7466
52 weeks		
n/nmiss	15/0	15/0
Mean (SD)	74.37 (9.20)	80.07 (9.13)
Median	75.00	81.00
Q1, Q3	67.00, 81.50	79.00, 87.50
Min, Max	57.5, 92.0	59.0, 92.0
Adjusted mean change (95% CI)	-2.32 (-6.58, 1.94)	1.40 (-2.92, 5.71)
p-value	0.2747	0.5123

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 203 Diastolic blood pressure (mmHg) and adjusted mean change from baseline to 52 weeks. Extension per-protocol analysis set

Diastolic blood pressure (mmHg)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=15)	Placebo/ Dapa 10mg+Exe 2mg (N=15)
Baseline		
n/nmiss	15/0	15/0
Mean (SD)	73.20 (10.59)	81.30 (11.90)
Median	75.00	82.00
Q1, Q3	69.00, 80.50	73.00, 91.50
Min, Max	45.0, 90.0	55.0, 97.5
4 weeks		
n/nmiss	15/0	15/0
Mean (SD)	70.60 (10.83)	76.27 (11.07)
Median	67.50	78.00
Q1, Q3	62.50, 80.00	71.00, 82.00
Min, Max	54.0, 89.0	55.0, 98.5
Adjusted mean change (95% CI)	-5.65 (-10.86, -0.44)	-3.50 (-8.79, 1.80)

Diastolic blood pressure (mmHg)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=15)	Placebo/ Dapa 10mg+Exe 2mg (N=15)
p-value	0.0347	0.1872
8 weeks		
n/nmiss	15/0	15/0
Mean (SD)	70.10 (10.76)	81.63 (11.13)
Median	70.00	80.00
Q1, Q3	61.00, 78.00	78.00, 91.00
Min, Max	55.0, 91.0	52.0, 96.5
Adjusted mean change (95% CI)	-6.15 (-11.07, -1.22)	1.87 (-3.14, 6.88)
p-value	0.0163	0.4521
12 weeks		
n/nmiss	15/0	15/0
Mean (SD)	72.50 (11.18)	76.77 (9.87)
Median	73.00	76.50
Q1, Q3	62.00, 80.00	71.00, 86.00
Min, Max	55.0, 93.5	56.0, 91.0
Adjusted mean change (95% CI)	-3.75 (-8.88, 1.39)	-3.00 (-8.22, 2.22)
p-value	0.1465	0.2501
24 weeks		
n/nmiss	15/0	15/0
Mean (SD)	75.13 (9.95)	80.87 (11.14)
Median	74.00	81.00
Q1, Q3	68.00, 82.50	72.50, 89.00
Min, Max	57.0, 91.0	66.0, 107.0
Adjusted mean change (95% CI)	-1.11 (-6.46, 4.23)	1.10 (-4.32, 6.53)
p-value	0.6732	0.6812
38 weeks		
n/nmiss	15/0	15/0
Mean (SD)	76.60 (7.02)	78.00 (8.51)
Median	76.00	79.00
Q1, Q3	70.00, 84.00	73.00, 84.50
Min, Max	63.5, 86.0	63.5, 95.0
Adjusted mean change (95% CI)	0.35 (-3.42, 4.13)	-1.76 (-5.66, 2.13)
p-value	0.8491	0.3619
52 weeks		
n/nmiss	15/0	15/0
Mean (SD)	74.37 (9.20)	80.07 (9.13)
Median	75.00	81.00
Q1, Q3	67.00, 81.50	79.00, 87.50
Min, Max	57.5, 92.0	59.0, 92.0
Adjusted mean change (95% CI)	-1.88 (-6.45, 2.69)	0.30 (-4.36, 4.97)
p-value	0.4065	0.8956

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

14.2.5.4.3 Pulse

Table 204 Pulse (beats/min) and adjusted mean change from baseline to 24 weeks. Extension full analysis set

Pulse (beats/min)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Baseline		
n/nmiss	21/0	17/0
Mean (SD)	67.1 (9.8)	66.4 (9.5)
Median	66.0	64.0
Q1, Q3	60.0, 72.0	60.0, 70.0
Min, Max	52, 88	52, 94
4 weeks		
n/nmiss	21/0	17/0
Mean (SD)	70.3 (8.2)	65.8 (7.6)
Median	68.0	66.0
Q1, Q3	64.0, 76.0	60.0, 70.0
Min, Max	58, 92	56, 82
Adjusted mean change (95% CI)	3.6 (0.6, 6.6)	-0.4 (-3.8, 2.9)
p-value	0.0195	0.7918
8 weeks		
n/nmiss	21/0	17/0
Mean (SD)	70.0 (10.0)	68.4 (10.2)
Median	68.0	70.0
Q1, Q3	64.0, 72.0	62.0, 78.0
Min, Max	55, 96	48, 82
Adjusted mean change (95% CI)	3.4 (-1.0, 7.8)	2.2 (-2.7, 7.0)
p-value	0.1297	0.3777
12 weeks		
n/nmiss	21/0	17/0
Mean (SD)	66.7 (7.9)	63.1 (8.1)
Median	66.0	62.0
Q1, Q3	62.0, 70.0	58.0, 68.0
Min, Max	52, 88	50, 78
Adjusted mean change (95% CI)	-0.0 (-3.1, 3.1)	-3.1 (-6.6, 0.3)
p-value	0.9908	0.0736
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	68.8 (10.0)	65.6 (9.6)
Median	66.0	64.0
Q1, Q3	62.0, 72.0	60.0, 70.0
Min, Max	52, 100	54, 86
Adjusted mean change (95% CI)	2.1 (-0.7, 5.0)	-0.6 (-3.7, 2.6)
p-value	0.1407	0.7267

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 205 Pulse (beats/min) and adjusted mean change from baseline to 24 weeks. Extension per-protocol analysis set

Pulse (beats/min)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=15)	Placebo/ Dapa 10mg+Exe 2mg (N=15)
Baseline		
n/nmiss	15/0	15/0
Mean (SD)	66.7 (10.3)	67.0 (10.0)
Median	68.0	66.0
Q1, Q3	59.0, 74.0	60.0, 70.0
Min, Max	52, 88	52, 94
4 weeks		
n/nmiss	15/0	15/0
Mean (SD)	71.5 (8.1)	65.9 (7.9)
Median	70.0	66.0
Q1, Q3	64.0, 78.0	58.0, 70.0
Min, Max	62, 92	56, 82
Adjusted mean change (95% CI)	5.1 (1.6, 8.7)	-0.4 (-4.0, 3.2)
p-value	0.0063	0.8083
8 weeks		
n/nmiss	15/0	15/0
Mean (SD)	70.1 (7.7)	68.5 (10.8)
Median	68.0	70.0
Q1, Q3	66.0, 72.0	58.0, 78.0
Min, Max	58, 88	48, 82
Adjusted mean change (95% CI)	3.8 (-1.5, 9.1)	2.2 (-3.2, 7.5)
p-value	0.1558	0.4153
12 weeks		
n/nmiss	15/0	15/0
Mean (SD)	67.5 (8.7)	63.7 (8.4)
Median	66.0	62.0
Q1, Q3	62.0, 72.0	58.0, 70.0
Min, Max	52, 88	50, 78
Adjusted mean change (95% CI)	1.1 (-2.5, 4.8)	-2.6 (-6.3, 1.1)
p-value	0.5294	0.1671
24 weeks		
n/nmiss	15/0	15/0
Mean (SD)	67.8 (7.9)	65.7 (10.1)
Median	66.0	64.0
Q1, Q3	62.0, 74.0	58.0, 70.0
Min, Max	52, 83	54, 86
Adjusted mean change (95% CI)	1.5 (-1.8, 4.7)	-0.6 (-3.9, 2.8)
p-value	0.3641	0.7301

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 206 Pulse (beats/min) and adjusted mean change from 24 weeks to 52 weeks. Extension per-protocol analysis set

Pulse (beats/min)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=15)	Placebo/ Dapa 10mg+Exe 2mg (N=15)
24 weeks		
n/nmiss	15/0	15/0
Mean (SD)	67.8 (7.9)	65.7 (10.1)
Median	66.0	64.0
Q1, Q3	62.0, 74.0	58.0, 70.0
Min, Max	52, 83	54, 86
38 weeks		
n/nmiss	15/0	15/0
Mean (SD)	70.5 (8.3)	74.7 (11.0)
Median	68.0	74.0
Q1, Q3	62.0, 80.0	66.0, 84.0
Min, Max	59, 82	58, 96
Adjusted mean change (95% CI)	4.0 (-1.1, 9.1)	9.2 (4.0, 14.4)
p-value	0.1192	0.0011
52 weeks		
n/nmiss	15/0	15/0
Mean (SD)	69.7 (10.9)	71.6 (8.1)
Median	68.0	72.0
Q1, Q3	62.0, 78.0	65.0, 78.0
Min, Max	58, 96	59, 85
Adjusted mean change (95% CI)	3.3 (-1.6, 8.1)	6.1 (1.2, 11.0)
p-value	0.1755	0.0169

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 207 Pulse (beats/min) and adjusted mean change from baseline to 52 weeks. Extension per-protocol analysis set

Pulse (beats/min)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=15)	Placebo/ Dapa 10mg+Exe 2mg (N=15)
Baseline		
n/nmiss	15/0	15/0
Mean (SD)	66.7 (10.3)	67.0 (10.0)
Median	68.0	66.0
Q1, Q3	59.0, 74.0	60.0, 70.0
Min, Max	52, 88	52, 94
4 weeks		
n/nmiss	15/0	15/0
Mean (SD)	71.5 (8.1)	65.9 (7.9)
Median	70.0	66.0
Q1, Q3	64.0, 78.0	58.0, 70.0
Min, Max	62, 92	56, 82
Adjusted mean change (95% CI)	5.2 (1.7, 8.7)	-0.3 (-3.9, 3.2)
p-value	0.0051	0.8577
8 weeks		
n/nmiss	15/0	15/0
Mean (SD)	70.1 (7.7)	68.5 (10.8)
Median	68.0	70.0
Q1, Q3	66.0, 72.0	58.0, 78.0
Min, Max	58, 88	48, 82
Adjusted mean change (95% CI)	3.9 (-1.4, 9.2)	2.3 (-3.1, 7.6)
p-value	0.1454	0.3879
12 weeks		
n/nmiss	15/0	15/0
Mean (SD)	67.5 (8.7)	63.7 (8.4)
Median	66.0	62.0
Q1, Q3	62.0, 72.0	58.0, 70.0
Min, Max	52, 88	50, 78
Adjusted mean change (95% CI)	1.2 (-2.4, 4.8)	-2.4 (-6.1, 1.2)
p-value	0.4967	0.1815
24 weeks		
n/nmiss	15/0	15/0
Mean (SD)	67.8 (7.9)	65.7 (10.1)
Median	66.0	64.0
Q1, Q3	62.0, 74.0	58.0, 70.0
Min, Max	52, 83	54, 86
Adjusted mean change (95% CI)	1.5 (-1.7, 4.8)	-0.4 (-3.8, 2.9)
p-value	0.3418	0.7850
38 weeks		
n/nmiss	15/0	15/0
Mean (SD)	70.5 (8.3)	74.7 (11.0)
Median	68.0	74.0
Q1, Q3	62.0, 80.0	66.0, 84.0
Min, Max	59, 82	58, 96
Adjusted mean change (95% CI)	4.2 (-0.5, 8.9)	8.6 (3.8, 13.3)

Pulse (beats/min)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=15)	Placebo/ Dapa 10mg+Exe 2mg (N=15)
p-value	0.0779	0.0010
52 weeks		
n/nmiss	15/0	15/0
Mean (SD)	69.7 (10.9)	71.6 (8.1)
Median	68.0	72.0
Q1, Q3	62.0, 78.0	65.0, 78.0
Min, Max	58, 96	59, 85
Adjusted mean change (95% CI)	3.5 (-1.1, 8.1)	5.4 (0.8, 10.0)
p-value	0.1299	0.0228

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

14.2.5.5 Other Anthropometric Measurements

14.2.5.5.1 Waist Circumference

Table 208 Waist circumference (cm) and adjusted mean change from baseline to 24 weeks. Extension per-protocol analysis set

Waist circumference (cm)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=15)	Placebo/ Dapa 10mg+Exe 2mg (N=15)
Baseline		
n/nmiss	15/0	15/0
Mean (SD)	113.13 (7.83)	112.63 (11.41)
Median	114.00	108.00
Q1, Q3	109.00, 120.00	107.00, 120.00
Min, Max	93.5, 125.0	94.0, 143.0
4 weeks		
n/nmiss	15/0	15/0
Mean (SD)	112.30 (8.13)	110.83 (10.86)
Median	110.00	109.00
Q1, Q3	108.00, 119.00	102.00, 114.50
Min, Max	96.0, 127.5	98.5, 141.5
Adjusted mean change (95% CI)	-0.51 (-2.85, 1.84)	-1.44 (-3.83, 0.96)
p-value	0.6611	0.2299
8 weeks		
n/nmiss	15/0	15/0
Mean (SD)	112.10 (7.48)	113.53 (10.91)
Median	112.00	113.00
Q1, Q3	107.00, 118.00	105.00, 117.00
Min, Max	95.0, 123.0	101.0, 144.0
Adjusted mean change (95% CI)	-0.71 (-2.66, 1.24)	1.26 (-0.75, 3.28)
p-value	0.4632	0.2087
12 weeks		
n/nmiss	15/0	15/0
Mean (SD)	109.80 (8.65)	110.33 (11.99)
Median	110.50	105.50
Q1, Q3	104.50, 119.00	101.00, 116.50
Min, Max	91.5, 121.0	96.5, 142.0
Adjusted mean change (95% CI)	-3.01 (-5.56, -0.45)	-1.94 (-4.53, 0.66)
p-value	0.0226	0.1384
24 weeks		
n/nmiss	15/0	15/0
Mean (SD)	107.77 (9.62)	109.80 (12.32)
Median	107.00	111.00
Q1, Q3	100.50, 116.00	96.00, 117.00
Min, Max	88.0, 121.0	94.0, 137.0
Adjusted mean change (95% CI)	-5.04 (-8.19, -1.89)	-2.47 (-5.66, 0.72)
p-value	0.0028	0.1244

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 209 Waist circumference (cm) and adjusted mean change from 24 weeks to 52 weeks. Extension per-protocol analysis set

Waist circumference (cm)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=15)	Placebo/ Dapa 10mg+Exe 2mg (N=15)
24 weeks		
n/nmiss	15/0	15/0
Mean (SD)	107.77 (9.62)	109.80 (12.32)
Median	107.00	111.00
Q1, Q3	100.50, 116.00	96.00, 117.00
Min, Max	88.0, 121.0	94.0, 137.0
38 weeks		
n/nmiss	15/0	15/0
Mean (SD)	106.30 (12.35)	106.07 (10.99)
Median	107.00	106.00
Q1, Q3	94.00, 119.00	99.00, 110.00
Min, Max	85.0, 121.0	87.0, 133.0
Adjusted mean change (95% CI)	-1.77 (-4.75, 1.21)	-4.12 (-7.31, -0.92)
p-value	0.2332	0.0135
52 weeks		
n/nmiss	15/0	15/0
Mean (SD)	105.67 (12.48)	105.37 (11.61)
Median	107.00	105.00
Q1, Q3	93.00, 120.00	97.00, 110.50
Min, Max	85.0, 122.0	87.0, 135.0
Adjusted mean change (95% CI)	-2.40 (-5.78, 0.97)	-4.82 (-8.38, -1.26)
p-value	0.1555	0.0098

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 210 Waist circumference (cm) and adjusted mean change from baseline to 52 weeks. Extension per-protocol analysis set

Waist circumference (cm)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=15)	Placebo/ Dapa 10mg+Exe 2mg (N=15)
Baseline		
n/nmiss	15/0	15/0
Mean (SD)	113.13 (7.83)	112.63 (11.41)
Median	114.00	108.00
Q1, Q3	109.00, 120.00	107.00, 120.00
Min, Max	93.5, 125.0	94.0, 143.0
4 weeks		
n/nmiss	15/0	15/0
Mean (SD)	112.30 (8.13)	110.83 (10.86)
Median	110.00	109.00
Q1, Q3	108.00, 119.00	102.00, 114.50
Min, Max	96.0, 127.5	98.5, 141.5
Adjusted mean change (95% CI)	-0.54 (-2.88, 1.81)	-1.47 (-3.87, 0.93)
p-value	0.6416	0.2197
8 weeks		
n/nmiss	15/0	15/0
Mean (SD)	112.10 (7.48)	113.53 (10.91)
Median	112.00	113.00
Q1, Q3	107.00, 118.00	105.00, 117.00
Min, Max	95.0, 123.0	101.0, 144.0
Adjusted mean change (95% CI)	-0.74 (-2.68, 1.20)	1.23 (-0.78, 3.24)
p-value	0.4421	0.2192
12 weeks		
n/nmiss	15/0	15/0
Mean (SD)	109.80 (8.65)	110.33 (11.99)
Median	110.50	105.50
Q1, Q3	104.50, 119.00	101.00, 116.50
Min, Max	91.5, 121.0	96.5, 142.0
Adjusted mean change (95% CI)	-3.04 (-5.57, -0.50)	-1.97 (-4.55, 0.61)
p-value	0.0205	0.1296
24 weeks		
n/nmiss	15/0	15/0
Mean (SD)	107.77 (9.62)	109.80 (12.32)
Median	107.00	111.00
Q1, Q3	100.50, 116.00	96.00, 117.00
Min, Max	88.0, 121.0	94.0, 137.0
Adjusted mean change (95% CI)	-5.07 (-8.22, -1.93)	-2.50 (-5.69, 0.68)
p-value	0.0026	0.1187
38 weeks		
n/nmiss	15/0	15/0
Mean (SD)	106.30 (12.35)	106.07 (10.99)
Median	107.00	106.00
Q1, Q3	94.00, 119.00	99.00, 110.00
Min, Max	85.0, 121.0	87.0, 133.0
Adjusted mean change (95% CI)	-6.54 (-10.63, -2.45)	-6.24 (-10.35, -2.12)

Waist circumference (cm)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=15)	Placebo/ Dapa 10mg+Exe 2mg (N=15)
p-value	0.0028	0.0043
52 weeks		
n/nmiss	15/0	15/0
Mean (SD)	105.67 (12.48)	105.37 (11.61)
Median	107.00	105.00
Q1, Q3	93.00, 120.00	97.00, 110.50
Min, Max	85.0, 122.0	87.0, 135.0
Adjusted mean change (95% CI)	-7.17 (-11.43, -2.92)	-6.94 (-11.22, -2.65)
p-value	0.0018	0.0025

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

14.2.5.5.2 Waist-Hip Ratio

Table 211 Waist-hip ratio and adjusted mean change from baseline to 24 weeks. Extension full analysis set

Waist-hip ratio	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Baseline		
n/nmiss	21/0	17/0
Mean (SD)	0.957 (0.088)	0.974 (0.098)
Median	0.960	0.970
Q1, Q3	0.890, 1.020	0.890, 1.030
Min, Max	0.79, 1.13	0.79, 1.18
4 weeks		
n/nmiss	21/0	17/0
Mean (SD)	0.956 (0.091)	0.962 (0.100)
Median	0.960	0.980
Q1, Q3	0.900, 1.010	0.890, 1.020
Min, Max	0.79, 1.14	0.81, 1.18
Adjusted mean change (95% CI)	0.002 (-0.012, 0.016)	-0.005 (-0.020, 0.011)
p-value	0.7627	0.5597
8 weeks		
n/nmiss	21/0	17/0
Mean (SD)	0.955 (0.089)	0.974 (0.084)
Median	0.940	0.980
Q1, Q3	0.920, 1.000	0.920, 1.030
Min, Max	0.80, 1.11	0.84, 1.10
Adjusted mean change (95% CI)	0.001 (-0.015, 0.017)	0.008 (-0.010, 0.026)
p-value	0.9365	0.3834
12 weeks		
n/nmiss	21/0	17/0
Mean (SD)	0.948 (0.081)	0.959 (0.098)
Median	0.940	0.950
Q1, Q3	0.900, 0.990	0.880, 1.040
Min, Max	0.80, 1.12	0.81, 1.09
Adjusted mean change (95% CI)	-0.007 (-0.025, 0.012)	-0.007 (-0.028, 0.013)
p-value	0.4769	0.4690
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	0.939 (0.107)	0.956 (0.112)
Median	0.950	0.990
Q1, Q3	0.860, 0.990	0.850, 1.040
Min, Max	0.77, 1.15	0.80, 1.14
Adjusted mean change (95% CI)	-0.016 (-0.036, 0.005)	-0.010 (-0.034, 0.013)
p-value	0.1379	0.3717

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 212 Waist-hip ratio and adjusted mean change from 24 weeks to 52 weeks. Extension full analysis set

Waist-hip ratio	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	0.939 (0.107)	0.956 (0.112)
Median	0.950	0.990
Q1, Q3	0.860, 0.990	0.850, 1.040
Min, Max	0.77, 1.15	0.80, 1.14
38 weeks		
n/nmiss	19/2	17/0
Mean (SD)	0.927 (0.103)	0.945 (0.100)
Median	0.940	0.970
Q1, Q3	0.840, 1.020	0.870, 1.000
Min, Max	0.77, 1.12	0.79, 1.10
Adjusted mean change (95% CI)	-0.013 (-0.028, 0.003)	-0.011 (-0.028, 0.006)
p-value	0.1085	0.2048
52 weeks		
n/nmiss	17/4	17/0
Mean (SD)	0.919 (0.089)	0.939 (0.097)
Median	0.910	0.960
Q1, Q3	0.850, 1.000	0.860, 1.000
Min, Max	0.78, 1.07	0.78, 1.08
Adjusted mean change (95% CI)	-0.016 (-0.037, 0.004)	-0.016 (-0.038, 0.006)
p-value	0.1202	0.1410

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 213 Waist-hip ratio and adjusted mean change from baseline to 24 weeks. Extension per-protocol analysis set

Waist-hip ratio	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=15)	Placebo/ Dapa 10mg+Exe 2mg (N=15)
Baseline		
n/nmiss	15/0	15/0
Mean (SD)	0.941 (0.079)	0.963 (0.099)
Median	0.960	0.960
Q1, Q3	0.870, 0.990	0.880, 1.030
Min, Max	0.79, 1.06	0.79, 1.18
4 weeks		
n/nmiss	15/0	15/0
Mean (SD)	0.940 (0.076)	0.949 (0.098)
Median	0.960	0.940
Q1, Q3	0.880, 1.010	0.880, 1.020
Min, Max	0.79, 1.03	0.81, 1.18
Adjusted mean change (95% CI)	0.003 (-0.014, 0.019)	-0.004 (-0.021, 0.014)
p-value	0.7528	0.6842
8 weeks		
n/nmiss	15/0	15/0
Mean (SD)	0.945 (0.074)	0.965 (0.083)
Median	0.940	0.970
Q1, Q3	0.930, 1.000	0.910, 1.030
Min, Max	0.80, 1.06	0.84, 1.10
Adjusted mean change (95% CI)	0.007 (-0.011, 0.025)	0.013 (-0.006, 0.032)
p-value	0.4104	0.1601
12 weeks		
n/nmiss	15/0	15/0
Mean (SD)	0.941 (0.062)	0.950 (0.101)
Median	0.940	0.930
Q1, Q3	0.920, 0.980	0.880, 1.040
Min, Max	0.80, 1.05	0.81, 1.09
Adjusted mean change (95% CI)	0.003 (-0.018, 0.025)	-0.002 (-0.024, 0.020)
p-value	0.7574	0.8400
24 weeks		
n/nmiss	15/0	15/0
Mean (SD)	0.925 (0.091)	0.943 (0.113)
Median	0.950	0.950
Q1, Q3	0.860, 0.990	0.800, 1.040
Min, Max	0.77, 1.09	0.80, 1.14
Adjusted mean change (95% CI)	-0.013 (-0.039, 0.014)	-0.009 (-0.036, 0.018)
p-value	0.3328	0.5070

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 214 Waist-hip ratio and adjusted mean change from 24 weeks to 52 weeks. Extension per-protocol analysis set

Waist-hip ratio	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=15)	Placebo/ Dapa 10mg+Exe 2mg (N=15)
24 weeks		
n/nmiss	15/0	15/0
Mean (SD)	0.925 (0.091)	0.943 (0.113)
Median	0.950	0.950
Q1, Q3	0.860, 0.990	0.800, 1.040
Min, Max	0.77, 1.09	0.80, 1.14
38 weeks		
n/nmiss	15/0	15/0
Mean (SD)	0.916 (0.089)	0.931 (0.098)
Median	0.940	0.950
Q1, Q3	0.840, 0.980	0.850, 1.000
Min, Max	0.77, 1.04	0.79, 1.10
Adjusted mean change (95% CI)	-0.011 (-0.030, 0.007)	-0.013 (-0.034, 0.007)
p-value	0.2175	0.1901
52 weeks		
n/nmiss	15/0	15/0
Mean (SD)	0.913 (0.085)	0.927 (0.095)
Median	0.910	0.950
Q1, Q3	0.850, 1.000	0.820, 1.000
Min, Max	0.78, 1.05	0.78, 1.06
Adjusted mean change (95% CI)	-0.015 (-0.039, 0.009)	-0.018 (-0.043, 0.007)
p-value	0.2172	0.1563

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 215 Waist-hip ratio and adjusted mean change from baseline to 52 weeks. Extension per-protocol analysis set

Waist-hip ratio	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=15)	Placebo/ Dapa 10mg+Exe 2mg (N=15)
Baseline		
n/nmiss	15/0	15/0
Mean (SD)	0.941 (0.079)	0.963 (0.099)
Median	0.960	0.960
Q1, Q3	0.870, 0.990	0.880, 1.030
Min, Max	0.79, 1.06	0.79, 1.18
4 weeks		
n/nmiss	15/0	15/0
Mean (SD)	0.940 (0.076)	0.949 (0.098)
Median	0.960	0.940
Q1, Q3	0.880, 1.010	0.880, 1.020
Min, Max	0.79, 1.03	0.81, 1.18
Adjusted mean change (95% CI)	0.002 (-0.015, 0.019)	-0.005 (-0.022, 0.013)

Waist-hip ratio	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=15)	Placebo/ Dapa 10mg+Exe 2mg (N=15)
p-value	0.8078	0.6012
8 weeks		
n/nmiss	15/0	15/0
Mean (SD)	0.945 (0.074)	0.965 (0.083)
Median	0.940	0.970
Q1, Q3	0.930, 1.000	0.910, 1.030
Min, Max	0.80, 1.06	0.84, 1.10
Adjusted mean change (95% CI)	0.007 (-0.011, 0.024)	0.012 (-0.007, 0.031)
p-value	0.4482	0.1948
12 weeks		
n/nmiss	15/0	15/0
Mean (SD)	0.941 (0.062)	0.950 (0.101)
Median	0.940	0.930
Q1, Q3	0.920, 0.980	0.880, 1.040
Min, Max	0.80, 1.05	0.81, 1.09
Adjusted mean change (95% CI)	0.003 (-0.019, 0.024)	-0.003 (-0.026, 0.019)
p-value	0.8017	0.7692
24 weeks		
n/nmiss	15/0	15/0
Mean (SD)	0.925 (0.091)	0.943 (0.113)
Median	0.950	0.950
Q1, Q3	0.860, 0.990	0.800, 1.040
Min, Max	0.77, 1.09	0.80, 1.14
Adjusted mean change (95% CI)	-0.013 (-0.040, 0.013)	-0.010 (-0.037, 0.017)
p-value	0.3160	0.4646
38 weeks		
n/nmiss	15/0	15/0
Mean (SD)	0.916 (0.089)	0.931 (0.098)
Median	0.940	0.950
Q1, Q3	0.840, 0.980	0.850, 1.000
Min, Max	0.77, 1.04	0.79, 1.10
Adjusted mean change (95% CI)	-0.022 (-0.046, 0.002)	-0.022 (-0.046, 0.002)
p-value	0.0672	0.0757
52 weeks		
n/nmiss	15/0	15/0
Mean (SD)	0.913 (0.085)	0.927 (0.095)
Median	0.910	0.950
Q1, Q3	0.850, 1.000	0.820, 1.000
Min, Max	0.78, 1.05	0.78, 1.06
Adjusted mean change (95% CI)	-0.025 (-0.049, -0.002)	-0.027 (-0.051, -0.002)
p-value	0.0364	0.0329

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

14.2.5.5.3 Body Mass Index

Table 216 BMI and adjusted mean change from baseline to 24 weeks. Extension per-protocol analysis set

Body mass index (BMI) (kg/m²)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=15)	Placebo/ Dapa 10mg+Exe 2mg (N=15)
Baseline		
n/nmiss	15/0	15/0
Mean (SD)	34.712 (2.278)	34.609 (3.266)
Median	34.660	33.710
Q1, Q3	33.450, 36.590	32.730, 35.750
Min, Max	30.85, 38.34	30.79, 44.77
4 weeks		
n/nmiss	15/0	15/0
Mean (SD)	34.549 (2.638)	34.387 (3.349)
Median	34.500	33.810
Q1, Q3	32.870, 36.840	32.420, 34.830
Min, Max	29.78, 39.70	30.64, 44.64
Adjusted mean change (95% CI)	-0.169 (-0.472, 0.133)	-0.227 (-0.539, 0.086)
p-value	0.2603	0.1481
8 weeks		
n/nmiss	15/0	15/0
Mean (SD)	34.191 (2.836)	34.485 (3.396)
Median	34.700	34.110
Q1, Q3	31.930, 36.550	32.430, 34.580
Min, Max	28.87, 39.64	30.64, 45.04
Adjusted mean change (95% CI)	-0.527 (-0.930, -0.125)	-0.129 (-0.538, 0.281)
p-value	0.0121	0.5250
12 weeks		
n/nmiss	15/0	15/0
Mean (SD)	33.601 (3.272)	34.365 (3.421)
Median	34.380	33.660
Q1, Q3	30.800, 35.880	32.430, 35.030
Min, Max	27.59, 39.94	30.34, 45.04
Adjusted mean change (95% CI)	-1.117 (-1.651, -0.584)	-0.249 (-0.787, 0.289)
p-value	0.0002	0.3506
24 weeks		
n/nmiss	15/0	15/0
Mean (SD)	33.204 (3.762)	34.505 (3.497)
Median	33.440	34.050
Q1, Q3	29.860, 36.400	32.430, 35.310
Min, Max	26.05, 40.56	31.16, 44.97
Adjusted mean change (95% CI)	-1.515 (-2.232, -0.797)	-0.109 (-0.830, 0.612)
p-value	0.0002	0.7598

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 217 BMI and adjusted mean change from 24 weeks to 52 weeks. Extension per-protocol analysis set

Body mass index (BMI) (kg/m²)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=15)	Placebo/ Dapa 10mg+Exe 2mg (N=15)
24 weeks		
n/nmiss	15/0	15/0
Mean (SD)	33.204 (3.762)	34.505 (3.497)
Median	33.440	34.050
Q1, Q3	29.860, 36.400	32.430, 35.310
Min, Max	26.05, 40.56	31.16, 44.97
38 weeks		
n/nmiss	15/0	15/0
Mean (SD)	33.135 (4.350)	33.347 (3.671)
Median	33.660	32.710
Q1, Q3	30.010, 36.410	31.020, 33.700
Min, Max	24.76, 41.65	29.62, 44.30
Adjusted mean change (95% CI)	-0.077 (-0.664, 0.510)	-1.287 (-1.903, -0.672)
p-value	0.7890	0.0002
52 weeks		
n/nmiss	15/0	15/0
Mean (SD)	32.817 (4.763)	32.943 (4.038)
Median	33.730	32.080
Q1, Q3	29.630, 35.560	30.110, 34.230
Min, Max	23.88, 43.09	29.20, 44.81
Adjusted mean change (95% CI)	-0.395 (-1.135, 0.345)	-1.691 (-2.452, -0.930)
p-value	0.2818	0.0001

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

Table 218 BMI and adjusted mean change from baseline to 52 weeks. Extension per-protocol analysis set

Body mass index (BMI) (kg/m²)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=15)	Placebo/ Dapa 10mg+Exe 2mg (N=15)
Baseline		
n/nmiss	15/0	15/0
Mean (SD)	34.712 (2.278)	34.609 (3.266)
Median	34.660	33.710
Q1, Q3	33.450, 36.590	32.730, 35.750
Min, Max	30.85, 38.34	30.79, 44.77
4 weeks		
n/nmiss	15/0	15/0
Mean (SD)	34.549 (2.638)	34.387 (3.349)
Median	34.500	33.810
Q1, Q3	32.870, 36.840	32.420, 34.830
Min, Max	29.78, 39.70	30.64, 44.64
Adjusted mean change (95% CI)	-0.154 (-0.460, 0.151)	-0.207 (-0.523, 0.108)

Body mass index (BMI) (kg/m²)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=15)	Placebo/ Dapa 10mg+Exe 2mg (N=15)
p-value	0.3085	0.1882
8 weeks		
n/nmiss	15/0	15/0
Mean (SD)	34.191 (2.836)	34.485 (3.396)
Median	34.700	34.110
Q1, Q3	31.930, 36.550	32.430, 34.580
Min, Max	28.87, 39.64	30.64, 45.04
Adjusted mean change (95% CI)	-0.512 (-0.919, -0.106)	-0.109 (-0.523, 0.304)
p-value	0.0154	0.5920
12 weeks		
n/nmiss	15/0	15/0
Mean (SD)	33.601 (3.272)	34.365 (3.421)
Median	34.380	33.660
Q1, Q3	30.800, 35.880	32.430, 35.030
Min, Max	27.59, 39.94	30.34, 45.04
Adjusted mean change (95% CI)	-1.102 (-1.643, -0.562)	-0.230 (-0.776, 0.316)
p-value	0.0003	0.3947
24 weeks		
n/nmiss	15/0	15/0
Mean (SD)	33.204 (3.762)	34.505 (3.497)
Median	33.440	34.050
Q1, Q3	29.860, 36.400	32.430, 35.310
Min, Max	26.05, 40.56	31.16, 44.97
Adjusted mean change (95% CI)	-1.500 (-2.225, -0.774)	-0.089 (-0.819, 0.640)
p-value	0.0002	0.8035
38 weeks		
n/nmiss	15/0	15/0
Mean (SD)	33.135 (4.350)	33.347 (3.671)
Median	33.660	32.710
Q1, Q3	30.010, 36.410	31.020, 33.700
Min, Max	24.76, 41.65	29.62, 44.30
Adjusted mean change (95% CI)	-1.568 (-2.612, -0.524)	-1.247 (-2.294, -0.201)
p-value	0.0047	0.0212
52 weeks		
n/nmiss	15/0	15/0
Mean (SD)	32.817 (4.763)	32.943 (4.038)
Median	33.730	32.080
Q1, Q3	29.630, 35.560	30.110, 34.230
Min, Max	23.88, 43.09	29.20, 44.81
Adjusted mean change (95% CI)	-1.886 (-3.141, -0.631)	-1.651 (-2.908, -0.394)
p-value	0.0046	0.0119

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
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 within treatment groups against a two-sided alternative hypothesis at the 5% level of significance.

14.3 SAFETY DATA

14.3.1 Safety Laboratory Variables

14.3.1.1 Haematology

Table 219 B-Haemoglobin (g/L) and mean change from baseline. Extension safety analysis set

B-Haemoglobin (Hb) (g/L)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Screening		
n/nmiss	21/0	17/0
Mean (SD)	140.3 (15.8)	142.9 (12.8)
Median	141.0	140.0
Q1, Q3	135.0, 152.0	136.0, 153.0
Min, Max	108, 164	123, 164
Mean change (95% CI)		
12 weeks		
n/nmiss	21/0	17/0
Mean (SD)	146.9 (17.2)	145.2 (14.3)
Median	151.0	142.0
Q1, Q3	140.0, 158.0	135.0, 153.0
Min, Max	104, 168	123, 175
Mean change (95% CI)	6.6 (2.0, 11.2)	2.4 (-0.5, 5.2)
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	144.0 (16.5)	142.4 (15.0)
Median	145.0	142.0
Q1, Q3	132.0, 156.0	134.0, 154.0
Min, Max	104, 167	116, 174
Mean change (95% CI)	3.7 (-2.1, 9.5)	-0.5 (-4.4, 3.4)
52 weeks		
n/nmiss	17/4	17/0
Mean (SD)	143.7 (12.3)	150.6 (14.6)
Median	142.0	151.0
Q1, Q3	135.0, 155.0	138.0, 158.0
Min, Max	122, 161	131, 186
Mean change (95% CI)	0.3 (-5.7, 6.3)	7.8 (3.5, 12.1)

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
Percentages are based on the number of subjects in the applicable analysis set.

14.3.1.2 Clinical Chemistry

Table 220 Albumin (g/L) and mean change from baseline. Extension safety analysis set

Albumin (g/L)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Screening		
n/nmiss	20/1	17/0
Mean (SD)	37.6 (2.3)	38.1 (2.2)
Median	37.0	38.0
Q1, Q3	36.0, 38.5	37.0, 40.0
Min, Max	33, 42	34, 42
Mean change (95% CI)		
12 weeks		
n/nmiss	21/0	17/0
Mean (SD)	38.3 (3.1)	39.4 (2.8)
Median	37.0	40.0
Q1, Q3	37.0, 41.0	37.0, 41.0
Min, Max	33, 43	34, 44
Mean change (95% CI)	0.8 (-0.3, 1.8)	1.3 (0.2, 2.4)
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	37.6 (3.0)	38.2 (2.1)
Median	38.0	39.0
Q1, Q3	35.0, 40.0	37.0, 40.0
Min, Max	32, 43	34, 41
Mean change (95% CI)	0.2 (-0.8, 1.2)	0.1 (-0.8, 1.0)
52 weeks		
n/nmiss	16/5	17/0
Mean (SD)	37.1 (2.8)	39.3 (2.1)
Median	36.0	40.0
Q1, Q3	34.5, 40.0	38.0, 41.0
Min, Max	34, 41	35, 43
Mean change (95% CI)	-0.6 (-1.7, 0.5)	1.2 (0.2, 2.3)

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
Percentages are based on the number of subjects in the applicable analysis set.

Table 221 Alkaline phosphatase (µkat/L) and mean change from baseline. Extension safety analysis set

Alkaline phosphatase (ALP) (µkat/L)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Screening		
n/nmiss	21/0	17/0
Mean (SD)	1.224 (0.275)	1.134 (0.267)
Median	1.200	1.100
Q1, Q3	1.100, 1.400	0.980, 1.300
Min, Max	0.79, 1.80	0.72, 1.70
Mean change (95% CI)		
12 weeks		
n/nmiss	21/0	15/2
Mean (SD)	1.203 (0.242)	1.139 (0.243)
Median	1.200	1.100
Q1, Q3	1.000, 1.400	0.880, 1.400
Min, Max	0.74, 1.60	0.84, 1.60
Mean change (95% CI)	-0.021 (-0.111, 0.069)	0.007 (-0.050, 0.065)
24 weeks		
n/nmiss	18/3	15/2
Mean (SD)	1.143 (0.207)	1.145 (0.236)
Median	1.200	1.100
Q1, Q3	0.970, 1.300	0.930, 1.300
Min, Max	0.83, 1.50	0.81, 1.60
Mean change (95% CI)	-0.096 (-0.184, -0.008)	-0.026 (-0.072, 0.020)
52 weeks		
n/nmiss	16/5	17/0
Mean (SD)	1.175 (0.277)	1.199 (0.286)
Median	1.200	1.200
Q1, Q3	0.970, 1.300	1.000, 1.400
Min, Max	0.77, 1.70	0.82, 1.80
Mean change (95% CI)	-0.079 (-0.205, 0.047)	0.065 (0.015, 0.116)

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
Percentages are based on the number of subjects in the applicable analysis set.

Table 222 Alanine transaminase (µkat/L) and mean change from baseline. Extension safety analysis set

Alanine transaminase (ALT) (µkat/L)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Screening		
n/nmiss	21/0	16/1
Mean (SD)	0.590 (0.365)	0.648 (0.342)
Median	0.530	0.605
Q1, Q3	0.330, 0.640	0.380, 0.855
Min, Max	0.17, 1.57	0.16, 1.37
Mean change (95% CI)		
12 weeks		
n/nmiss	21/0	17/0
Mean (SD)	0.575 (0.303)	0.651 (0.300)
Median	0.540	0.570
Q1, Q3	0.350, 0.730	0.400, 0.970
Min, Max	0.23, 1.51	0.25, 1.16
Mean change (95% CI)	-0.014 (-0.103, 0.075)	0.019 (-0.103, 0.142)
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	0.568 (0.329)	0.577 (0.292)
Median	0.550	0.520
Q1, Q3	0.300, 0.710	0.360, 0.760
Min, Max	0.24, 1.55	0.22, 1.19
Mean change (95% CI)	-0.022 (-0.129, 0.085)	-0.064 (-0.164, 0.037)
52 weeks		
n/nmiss	16/5	17/0
Mean (SD)	0.478 (0.218)	0.502 (0.227)
Median	0.415	0.460
Q1, Q3	0.300, 0.630	0.390, 0.550
Min, Max	0.25, 0.97	0.24, 1.11
Mean change (95% CI)	-0.053 (-0.140, 0.034)	-0.145 (-0.258, -0.032)

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
Percentages are based on the number of subjects in the applicable analysis set.

Table 223 Aspartate transaminase (µkat/L). Extension safety analysis set

Aspartate transaminase (AST) (ukat/L)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Screening		
n/nmiss	21/0	16/1
Mean (SD)	0.518 (0.180)	0.516 (0.131)
Median	0.500	0.490
Q1, Q3	0.410, 0.540	0.425, 0.620
Min, Max	0.33, 1.17	0.29, 0.77
Mean change (95% CI)		
12 weeks		
n/nmiss	21/0	17/0
Mean (SD)	0.480 (0.125)	0.491 (0.128)
Median	0.460	0.490
Q1, Q3	0.410, 0.540	0.390, 0.600
Min, Max	0.31, 0.84	0.28, 0.70
Mean change (95% CI)	-0.038 (-0.083, 0.006)	-0.019 (-0.084, 0.047)
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	0.476 (0.156)	0.444 (0.095)
Median	0.430	0.420
Q1, Q3	0.370, 0.510	0.380, 0.480
Min, Max	0.31, 0.95	0.29, 0.64
Mean change (95% CI)	-0.042 (-0.107, 0.022)	-0.071 (-0.129, -0.012)
52 weeks		
n/nmiss	16/5	17/0
Mean (SD)	0.457 (0.112)	0.415 (0.067)
Median	0.430	0.410
Q1, Q3	0.375, 0.535	0.380, 0.440
Min, Max	0.30, 0.74	0.31, 0.58
Mean change (95% CI)	-0.035 (-0.098, 0.028)	-0.101 (-0.155, -0.047)

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
Percentages are based on the number of subjects in the applicable analysis set.

Table 224 Total bilirubin (µmol/L) and mean change from baseline. Extension safety analysis set

Total bilirubin (µmol/L)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Screening		
n/nmiss	21/0	17/0
Mean (SD)	12.51 (5.91)	10.26 (3.18)
Median	10.00	9.50
Q1, Q3	8.60, 16.00	7.60, 12.00
Min, Max	6.5, 31.0	6.2, 16.0
Mean change (95% CI)		
12 weeks		
n/nmiss	21/0	16/1
Mean (SD)	12.68 (7.14)	12.21 (3.76)
Median	11.00	11.50
Q1, Q3	8.60, 12.00	9.25, 14.50
Min, Max	6.2, 34.0	5.9, 20.0
Mean change (95% CI)	0.17 (-1.88, 2.21)	1.87 (-0.52, 4.26)
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	12.46 (5.96)	11.31 (3.95)
Median	10.00	11.00
Q1, Q3	9.00, 14.00	9.40, 13.00
Min, Max	5.5, 27.0	5.1, 18.0
Mean change (95% CI)	-0.05 (-1.59, 1.49)	1.05 (-0.54, 2.64)
52 weeks		
n/nmiss	16/5	16/1
Mean (SD)	13.53 (6.81)	11.48 (2.99)
Median	11.50	11.00
Q1, Q3	8.10, 16.50	9.50, 12.50
Min, Max	6.1, 28.0	7.3, 19.0
Mean change (95% CI)	0.41 (-1.22, 2.04)	1.17 (-0.59, 2.93)

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
Percentages are based on the number of subjects in the applicable analysis set.

Table 225 Total calcium (mmol/L) and mean change from baseline. Extension safety analysis set

Total calcium (mmol/L)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Screening		
n/nmiss	21/0	17/0
Mean (SD)	2.276 (0.083)	2.287 (0.079)
Median	2.280	2.280
Q1, Q3	2.200, 2.340	2.230, 2.340
Min, Max	2.14, 2.42	2.14, 2.44
Mean change (95% CI)		
12 weeks		
n/nmiss	20/1	17/0
Mean (SD)	2.285 (0.046)	2.349 (0.054)
Median	2.295	2.350
Q1, Q3	2.255, 2.325	2.310, 2.390
Min, Max	2.19, 2.35	2.26, 2.45
Mean change (95% CI)	0.016 (-0.023, 0.055)	0.062 (0.025, 0.100)
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	2.330 (0.056)	2.380 (0.072)
Median	2.320	2.350
Q1, Q3	2.290, 2.370	2.320, 2.420
Min, Max	2.23, 2.46	2.28, 2.53
Mean change (95% CI)	0.055 (0.019, 0.090)	0.093 (0.062, 0.124)
52 weeks		
n/nmiss	16/5	17/0
Mean (SD)	2.327 (0.072)	2.384 (0.064)
Median	2.360	2.370
Q1, Q3	2.265, 2.385	2.350, 2.430
Min, Max	2.19, 2.39	2.26, 2.48
Mean change (95% CI)	0.043 (-0.002, 0.088)	0.097 (0.049, 0.145)

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
Percentages are based on the number of subjects in the applicable analysis set.

Table 226 Creatine kinase (µkat/L) and mean change from baseline. Extension safety analysis set

Creatine kinase (CK) (µkat/L)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Screening		
n/nmiss	21/0	16/1
Mean (SD)	2.09 (1.32)	1.98 (0.91)
Median	1.80	1.75
Q1, Q3	1.30, 2.20	1.20, 2.35
Min, Max	0.7, 6.2	1.1, 3.8
Mean change (95% CI)		
12 weeks		
n/nmiss	21/0	17/0
Mean (SD)	2.29 (2.19)	2.05 (0.97)
Median	1.60	1.80
Q1, Q3	1.30, 2.60	1.40, 2.50
Min, Max	0.7, 10.9	0.8, 3.9
Mean change (95% CI)	0.20 (-0.70, 1.10)	0.11 (-0.18, 0.40)
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	2.32 (2.14)	1.69 (0.75)
Median	1.80	1.40
Q1, Q3	1.30, 2.00	1.20, 2.40
Min, Max	0.6, 8.5	0.9, 3.5
Mean change (95% CI)	0.24 (-0.83, 1.31)	-0.25 (-0.59, 0.09)
52 weeks		
n/nmiss	16/5	17/0
Mean (SD)	2.42 (1.70)	1.79 (0.72)
Median	1.80	1.70
Q1, Q3	1.45, 2.70	1.20, 2.40
Min, Max	0.5, 6.2	0.8, 3.1
Mean change (95% CI)	0.25 (-0.74, 1.24)	-0.27 (-0.61, 0.08)

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
Percentages are based on the number of subjects in the applicable analysis set.

Table 227 Creatinine (µmol/L) and mean change from baseline. Extension safety analysis set

Creatinine (umol/L)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Screening		
n/nmiss	21/0	16/1
Mean (SD)	73.0 (14.4)	73.7 (11.3)
Median	72.0	71.5
Q1, Q3	63.0, 78.0	66.5, 83.0
Min, Max	49, 106	54, 92
Mean change (95% CI)		
12 weeks		
n/nmiss	21/0	17/0
Mean (SD)	72.0 (16.7)	72.2 (13.2)
Median	71.0	69.0
Q1, Q3	64.0, 79.0	62.0, 76.0
Min, Max	44, 116	57, 101
Mean change (95% CI)	-1.1 (-3.9, 1.7)	-0.6 (-3.4, 2.3)
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	73.7 (15.1)	72.4 (14.6)
Median	72.0	72.0
Q1, Q3	67.0, 77.0	62.0, 84.0
Min, Max	48, 111	50, 101
Mean change (95% CI)	0.6 (-2.6, 3.8)	-0.6 (-3.8, 2.7)
52 weeks		
n/nmiss	16/5	17/0
Mean (SD)	74.5 (15.5)	73.0 (10.3)
Median	74.0	72.0
Q1, Q3	62.5, 82.0	70.0, 77.0
Min, Max	48, 108	55, 94
Mean change (95% CI)	-0.3 (-5.3, 4.8)	-0.1 (-2.5, 2.3)

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
Percentages are based on the number of subjects in the applicable analysis set.

Table 228 C-reactive protein (mg/L) and mean change from baseline. Extension safety analysis set

C-reactive protein (mg/L)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Screening		
n/nmiss	21/0	16/1
Mean (SD)	3.429 (2.527)	3.121 (2.667)
Median	2.600	2.100
Q1, Q3	2.200, 4.100	1.150, 4.650
Min, Max	0.85, 9.70	0.56, 9.20
Mean change (95% CI)		
12 weeks		
n/nmiss	17/4	16/1
Mean (SD)	9.618 (20.119)	3.441 (2.454)
Median	1.900	2.200
Q1, Q3	1.300, 10.000	1.700, 4.950
Min, Max	0.61, 84.00	0.62, 8.50
Mean change (95% CI)	6.142 (-4.100, 16.385)	0.302 (-1.091, 1.695)
24 weeks		
n/nmiss	20/1	17/0
Mean (SD)	3.206 (2.876)	2.491 (2.187)
Median	2.650	2.000
Q1, Q3	1.200, 4.000	1.200, 2.600
Min, Max	0.31, 13.00	0.74, 10.00
Mean change (95% CI)	0.090 (-0.975, 1.156)	-0.543 (-1.636, 0.550)
52 weeks		
n/nmiss	16/5	17/0
Mean (SD)	5.241 (7.788)	2.364 (1.423)
Median	2.300	2.200
Q1, Q3	1.350, 4.400	1.200, 2.800
Min, Max	0.36, 28.00	0.58, 5.80
Mean change (95% CI)	1.903 (-1.710, 5.515)	-0.747 (-1.740, 0.247)

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
Percentages are based on the number of subjects in the applicable analysis set.

Table 229 Potassium (mmol/L) and mean change from baseline. Extension safety analysis set

Potassium (mmol/L)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Screening		
n/nmiss	21/0	17/0
Mean (SD)	3.74 (0.29)	3.69 (0.24)
Median	3.70	3.60
Q1, Q3	3.60, 3.90	3.60, 3.70
Min, Max	3.0, 4.2	3.4, 4.3
Mean change (95% CI)		
12 weeks		
n/nmiss	21/0	17/0
Mean (SD)	3.93 (0.29)	3.89 (0.25)
Median	4.00	3.90
Q1, Q3	3.80, 4.20	3.80, 4.10
Min, Max	3.1, 4.3	3.4, 4.3
Mean change (95% CI)	0.20 (0.07, 0.32)	0.21 (0.09, 0.32)
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	3.74 (0.30)	3.81 (0.23)
Median	3.80	3.80
Q1, Q3	3.60, 3.90	3.70, 4.00
Min, Max	3.1, 4.3	3.3, 4.2
Mean change (95% CI)	-0.00 (-0.09, 0.09)	0.12 (0.03, 0.20)
52 weeks		
n/nmiss	16/5	17/0
Mean (SD)	3.78 (0.47)	3.86 (0.30)
Median	3.80	3.90
Q1, Q3	3.60, 4.10	3.60, 4.00
Min, Max	2.4, 4.4	3.3, 4.4
Mean change (95% CI)	0.10 (-0.07, 0.27)	0.17 (0.06, 0.28)

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
Percentages are based on the number of subjects in the applicable analysis set.

Table 230 Sodium (mmol/L) and mean change from baseline. Extension safety analysis set

Sodium (mmol/L)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Screening		
n/nmiss	20/1	17/0
Mean (SD)	142.0 (1.7)	143.0 (1.1)
Median	142.0	143.0
Q1, Q3	141.0, 143.0	142.0, 144.0
Min, Max	139, 146	141, 145
Mean change (95% CI)		
12 weeks		
n/nmiss	21/0	17/0
Mean (SD)	141.0 (2.1)	142.1 (1.1)
Median	141.0	142.0
Q1, Q3	140.0, 142.0	141.0, 143.0
Min, Max	137, 147	140, 144
Mean change (95% CI)	-1.0 (-1.9, -0.1)	-0.9 (-1.5, -0.3)
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	141.9 (1.5)	142.4 (1.3)
Median	142.0	142.0
Q1, Q3	141.0, 142.0	142.0, 143.0
Min, Max	140, 147	139, 144
Mean change (95% CI)	-0.1 (-0.7, 0.5)	-0.6 (-1.3, 0.0)
52 weeks		
n/nmiss	16/5	17/0
Mean (SD)	140.6 (1.5)	141.8 (1.3)
Median	141.0	142.0
Q1, Q3	139.0, 142.0	141.0, 143.0
Min, Max	138, 143	139, 144
Mean change (95% CI)	-1.7 (-2.5, -0.8)	-1.2 (-1.9, -0.6)

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
Percentages are based on the number of subjects in the applicable analysis set.

14.3.1.3 Derived Safety Variables

Table 231 Creatinine clearance (mL/min) and mean change from baseline. Extension safety analysis set

Creatinine clearance (mL/min)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Screening		
n/nmiss	21/0	16/1
Mean (SD)	146.411 (44.816)	144.067 (37.024)
Median	127.600	131.445
Q1, Q3	109.810, 187.870	121.805, 167.185
Min, Max	89.89, 211.96	97.60, 230.82
Mean change (95% CI)		
12 weeks		
n/nmiss	21/0	17/0
Mean (SD)	145.652 (51.521)	143.681 (35.665)
Median	132.460	134.030
Q1, Q3	101.180, 180.070	121.290, 151.970
Min, Max	81.10, 245.70	99.04, 239.52
Mean change (95% CI)	-0.759 (-8.790, 7.272)	-0.019 (-4.875, 4.836)
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	139.026 (46.641)	144.368 (36.193)
Median	117.860	135.670
Q1, Q3	99.740, 175.300	118.640, 152.620
Min, Max	87.44, 228.70	99.04, 247.05
Mean change (95% CI)	-7.385 (-16.126, 1.357)	0.844 (-5.907, 7.596)
52 weeks		
n/nmiss	16/5	17/0
Mean (SD)	130.374 (54.038)	135.925 (35.853)
Median	105.855	128.930
Q1, Q3	97.925, 149.380	114.820, 147.130
Min, Max	80.22, 242.97	88.26, 218.70
Mean change (95% CI)	-4.239 (-17.667, 9.190)	-7.705 (-13.291, -2.119)

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
Percentages are based on the number of subjects in the applicable analysis set.

Table 232 Estimated glomerular filtration rate (mL/min/1.73 m²) and mean change from baseline. Extension safety analysis set

eGFR (mL/min/1.73 m²)	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)	Placebo/ Dapa 10mg+Exe 2mg (N=17)
Screening		
n/nmiss	21/0	16/1
Mean (SD)	84.924 (17.544)	83.678 (11.818)
Median	83.330	80.690
Q1, Q3	68.980, 96.950	76.195, 92.630
Min, Max	60.82, 126.95	64.29, 108.59
Mean change (95% CI)		
12 weeks		
n/nmiss	21/0	17/0
Mean (SD)	87.767 (20.907)	85.224 (12.027)
Median	84.880	85.580
Q1, Q3	74.680, 98.890	78.250, 91.120
Min, Max	54.81, 133.20	66.25, 115.49
Mean change (95% CI)	2.842 (-1.644, 7.329)	1.064 (-2.305, 4.434)
24 weeks		
n/nmiss	21/0	17/0
Mean (SD)	83.984 (15.698)	85.814 (14.469)
Median	81.040	82.500
Q1, Q3	71.660, 96.570	77.920, 91.120
Min, Max	57.67, 118.27	66.25, 117.34
Mean change (95% CI)	-0.940 (-6.321, 4.440)	1.913 (-2.642, 6.468)
52 weeks		
n/nmiss	16/5	17/0
Mean (SD)	82.061 (16.778)	83.908 (13.775)
Median	82.640	82.500
Q1, Q3	68.885, 89.495	75.350, 87.850
Min, Max	59.52, 118.27	65.26, 119.25
Mean change (95% CI)	1.340 (-5.386, 8.066)	0.195 (-3.145, 3.535)

n/nmiss is the number of subjects with evaluable/missing data, SD = standard deviation, Q1, Q3 = first and third quartiles, CI = confidence interval.
Percentages are based on the number of subjects in the applicable analysis set.

14.3.2 Displays of Adverse Events

14.3.2.1 Overview of Adverse Events

Table 233 Overview of adverse events - Baseline to 52 weeks. Extension safety analysis set

	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)		Placebo/Dapa 10mg+Exe 2mg (N=17)	
	n (%)	m	n (%)	m
Any adverse events	21 (100.0%)	207	17 (100.0%)	133
Any serious adverse events	3 (14.3%)	4	0	0
Adverse events leading to withdrawal	4 (19.0%)	7	0	0
Severity of adverse events				
Mild	21 (100.0%)	148	17 (100.0%)	103
Moderate	15 (71.4%)	55	10 (58.8%)	28
Severe	4 (19.0%)	4	2 (11.8%)	2
Causality of adverse events				
Unlikely related	18 (85.7%)	74	15 (88.2%)	49
Possibly related	20 (95.2%)	128	17 (100.0%)	82
Related	5 (23.8%)	5	2 (11.8%)	2

n is the number of subjects, m is the number of events.
Percentages are based on the number of subjects in the extension safety analysis set.

14.3.2.2 Adverse Events by System Organ Class and Preferred Term

Table 234 Adverse events - Baseline to 24 weeks. Extension safety analysis set

	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21)		Placebo/ Dapa 10mg+Exe 2mg (N=17)	
System organ class/Preferred term	n (%)	m	n (%)	m
Infections and infestations	10 (47.6%)	13	7 (41.2%)	9
Ear infection	1 (4.8%)	1	0	0
Gastroenteritis	0	0	1 (5.9%)	1
Influenza	0	0	2 (11.8%)	2
Localised infection	1 (4.8%)	1	0	0
Nasopharyngitis	8 (38.1%)	8	3 (17.6%)	3
Oral herpes	0	0	1 (5.9%)	1
Pneumonia	1 (4.8%)	1	1 (5.9%)	1
Urinary tract infection	0	0	1 (5.9%)	1
Urinary tract infection fungal	1 (4.8%)	1	0	0
Vaginal infection	1 (4.8%)	1	0	0
Blood and lymphatic system disorders	1 (4.8%)	1	0	0
Anaemia	1 (4.8%)	1	0	0
Metabolism and nutrition disorders	8 (38.1%)	9	3 (17.6%)	3
Decreased appetite	6 (28.6%)	6	2 (11.8%)	2
Hyperlipidaemia	0	0	1 (5.9%)	1
Hypokalaemia	1 (4.8%)	1	0	0
Increased appetite	1 (4.8%)	1	0	0

System organ class/Preferred term	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21) n (%)	m	Placebo/ Dapa 10mg+Exe 2mg (N=17) n (%)	m
Vitamin B12 deficiency	1 (4.8%)	1	0	0
Psychiatric disorders	1 (4.8%)	2	2 (11.8%)	2
Anger	1 (4.8%)	1	0	0
Nervousness	1 (4.8%)	1	0	0
Restlessness	0	0	1 (5.9%)	1
Sleep disorder	0	0	1 (5.9%)	1
Nervous system disorders	10 (47.6%)	19	5 (29.4%)	8
Dizziness	5 (23.8%)	5	2 (11.8%)	2
Head discomfort	1 (4.8%)	1	0	0
Headache	6 (28.6%)	10	4 (23.5%)	4
Hypoaesthesia	1 (4.8%)	1	0	0
Migraine	0	0	1 (5.9%)	1
Tremor	2 (9.5%)	2	1 (5.9%)	1
Eye disorders	1 (4.8%)	1	0	0
Eye allergy	1 (4.8%)	1	0	0
Cardiac disorders	1 (4.8%)	1	0	0
Arrhythmia	1 (4.8%)	1	0	0
Vascular disorders	2 (9.5%)	2	4 (23.5%)	4
Flushing	0	0	1 (5.9%)	1
Hypertension	1 (4.8%)	1	2 (11.8%)	2
Hypotension	0	0	1 (5.9%)	1
Varicose vein	1 (4.8%)	1	0	0
Respiratory, thoracic and mediastinal disorders	4 (19.0%)	6	3 (17.6%)	3
Cough	1 (4.8%)	1	1 (5.9%)	1
Dyspnoea	1 (4.8%)	1	0	0
Oropharyngeal pain	3 (14.3%)	4	0	0
Pharyngeal disorder	0	0	1 (5.9%)	1
Rhinitis allergic	0	0	1 (5.9%)	1
Gastrointestinal disorders	14 (66.7%)	31	10 (58.8%)	12
Abdominal discomfort	1 (4.8%)	1	0	0
Abdominal distension	2 (9.5%)	2	2 (11.8%)	2
Abdominal pain upper	3 (14.3%)	4	2 (11.8%)	2
Constipation	2 (9.5%)	2	1 (5.9%)	1
Diarrhoea	2 (9.5%)	2	2 (11.8%)	2
Dry mouth	1 (4.8%)	1	0	0
Dyspepsia	2 (9.5%)	2	0	0
Gastritis	1 (4.8%)	1	0	0
Gastrooesophageal reflux disease	2 (9.5%)	2	1 (5.9%)	1
Lip swelling	1 (4.8%)	1	0	0
Nausea	7 (33.3%)	8	3 (17.6%)	3
Oesophagitis	1 (4.8%)	1	0	0
Oral pain	1 (4.8%)	1	0	0
Vomiting	2 (9.5%)	3	1 (5.9%)	1

System organ class/Preferred term	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21) n (%)	m	Placebo/ Dapa 10mg+Exe 2mg (N=17) n (%)	m
Hepatobiliary disorders	2 (9.5%)	2	0	0
Cholelithiasis	1 (4.8%)	1	0	0
Hyperbilirubinaemia	1 (4.8%)	1	0	0
Skin and subcutaneous tissue disorders	7 (33.3%)	9	1 (5.9%)	1
Blister	1 (4.8%)	1	0	0
Cold sweat	2 (9.5%)	2	0	0
Erythema	1 (4.8%)	1	0	0
Hyperhidrosis	3 (14.3%)	3	1 (5.9%)	1
Rash pruritic	1 (4.8%)	1	0	0
Skin mass	1 (4.8%)	1	0	0
Musculoskeletal and connective tissue disorders	9 (42.9%)	13	6 (35.3%)	10
Arthralgia	3 (14.3%)	3	3 (17.6%)	3
Back pain	3 (14.3%)	3	2 (11.8%)	3
Joint swelling	2 (9.5%)	3	0	0
Muscle spasms	0	0	1 (5.9%)	1
Myalgia	1 (4.8%)	2	0	0
Osteitis	0	0	1 (5.9%)	1
Pain in extremity	1 (4.8%)	1	0	0
Spinal column stenosis	0	0	1 (5.9%)	1
Synovial cyst	0	0	1 (5.9%)	1
Tendon pain	1 (4.8%)	1	0	0
Renal and urinary disorders	4 (19.0%)	4	6 (35.3%)	6
Pollakiuria	4 (19.0%)	4	5 (29.4%)	5
Urinary incontinence	0	0	1 (5.9%)	1
Congenital, familial and genetic disorders	1 (4.8%)	1	0	0
Polycystic liver disease	1 (4.8%)	1	0	0
General disorders and administration site conditions	14 (66.7%)	30	13 (76.5%)	26
Asthenia	2 (9.5%)	2	0	0
Chest pain	1 (4.8%)	1	1 (5.9%)	1
Early satiety	1 (4.8%)	1	1 (5.9%)	1
Fatigue	3 (14.3%)	3	5 (29.4%)	5
Feeling hot	1 (4.8%)	1	2 (11.8%)	2
Hunger	1 (4.8%)	1	2 (11.8%)	2
Inflammation	1 (4.8%)	2	0	0
Injection site erythema	2 (9.5%)	2	1 (5.9%)	1
Injection site mass	6 (28.6%)	6	5 (29.4%)	5
Injection site nodule	2 (9.5%)	2	0	0
Injection site pruritus	6 (28.6%)	6	2 (11.8%)	2
Injection site rash	0	0	1 (5.9%)	1
Injection site swelling	0	0	1 (5.9%)	1
Peripheral swelling	0	0	2 (11.8%)	2
Pyrexia	2 (9.5%)	2	1 (5.9%)	1
Thirst	1 (4.8%)	1	2 (11.8%)	2
Investigations	0	0	1 (5.9%)	1

System organ class/Preferred term	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21) n (%)	m	Placebo/ Dapa 10mg+Exe 2mg (N=17) n (%)	m
General physical condition abnormal	0	0	1 (5.9%)	1
Injury, poisoning and procedural complications	2 (9.5%)	3	3 (17.6%)	4
Injury	1 (4.8%)	1	0	0
Ligament sprain	1 (4.8%)	1	1 (5.9%)	2
Meniscus injury	0	0	1 (5.9%)	1
Post concussion syndrome	1 (4.8%)	1	0	0
Upper limb fracture	0	0	1 (5.9%)	1
Surgical and medical procedures	0	0	2 (11.8%)	2
Meniscus operation	0	0	1 (5.9%)	1
Spinal laminectomy	0	0	1 (5.9%)	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 extension safety analysis set

Table 235 Adverse events - 24 to 52 weeks. Extension safety analysis set

System organ class/Preferred term	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21) n (%)	m	Placebo/ Dapa 10mg+Exe 2mg (N=17) n (%)	m
Infections and infestations	6 (28.6%)	10	4 (23.5%)	6
Fungal infection	0	0	1 (5.9%)	2
Fungal skin infection	0	0	1 (5.9%)	1
Gastroenteritis	1 (4.8%)	1	0	0
Genital infection fungal	0	0	1 (5.9%)	1
Influenza	1 (4.8%)	1	1 (5.9%)	1
Pneumonia	1 (4.8%)	1	0	0
Post procedural infection	1 (4.8%)	1	0	0
Respiratory tract infection viral	1 (4.8%)	1	0	0
Upper respiratory tract infection	0	0	1 (5.9%)	1
Vaginal infection	2 (9.5%)	5	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (4.8%)	1	1 (5.9%)	1
Adenocarcinoma of colon	1 (4.8%)	1	0	0
Lipoma	0	0	1 (5.9%)	1
Metabolism and nutrition disorders	3 (14.3%)	3	3 (17.6%)	3
Decreased appetite	1 (4.8%)	1	1 (5.9%)	1
Hypercholesterolaemia	0	0	1 (5.9%)	1
Hypokalaemia	1 (4.8%)	1	0	0
Increased appetite	1 (4.8%)	1	1 (5.9%)	1
Nervous system disorders	6 (28.6%)	9	3 (17.6%)	3
Dizziness	3 (14.3%)	3	1 (5.9%)	1
Headache	2 (9.5%)	3	1 (5.9%)	1
Migraine	1 (4.8%)	1	0	0
Tremor	2 (9.5%)	2	1 (5.9%)	1

System organ class/Preferred term	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21) n (%)	m	Placebo/ Dapa 10mg+Exe 2mg (N=17) n (%)	m
Cardiac disorders	0	0	2 (11.8%)	2
Arrhythmia	0	0	1 (5.9%)	1
Ventricular extrasystoles	0	0	1 (5.9%)	1
Vascular disorders	0	0	1 (5.9%)	1
Hypertension	0	0	1 (5.9%)	1
Respiratory, thoracic and mediastinal disorders	1 (4.8%)	2	0	0
Epistaxis	1 (4.8%)	2	0	0
Gastrointestinal disorders	7 (33.3%)	19	8 (47.1%)	10
Abdominal distension	0	0	1 (5.9%)	1
Abdominal pain upper	0	0	2 (11.8%)	2
Constipation	1 (4.8%)	1	1 (5.9%)	1
Diarrhoea	1 (4.8%)	4	1 (5.9%)	1
Dry mouth	0	0	1 (5.9%)	1
Dyspepsia	1 (4.8%)	1	0	0
Gastrointestinal haemorrhage	1 (4.8%)	1	0	0
Gastrooesophageal reflux disease	0	0	1 (5.9%)	1
Haemorrhoids	0	0	1 (5.9%)	1
Nausea	5 (23.8%)	8	1 (5.9%)	1
Vomiting	1 (4.8%)	4	1 (5.9%)	1
Skin and subcutaneous tissue disorders	3 (14.3%)	3	2 (11.8%)	2
Angioedema	1 (4.8%)	1	0	0
Hyperhidrosis	1 (4.8%)	1	1 (5.9%)	1
Rash	0	0	1 (5.9%)	1
Skin ulcer	1 (4.8%)	1	0	0
Musculoskeletal and connective tissue disorders	0	0	2 (11.8%)	2
Arthralgia	0	0	1 (5.9%)	1
Pain in extremity	0	0	1 (5.9%)	1
Renal and urinary disorders	2 (9.5%)	2	6 (35.3%)	6
Nocturia	1 (4.8%)	1	0	0
Pollakiuria	1 (4.8%)	1	6 (35.3%)	6
General disorders and administration site conditions	6 (28.6%)	8	3 (17.6%)	3
Fatigue	3 (14.3%)	3	1 (5.9%)	1
Injection site mass	0	0	1 (5.9%)	1
Peripheral swelling	1 (4.8%)	3	0	0
Pyrexia	1 (4.8%)	1	0	0
Thirst	1 (4.8%)	1	1 (5.9%)	1
Injury, poisoning and procedural complications	2 (9.5%)	2	1 (5.9%)	1
Ligament sprain	1 (4.8%)	1	0	0
Procedural haemorrhage	1 (4.8%)	1	0	0

System organ class/Preferred term	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21) n (%)	m	Placebo/ Dapa 10mg+Exe 2mg (N=17) n (%)	m
Radius fracture	0	0	1 (5.9%)	1
Surgical and medical procedures	1 (4.8%)	1	1 (5.9%)	2
Hip arthroplasty	1 (4.8%)	1	0	0
Skin neoplasm excision	0	0	1 (5.9%)	2

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 extension safety analysis set

Table 236 Adverse events - Baseline to 52 weeks. Extension safety analysis set

System organ class/Preferred term	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21) n (%)	m	Placebo/ Dapa 10mg+Exe 2mg (N=17) n (%)	m
Infections and infestations	13 (61.9%)	23	9 (52.9%)	15
Ear infection	1 (4.8%)	1	0	0
Fungal infection	0	0	1 (5.9%)	2
Fungal skin infection	0	0	1 (5.9%)	1
Gastroenteritis	1 (4.8%)	1	1 (5.9%)	1
Genital infection fungal	0	0	1 (5.9%)	1
Influenza	1 (4.8%)	1	3 (17.6%)	3
Localised infection	1 (4.8%)	1	0	0
Nasopharyngitis	8 (38.1%)	8	3 (17.6%)	3
Oral herpes	0	0	1 (5.9%)	1
Pneumonia	2 (9.5%)	2	1 (5.9%)	1
Post procedural infection	1 (4.8%)	1	0	0
Respiratory tract infection viral	1 (4.8%)	1	0	0
Upper respiratory tract infection	0	0	1 (5.9%)	1
Urinary tract infection	0	0	1 (5.9%)	1
Urinary tract infection fungal	1 (4.8%)	1	0	0
Vaginal infection	2 (9.5%)	6	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (4.8%)	1	1 (5.9%)	1
Adenocarcinoma of colon	1 (4.8%)	1	0	0
Lipoma	0	0	1 (5.9%)	1
Blood and lymphatic system disorders	1 (4.8%)	1	0	0
Anaemia	1 (4.8%)	1	0	0
Metabolism and nutrition disorders	11 (52.4%)	12	5 (29.4%)	6
Decreased appetite	7 (33.3%)	7	2 (11.8%)	3
Hypercholesterolaemia	0	0	1 (5.9%)	1
Hyperlipidaemia	0	0	1 (5.9%)	1
Hypokalaemia	2 (9.5%)	2	0	0
Increased appetite	2 (9.5%)	2	1 (5.9%)	1
Vitamin B12 deficiency	1 (4.8%)	1	0	0
Psychiatric disorders	1 (4.8%)	2	2 (11.8%)	2
Anger	1 (4.8%)	1	0	0

System organ class/Preferred term	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21) n (%)	m	Placebo/ Dapa 10mg+Exe 2mg (N=17) n (%)	m
Nervousness	1 (4.8%)	1	0	0
Restlessness	0	0	1 (5.9%)	1
Sleep disorder	0	0	1 (5.9%)	1
Nervous system disorders	12 (57.1%)	28	7 (41.2%)	11
Dizziness	7 (33.3%)	8	3 (17.6%)	3
Head discomfort	1 (4.8%)	1	0	0
Headache	6 (28.6%)	13	4 (23.5%)	5
Hypoaesthesia	1 (4.8%)	1	0	0
Migraine	1 (4.8%)	1	1 (5.9%)	1
Tremor	3 (14.3%)	4	2 (11.8%)	2
Eye disorders	1 (4.8%)	1	0	0
Eye allergy	1 (4.8%)	1	0	0
Cardiac disorders	1 (4.8%)	1	2 (11.8%)	2
Arrhythmia	1 (4.8%)	1	1 (5.9%)	1
Ventricular extrasystoles	0	0	1 (5.9%)	1
Vascular disorders	2 (9.5%)	2	5 (29.4%)	5
Flushing	0	0	1 (5.9%)	1
Hypertension	1 (4.8%)	1	3 (17.6%)	3
Hypotension	0	0	1 (5.9%)	1
Varicose vein	1 (4.8%)	1	0	0
Respiratory, thoracic and mediastinal disorders	5 (23.8%)	8	3 (17.6%)	3
Cough	1 (4.8%)	1	1 (5.9%)	1
Dyspnoea	1 (4.8%)	1	0	0
Epistaxis	1 (4.8%)	2	0	0
Oropharyngeal pain	3 (14.3%)	4	0	0
Pharyngeal disorder	0	0	1 (5.9%)	1
Rhinitis allergic	0	0	1 (5.9%)	1
Gastrointestinal disorders	15 (71.4%)	50	13 (76.5%)	22
Abdominal discomfort	1 (4.8%)	1	0	0
Abdominal distension	2 (9.5%)	2	2 (11.8%)	3
Abdominal pain upper	3 (14.3%)	4	4 (23.5%)	4
Constipation	3 (14.3%)	3	2 (11.8%)	2
Diarrhoea	3 (14.3%)	6	3 (17.6%)	3
Dry mouth	1 (4.8%)	1	1 (5.9%)	1
Dyspepsia	3 (14.3%)	3	0	0
Gastritis	1 (4.8%)	1	0	0
Gastrointestinal haemorrhage	1 (4.8%)	1	0	0
Gastrooesophageal reflux disease	2 (9.5%)	2	2 (11.8%)	2
Haemorrhoids	0	0	1 (5.9%)	1
Lip swelling	1 (4.8%)	1	0	0
Nausea	9 (42.9%)	16	4 (23.5%)	4
Oesophagitis	1 (4.8%)	1	0	0
Oral pain	1 (4.8%)	1	0	0
Vomiting	3 (14.3%)	7	2 (11.8%)	2

System organ class/Preferred term	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21) n (%)	m	Placebo/ Dapa 10mg+Exe 2mg (N=17) n (%)	m
Hepatobiliary disorders	2 (9.5%)	2	0	0
Cholelithiasis	1 (4.8%)	1	0	0
Hyperbilirubinaemia	1 (4.8%)	1	0	0
Skin and subcutaneous tissue disorders	9 (42.9%)	12	3 (17.6%)	3
Angioedema	1 (4.8%)	1	0	0
Blister	1 (4.8%)	1	0	0
Cold sweat	2 (9.5%)	2	0	0
Erythema	1 (4.8%)	1	0	0
Hyperhidrosis	3 (14.3%)	4	2 (11.8%)	2
Rash	0	0	1 (5.9%)	1
Rash pruritic	1 (4.8%)	1	0	0
Skin mass	1 (4.8%)	1	0	0
Skin ulcer	1 (4.8%)	1	0	0
Musculoskeletal and connective tissue disorders	9 (42.9%)	13	7 (41.2%)	12
Arthralgia	3 (14.3%)	3	4 (23.5%)	4
Back pain	3 (14.3%)	3	2 (11.8%)	3
Joint swelling	2 (9.5%)	3	0	0
Muscle spasms	0	0	1 (5.9%)	1
Myalgia	1 (4.8%)	2	0	0
Osteitis	0	0	1 (5.9%)	1
Pain in extremity	1 (4.8%)	1	1 (5.9%)	1
Spinal column stenosis	0	0	1 (5.9%)	1
Synovial cyst	0	0	1 (5.9%)	1
Tendon pain	1 (4.8%)	1	0	0
Renal and urinary disorders	6 (28.6%)	6	12 (70.6%)	12
Nocturia	1 (4.8%)	1	0	0
Pollakiuria	5 (23.8%)	5	11 (64.7%)	11
Urinary incontinence	0	0	1 (5.9%)	1
Congenital, familial and genetic disorders	1 (4.8%)	1	0	0
Polycystic liver disease	1 (4.8%)	1	0	0
General disorders and administration site conditions	16 (76.2%)	38	13 (76.5%)	29
Asthenia	2 (9.5%)	2	0	0
Chest pain	1 (4.8%)	1	1 (5.9%)	1
Early satiety	1 (4.8%)	1	1 (5.9%)	1
Fatigue	4 (19.0%)	6	6 (35.3%)	6
Feeling hot	1 (4.8%)	1	2 (11.8%)	2
Hunger	1 (4.8%)	1	2 (11.8%)	2
Inflammation	1 (4.8%)	2	0	0
Injection site erythema	2 (9.5%)	2	1 (5.9%)	1
Injection site mass	6 (28.6%)	6	6 (35.3%)	6
Injection site nodule	2 (9.5%)	2	0	0
Injection site pruritus	6 (28.6%)	6	2 (11.8%)	2
Injection site rash	0	0	1 (5.9%)	1
Injection site swelling	0	0	1 (5.9%)	1
Peripheral swelling	1 (4.8%)	3	2 (11.8%)	2

System organ class/Preferred term	Dapa 10mg+Exe 2mg/ Dapa 10mg+Exe 2mg (N=21) n (%)	m	Placebo/ Dapa 10mg+Exe 2mg (N=17) n (%)	m
Pyrexia	3 (14.3%)	3	1 (5.9%)	1
Thirst	2 (9.5%)	2	3 (17.6%)	3
Investigations	0	0	1 (5.9%)	1
General physical condition abnormal	0	0	1 (5.9%)	1
Injury, poisoning and procedural complications	4 (19.0%)	5	4 (23.5%)	5
Injury	1 (4.8%)	1	0	0
Ligament sprain	2 (9.5%)	2	1 (5.9%)	2
Meniscus injury	0	0	1 (5.9%)	1
Post concussion syndrome	1 (4.8%)	1	0	0
Procedural haemorrhage	1 (4.8%)	1	0	0
Radius fracture	0	0	1 (5.9%)	1
Upper limb fracture	0	0	1 (5.9%)	1
Surgical and medical procedures	1 (4.8%)	1	3 (17.6%)	4
Hip arthroplasty	1 (4.8%)	1	0	0
Meniscus operation	0	0	1 (5.9%)	1
Skin neoplasm excision	0	0	1 (5.9%)	2
Spinal laminectomy	0	0	1 (5.9%)	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 extension safety analysis set

14.3.2.3 Adverse Events by Severity. Dapa+Exe/Dapa+Exe Group

Table 237 Adverse events by severity - Baseline to 24 weeks. Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension safety analysis set

	MILD		MODERATE		SEVERE	
System organ class/Preferred term	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**
Infections and infestations	8 (38.1%)	10	2 (9.5%)	3	0	0
Ear infection	0	0	1 (4.8%)	1	0	0
Localised infection	1 (4.8%)	1	0	0	0	0
Nasopharyngitis	7 (33.3%)	7	1 (4.8%)	1	0	0
Pneumonia	1 (4.8%)	1	0	0	0	0
Urinary tract infection fungal	1 (4.8%)	1	0	0	0	0
Vaginal infection	0	0	1 (4.8%)	1	0	0
Blood and lymphatic system disorders	0	0	1 (4.8%)	1	0	0
Anaemia	0	0	1 (4.8%)	1	0	0
Metabolism and nutrition disorders	8 (38.1%)	9	0	0	0	0
Decreased appetite	6 (28.6%)	6	0	0	0	0
Hypokalaemia	1 (4.8%)	1	0	0	0	0
Increased appetite	1 (4.8%)	1	0	0	0	0
Vitamin B12 deficiency	1 (4.8%)	1	0	0	0	0
Psychiatric disorders	1 (4.8%)	2	0	0	0	0
Anger	1 (4.8%)	1	0	0	0	0
Nervousness	1 (4.8%)	1	0	0	0	0
Nervous system disorders	9 (42.9%)	17	2 (9.5%)	2	0	0
Dizziness	5 (23.8%)	5	0	0	0	0
Head discomfort	1 (4.8%)	1	0	0	0	0
Headache	5 (23.8%)	8	2 (9.5%)	2	0	0
Hypoaesthesia	1 (4.8%)	1	0	0	0	0
Tremor	2 (9.5%)	2	0	0	0	0
Eye disorders	1 (4.8%)	1	0	0	0	0

System organ class/Preferred term	MILD n (%)	MILD m	MODERATE n (%)	MODERATE m	SEVERE n (%)	SEVERE m
Eye allergy	1 (4.8%)	1	0	0	0	0
Cardiac disorders	0	0	1 (4.8%)	1	0	0
Arrhythmia	0	0	1 (4.8%)	1	0	0
Vascular disorders	1 (4.8%)	1	1 (4.8%)	1	0	0
Hypertension	1 (4.8%)	1	0	0	0	0
Varicose vein	0	0	1 (4.8%)	1	0	0
Respiratory, thoracic and mediastinal disorders	4 (19.0%)	4	1 (4.8%)	2	0	0
Cough	0	0	1 (4.8%)	1	0	0
Dyspnoea	1 (4.8%)	1	0	0	0	0
Oropharyngeal pain	3 (14.3%)	3	1 (4.8%)	1	0	0
Gastrointestinal disorders	12 (57.1%)	22	6 (28.6%)	9	0	0
Abdominal discomfort	1 (4.8%)	1	0	0	0	0
Abdominal distension	2 (9.5%)	2	0	0	0	0
Abdominal pain upper	1 (4.8%)	1	3 (14.3%)	3	0	0
Constipation	2 (9.5%)	2	0	0	0	0
Diarrhoea	0	0	2 (9.5%)	2	0	0
Dry mouth	1 (4.8%)	1	0	0	0	0
Dyspepsia	2 (9.5%)	2	0	0	0	0
Gastritis	1 (4.8%)	1	0	0	0	0
Gastrooesophageal reflux disease	2 (9.5%)	2	0	0	0	0
Lip swelling	0	0	1 (4.8%)	1	0	0
Nausea	5 (23.8%)	6	2 (9.5%)	2	0	0
Oesophagitis	1 (4.8%)	1	0	0	0	0
Oral pain	0	0	1 (4.8%)	1	0	0
Vomiting	2 (9.5%)	3	0	0	0	0
Hepatobiliary disorders	2 (9.5%)	2	0	0	0	0
Cholelithiasis	1 (4.8%)	1	0	0	0	0
Hyperbilirubinaemia	1 (4.8%)	1	0	0	0	0

	MILD		MODERATE		SEVERE	
System organ class/Preferred term	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**
Skin and subcutaneous tissue disorders	4 (19.0%)	5	3 (14.3%)	4	0	0
Blister	0	0	1 (4.8%)	1	0	0
Cold sweat	1 (4.8%)	1	1 (4.8%)	1	0	0
Erythema	0	0	1 (4.8%)	1	0	0
Hyperhidrosis	3 (14.3%)	3	0	0	0	0
Rash pruritic	0	0	1 (4.8%)	1	0	0
Skin mass	1 (4.8%)	1	0	0	0	0
Musculoskeletal and connective tissue disorders	4 (19.0%)	5	5 (23.8%)	8	0	0
Arthralgia	1 (4.8%)	1	2 (9.5%)	2	0	0
Back pain	2 (9.5%)	2	1 (4.8%)	1	0	0
Joint swelling	0	0	2 (9.5%)	3	0	0
Myalgia	1 (4.8%)	2	0	0	0	0
Pain in extremity	0	0	1 (4.8%)	1	0	0
Tendon pain	0	0	1 (4.8%)	1	0	0
Renal and urinary disorders	4 (19.0%)	4	0	0	0	0
Pollakiuria	4 (19.0%)	4	0	0	0	0
Congenital, familial and genetic disorders	1 (4.8%)	1	0	0	0	0
Polycystic liver disease	1 (4.8%)	1	0	0	0	0
General disorders and administration site conditions	14 (66.7%)	27	2 (9.5%)	3	0	0
Asthenia	2 (9.5%)	2	0	0	0	0
Chest pain	1 (4.8%)	1	0	0	0	0
Early satiety	1 (4.8%)	1	0	0	0	0
Fatigue	3 (14.3%)	3	0	0	0	0
Feeling hot	1 (4.8%)	1	0	0	0	0
Hunger	1 (4.8%)	1	0	0	0	0
Inflammation	0	0	1 (4.8%)	2	0	0
Injection site erythema	2 (9.5%)	2	0	0	0	0
Injection site mass	6 (28.6%)	6	0	0	0	0
Injection site nodule	2 (9.5%)	2	0	0	0	0
Injection site pruritus	6 (28.6%)	6	0	0	0	0

	MILD		MODERATE		SEVERE	
System organ class/Preferred term	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**
Pyrexia	1 (4.8%)	1	1 (4.8%)	1	0	0
Thirst	1 (4.8%)	1	0	0	0	0
Injury, poisoning and procedural complications	0	0	2 (9.5%)	2	1 (4.8%)	1
Injury	0	0	0	0	1 (4.8%)	1
Ligament sprain	0	0	1 (4.8%)	1	0	0
Post concussion syndrome	0	0	1 (4.8%)	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 extension safety analysis set.

Table 238 Adverse events by severity - 24 to 52 weeks. Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension safety analysis set

	MILD		MODERATE		SEVERE	
System organ class/Preferred term	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**
Infections and infestations	4 (19.0%)	7	2 (9.5%)	3	0	0
Gastroenteritis	1 (4.8%)	1	0	0	0	0
Influenza	1 (4.8%)	1	0	0	0	0
Pneumonia	0	0	1 (4.8%)	1	0	0
Post procedural infection	0	0	1 (4.8%)	1	0	0
Respiratory tract infection viral	0	0	1 (4.8%)	1	0	0
Vaginal infection	2 (9.5%)	5	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	0	1 (4.8%)	1
Adenocarcinoma of colon	0	0	0	0	1 (4.8%)	1
Metabolism and nutrition disorders	3 (14.3%)	3	0	0	0	0
Decreased appetite	1 (4.8%)	1	0	0	0	0
Hypokalaemia	1 (4.8%)	1	0	0	0	0
Increased appetite	1 (4.8%)	1	0	0	0	0
Nervous system disorders	6 (28.6%)	8	1 (4.8%)	1	0	0
Dizziness	3 (14.3%)	3	0	0	0	0
Headache	2 (9.5%)	3	0	0	0	0
Migraine	0	0	1 (4.8%)	1	0	0
Tremor	2 (9.5%)	2	0	0	0	0
Respiratory, thoracic and mediastinal disorders	1 (4.8%)	2	0	0	0	0
Epistaxis	1 (4.8%)	2	0	0	0	0
Gastrointestinal disorders	5 (23.8%)	6	2 (9.5%)	13	0	0
Constipation	1 (4.8%)	1	0	0	0	0
Diarrhoea	0	0	1 (4.8%)	4	0	0
Dyspepsia	1 (4.8%)	1	0	0	0	0
Gastrointestinal haemorrhage	0	0	1 (4.8%)	1	0	0
Nausea	4 (19.0%)	4	1 (4.8%)	4	0	0
Vomiting	0	0	1 (4.8%)	4	0	0

System organ class/Preferred term	MILD n (%)	MILD m	MODERATE n (%)	MODERATE m	SEVERE n (%)	SEVERE m
Skin and subcutaneous tissue disorders	2 (9.5%)	2	0	0	1 (4.8%)	1
Angioedema	0	0	0	0	1 (4.8%)	1
Hyperhidrosis	1 (4.8%)	1	0	0	0	0
Skin ulcer	1 (4.8%)	1	0	0	0	0
Renal and urinary disorders	2 (9.5%)	2	0	0	0	0
Nocturia	1 (4.8%)	1	0	0	0	0
Pollakiuria	1 (4.8%)	1	0	0	0	0
General disorders and administration site conditions	5 (23.8%)	7	1 (4.8%)	1	0	0
Fatigue	3 (14.3%)	3	0	0	0	0
Peripheral swelling	1 (4.8%)	3	0	0	0	0
Pyrexia	0	0	1 (4.8%)	1	0	0
Thirst	1 (4.8%)	1	0	0	0	0
Injury, poisoning and procedural complications	1 (4.8%)	1	1 (4.8%)	1	0	0
Ligament sprain	1 (4.8%)	1	0	0	0	0
Procedural haemorrhage	0	0	1 (4.8%)	1	0	0
Surgical and medical procedures	0	0	0	0	1 (4.8%)	1
Hip arthroplasty	0	0	0	0	1 (4.8%)	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 extension safety analysis set.

Table 239 Adverse events by severity - Baseline to 52 weeks. Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg. Extension safety analysis set

	MILD		MODERATE		SEVERE	
System organ class/Preferred term	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**
Infections and infestations	10 (47.6%)	17	4 (19.0%)	6	0	0
Ear infection	0	0	1 (4.8%)	1	0	0
Gastroenteritis	1 (4.8%)	1	0	0	0	0
Influenza	1 (4.8%)	1	0	0	0	0
Localised infection	1 (4.8%)	1	0	0	0	0
Nasopharyngitis	7 (33.3%)	7	1 (4.8%)	1	0	0
Pneumonia	1 (4.8%)	1	1 (4.8%)	1	0	0
Post procedural infection	0	0	1 (4.8%)	1	0	0
Respiratory tract infection viral	0	0	1 (4.8%)	1	0	0
Urinary tract infection fungal	1 (4.8%)	1	0	0	0	0
Vaginal infection	2 (9.5%)	5	1 (4.8%)	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	0	1 (4.8%)	1
Adenocarcinoma of colon	0	0	0	0	1 (4.8%)	1
Blood and lymphatic system disorders	0	0	1 (4.8%)	1	0	0
Anaemia	0	0	1 (4.8%)	1	0	0
Metabolism and nutrition disorders	11 (52.4%)	12	0	0	0	0
Decreased appetite	7 (33.3%)	7	0	0	0	0
Hypokalaemia	2 (9.5%)	2	0	0	0	0
Increased appetite	2 (9.5%)	2	0	0	0	0
Vitamin B12 deficiency	1 (4.8%)	1	0	0	0	0
Psychiatric disorders	1 (4.8%)	2	0	0	0	0
Anger	1 (4.8%)	1	0	0	0	0
Nervousness	1 (4.8%)	1	0	0	0	0
Nervous system disorders	11 (52.4%)	25	3 (14.3%)	3	0	0
Dizziness	7 (33.3%)	8	0	0	0	0
Head discomfort	1 (4.8%)	1	0	0	0	0
Headache	5 (23.8%)	11	2 (9.5%)	2	0	0

System organ class/Preferred term	MILD n (%)	MILD m	MODERATE n (%)	MODERATE m	SEVERE n (%)	SEVERE m
Hypoaesthesia	1 (4.8%)	1	0	0	0	0
Migraine	0	0	1 (4.8%)	1	0	0
Tremor	3 (14.3%)	4	0	0	0	0
Eye disorders	1 (4.8%)	1	0	0	0	0
Eye allergy	1 (4.8%)	1	0	0	0	0
Cardiac disorders	0	0	1 (4.8%)	1	0	0
Arrhythmia	0	0	1 (4.8%)	1	0	0
Vascular disorders	1 (4.8%)	1	1 (4.8%)	1	0	0
Hypertension	1 (4.8%)	1	0	0	0	0
Varicose vein	0	0	1 (4.8%)	1	0	0
Respiratory, thoracic and mediastinal disorders	5 (23.8%)	6	1 (4.8%)	2	0	0
Cough	0	0	1 (4.8%)	1	0	0
Dyspnoea	1 (4.8%)	1	0	0	0	0
Epistaxis	1 (4.8%)	2	0	0	0	0
Oropharyngeal pain	3 (14.3%)	3	1 (4.8%)	1	0	0
Gastrointestinal disorders	12 (57.1%)	28	8 (38.1%)	22	0	0
Abdominal discomfort	1 (4.8%)	1	0	0	0	0
Abdominal distension	2 (9.5%)	2	0	0	0	0
Abdominal pain upper	1 (4.8%)	1	3 (14.3%)	3	0	0
Constipation	3 (14.3%)	3	0	0	0	0
Diarrhoea	0	0	3 (14.3%)	6	0	0
Dry mouth	1 (4.8%)	1	0	0	0	0
Dyspepsia	3 (14.3%)	3	0	0	0	0
Gastritis	1 (4.8%)	1	0	0	0	0
Gastrointestinal haemorrhage	0	0	1 (4.8%)	1	0	0
Gastrooesophageal reflux disease	2 (9.5%)	2	0	0	0	0
Lip swelling	0	0	1 (4.8%)	1	0	0
Nausea	7 (33.3%)	10	3 (14.3%)	6	0	0
Oesophagitis	1 (4.8%)	1	0	0	0	0

System organ class/Preferred term	MILD n (%)	MILD m	MODERATE n (%)	MODERATE m	SEVERE n (%)	SEVERE m
Oral pain	0	0	1 (4.8%)	1	0	0
Vomiting	2 (9.5%)	3	1 (4.8%)	4	0	0
Hepatobiliary disorders	2 (9.5%)	2	0	0	0	0
Cholelithiasis	1 (4.8%)	1	0	0	0	0
Hyperbilirubinaemia	1 (4.8%)	1	0	0	0	0
Skin and subcutaneous tissue disorders	5 (23.8%)	7	3 (14.3%)	4	1 (4.8%)	1
Angioedema	0	0	0	0	1 (4.8%)	1
Blister	0	0	1 (4.8%)	1	0	0
Cold sweat	1 (4.8%)	1	1 (4.8%)	1	0	0
Erythema	0	0	1 (4.8%)	1	0	0
Hyperhidrosis	3 (14.3%)	4	0	0	0	0
Rash pruritic	0	0	1 (4.8%)	1	0	0
Skin mass	1 (4.8%)	1	0	0	0	0
Skin ulcer	1 (4.8%)	1	0	0	0	0
Musculoskeletal and connective tissue disorders	4 (19.0%)	5	5 (23.8%)	8	0	0
Arthralgia	1 (4.8%)	1	2 (9.5%)	2	0	0
Back pain	2 (9.5%)	2	1 (4.8%)	1	0	0
Joint swelling	0	0	2 (9.5%)	3	0	0
Myalgia	1 (4.8%)	2	0	0	0	0
Pain in extremity	0	0	1 (4.8%)	1	0	0
Tendon pain	0	0	1 (4.8%)	1	0	0
Renal and urinary disorders	6 (28.6%)	6	0	0	0	0
Nocturia	1 (4.8%)	1	0	0	0	0
Pollakiuria	5 (23.8%)	5	0	0	0	0
Congenital, familial and genetic disorders	1 (4.8%)	1	0	0	0	0
Polycystic liver disease	1 (4.8%)	1	0	0	0	0
General disorders and administration site conditions	15 (71.4%)	34	3 (14.3%)	4	0	0
Asthenia	2 (9.5%)	2	0	0	0	0

System organ class/Preferred term	MILD n (%)	MILD m	MODERATE n (%)	MODERATE m	SEVERE n (%)	SEVERE m
Chest pain	1 (4.8%)	1	0	0	0	0
Early satiety	1 (4.8%)	1	0	0	0	0
Fatigue	4 (19.0%)	6	0	0	0	0
Feeling hot	1 (4.8%)	1	0	0	0	0
Hunger	1 (4.8%)	1	0	0	0	0
Inflammation	0	0	1 (4.8%)	2	0	0
Injection site erythema	2 (9.5%)	2	0	0	0	0
Injection site mass	6 (28.6%)	6	0	0	0	0
Injection site nodule	2 (9.5%)	2	0	0	0	0
Injection site pruritus	6 (28.6%)	6	0	0	0	0
Peripheral swelling	1 (4.8%)	3	0	0	0	0
Pyrexia	1 (4.8%)	1	2 (9.5%)	2	0	0
Thirst	2 (9.5%)	2	0	0	0	0
Injury, poisoning and procedural complications	1 (4.8%)	1	3 (14.3%)	3	1 (4.8%)	1
Injury	0	0	0	0	1 (4.8%)	1
Ligament sprain	1 (4.8%)	1	1 (4.8%)	1	0	0
Post concussion syndrome	0	0	1 (4.8%)	1	0	0
Procedural haemorrhage	0	0	1 (4.8%)	1	0	0
Surgical and medical procedures	0	0	0	0	1 (4.8%)	1
Hip arthroplasty	0	0	0	0	1 (4.8%)	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 extension safety analysis set.

14.3.2.4 Adverse Events by Severity. Placebo/Dapa+Exe Group

Table 240 Adverse events by severity - Baseline to 24 weeks. Placebo/Dapa 10mg+Exe 2mg. Extension safety analysis set

	MILD		MODERATE		SEVERE	
System organ class/Preferred term	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**
Infections and infestations	3 (17.6%)	5	4 (23.5%)	4	0	0
Gastroenteritis	0	0	1 (5.9%)	1	0	0
Influenza	0	0	2 (11.8%)	2	0	0
Nasopharyngitis	3 (17.6%)	3	0	0	0	0
Oral herpes	1 (5.9%)	1	0	0	0	0
Pneumonia	0	0	1 (5.9%)	1	0	0
Urinary tract infection	1 (5.9%)	1	0	0	0	0
Metabolism and nutrition disorders	3 (17.6%)	3	0	0	0	0
Decreased appetite	2 (11.8%)	2	0	0	0	0
Hyperlipidaemia	1 (5.9%)	1	0	0	0	0
Psychiatric disorders	2 (11.8%)	2	0	0	0	0
Restlessness	1 (5.9%)	1	0	0	0	0
Sleep disorder	1 (5.9%)	1	0	0	0	0
Nervous system disorders	4 (23.5%)	6	2 (11.8%)	2	0	0
Dizziness	2 (11.8%)	2	0	0	0	0
Headache	3 (17.6%)	3	1 (5.9%)	1	0	0
Migraine	0	0	1 (5.9%)	1	0	0
Tremor	1 (5.9%)	1	0	0	0	0
Vascular disorders	4 (23.5%)	4	0	0	0	0
Flushing	1 (5.9%)	1	0	0	0	0
Hypertension	2 (11.8%)	2	0	0	0	0
Hypotension	1 (5.9%)	1	0	0	0	0
Respiratory, thoracic and mediastinal disorders	2 (11.8%)	2	1 (5.9%)	1	0	0
Cough	0	0	1 (5.9%)	1	0	0
Pharyngeal disorder	1 (5.9%)	1	0	0	0	0

System organ class/Preferred term	MILD n (%)	MILD m	MODERATE n (%)	MODERATE m	SEVERE n (%)	SEVERE m
Rhinitis allergic	1 (5.9%)	1	0	0	0	0
Gastrointestinal disorders	10 (58.8%)	11	1 (5.9%)	1	0	0
Abdominal distension	2 (11.8%)	2	0	0	0	0
Abdominal pain upper	2 (11.8%)	2	0	0	0	0
Constipation	1 (5.9%)	1	0	0	0	0
Diarrhoea	2 (11.8%)	2	0	0	0	0
Gastrooesophageal reflux disease	1 (5.9%)	1	0	0	0	0
Nausea	3 (17.6%)	3	0	0	0	0
Vomiting	0	0	1 (5.9%)	1	0	0
Skin and subcutaneous tissue disorders	1 (5.9%)	1	0	0	0	0
Hyperhidrosis	1 (5.9%)	1	0	0	0	0
Musculoskeletal and connective tissue disorders	3 (17.6%)	4	4 (23.5%)	6	0	0
Arthralgia	0	0	3 (17.6%)	3	0	0
Back pain	1 (5.9%)	2	1 (5.9%)	1	0	0
Muscle spasms	0	0	1 (5.9%)	1	0	0
Osteitis	1 (5.9%)	1	0	0	0	0
Spinal column stenosis	0	0	1 (5.9%)	1	0	0
Synovial cyst	1 (5.9%)	1	0	0	0	0
Renal and urinary disorders	6 (35.3%)	6	0	0	0	0
Pollakiuria	5 (29.4%)	5	0	0	0	0
Urinary incontinence	1 (5.9%)	1	0	0	0	0
General disorders and administration site conditions	12 (70.6%)	22	4 (23.5%)	4	0	0
Chest pain	0	0	1 (5.9%)	1	0	0
Early satiety	1 (5.9%)	1	0	0	0	0
Fatigue	5 (29.4%)	5	0	0	0	0
Feeling hot	2 (11.8%)	2	0	0	0	0
Hunger	2 (11.8%)	2	0	0	0	0
Injection site erythema	1 (5.9%)	1	0	0	0	0
Injection site mass	3 (17.6%)	3	2 (11.8%)	2	0	0

	MILD		MODERATE		SEVERE	
System organ class/Preferred term	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**
Injection site pruritus	2 (11.8%)	2	0	0	0	0
Injection site rash	1 (5.9%)	1	0	0	0	0
Injection site swelling	1 (5.9%)	1	0	0	0	0
Peripheral swelling	2 (11.8%)	2	0	0	0	0
Pyrexia	0	0	1 (5.9%)	1	0	0
Thirst	2 (11.8%)	2	0	0	0	0
Investigations	1 (5.9%)	1	0	0	0	0
General physical condition abnormal	1 (5.9%)	1	0	0	0	0
Injury, poisoning and procedural complications	1 (5.9%)	1	2 (11.8%)	3	0	0
Ligament sprain	0	0	1 (5.9%)	2	0	0
Meniscus injury	1 (5.9%)	1	0	0	0	0
Upper limb fracture	0	0	1 (5.9%)	1	0	0
Surgical and medical procedures	0	0	1 (5.9%)	1	1 (5.9%)	1
Meniscus operation	0	0	0	0	1 (5.9%)	1
Spinal laminectomy	0	0	1 (5.9%)	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 extension safety analysis set.

Table 241 Adverse events by severity - 24 to 52 weeks. Placebo/Dapa 10mg+Exe 2mg. Extension safety analysis set

	MILD		MODERATE		SEVERE	
System organ class/Preferred term	n (%)	m	n (%)	m	n (%)	m
Infections and infestations	4 (23.5%)	6	0	0	0	0
Fungal infection	1 (5.9%)	2	0	0	0	0
Fungal skin infection	1 (5.9%)	1	0	0	0	0
Genital infection fungal	1 (5.9%)	1	0	0	0	0
Influenza	1 (5.9%)	1	0	0	0	0
Upper respiratory tract infection	1 (5.9%)	1	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (5.9%)	1	0	0	0	0
Lipoma	1 (5.9%)	1	0	0	0	0
Metabolism and nutrition disorders	3 (17.6%)	3	0	0	0	0
Decreased appetite	1 (5.9%)	1	0	0	0	0
Hypercholesterolaemia	1 (5.9%)	1	0	0	0	0
Increased appetite	1 (5.9%)	1	0	0	0	0
Nervous system disorders	3 (17.6%)	3	0	0	0	0
Dizziness	1 (5.9%)	1	0	0	0	0
Headache	1 (5.9%)	1	0	0	0	0
Tremor	1 (5.9%)	1	0	0	0	0
Cardiac disorders	1 (5.9%)	1	1 (5.9%)	1	0	0
Arrhythmia	0	0	1 (5.9%)	1	0	0
Ventricular extrasystoles	1 (5.9%)	1	0	0	0	0
Vascular disorders	1 (5.9%)	1	0	0	0	0
Hypertension	1 (5.9%)	1	0	0	0	0
Gastrointestinal disorders	7 (41.2%)	8	1 (5.9%)	2	0	0
Abdominal distension	1 (5.9%)	1	0	0	0	0
Abdominal pain upper	2 (11.8%)	2	0	0	0	0
Constipation	1 (5.9%)	1	0	0	0	0
Diarrhoea	0	0	1 (5.9%)	1	0	0

System organ class/Preferred term	MILD n (%)	MILD m	MODERATE n (%)	MODERATE m	SEVERE n (%)	SEVERE m
Dry mouth	1 (5.9%)	1	0	0	0	0
Gastrooesophageal reflux disease	0	0	1 (5.9%)	1	0	0
Haemorrhoids	1 (5.9%)	1	0	0	0	0
Nausea	1 (5.9%)	1	0	0	0	0
Vomiting	1 (5.9%)	1	0	0	0	0
Skin and subcutaneous tissue disorders	2 (11.8%)	2	0	0	0	0
Hyperhidrosis	1 (5.9%)	1	0	0	0	0
Rash	1 (5.9%)	1	0	0	0	0
Musculoskeletal and connective tissue disorders	0	0	2 (11.8%)	2	0	0
Arthralgia	0	0	1 (5.9%)	1	0	0
Pain in extremity	0	0	1 (5.9%)	1	0	0
Renal and urinary disorders	6 (35.3%)	6	0	0	0	0
Pollakiuria	6 (35.3%)	6	0	0	0	0
General disorders and administration site conditions	3 (17.6%)	3	0	0	0	0
Fatigue	1 (5.9%)	1	0	0	0	0
Injection site mass	1 (5.9%)	1	0	0	0	0
Thirst	1 (5.9%)	1	0	0	0	0
Injury, poisoning and procedural complications	0	0	1 (5.9%)	1	0	0
Radius fracture	0	0	1 (5.9%)	1	0	0
Surgical and medical procedures	1 (5.9%)	1	0	0	1 (5.9%)	1
Skin neoplasm excision	1 (5.9%)	1	0	0	1 (5.9%)	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 extension safety analysis set.

Table 242 Adverse events by severity - Baseline to 52 weeks. Placebo/Dapa 10mg+Exe 2mg. Extension safety analysis set

	MILD		MODERATE		SEVERE	
System organ class/Preferred term	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**
Infections and infestations	7 (41.2%)	11	4 (23.5%)	4	0	0
Fungal infection	1 (5.9%)	2	0	0	0	0
Fungal skin infection	1 (5.9%)	1	0	0	0	0
Gastroenteritis	0	0	1 (5.9%)	1	0	0
Genital infection fungal	1 (5.9%)	1	0	0	0	0
Influenza	1 (5.9%)	1	2 (11.8%)	2	0	0
Nasopharyngitis	3 (17.6%)	3	0	0	0	0
Oral herpes	1 (5.9%)	1	0	0	0	0
Pneumonia	0	0	1 (5.9%)	1	0	0
Upper respiratory tract infection	1 (5.9%)	1	0	0	0	0
Urinary tract infection	1 (5.9%)	1	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (5.9%)	1	0	0	0	0
Lipoma	1 (5.9%)	1	0	0	0	0
Metabolism and nutrition disorders	5 (29.4%)	6	0	0	0	0
Decreased appetite	2 (11.8%)	3	0	0	0	0
Hypercholesterolaemia	1 (5.9%)	1	0	0	0	0
Hyperlipidaemia	1 (5.9%)	1	0	0	0	0
Increased appetite	1 (5.9%)	1	0	0	0	0
Psychiatric disorders	2 (11.8%)	2	0	0	0	0
Restlessness	1 (5.9%)	1	0	0	0	0
Sleep disorder	1 (5.9%)	1	0	0	0	0
Nervous system disorders	6 (35.3%)	9	2 (11.8%)	2	0	0
Dizziness	3 (17.6%)	3	0	0	0	0
Headache	3 (17.6%)	4	1 (5.9%)	1	0	0
Migraine	0	0	1 (5.9%)	1	0	0
Tremor	2 (11.8%)	2	0	0	0	0
Cardiac disorders	1 (5.9%)	1	1 (5.9%)	1	0	0

	MILD		MODERATE		SEVERE	
System organ class/Preferred term	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**
Arrhythmia	0	0	1 (5.9%)	1	0	0
Ventricular extrasystoles	1 (5.9%)	1	0	0	0	0
Vascular disorders	5 (29.4%)	5	0	0	0	0
Flushing	1 (5.9%)	1	0	0	0	0
Hypertension	3 (17.6%)	3	0	0	0	0
Hypotension	1 (5.9%)	1	0	0	0	0
Respiratory, thoracic and mediastinal disorders	2 (11.8%)	2	1 (5.9%)	1	0	0
Cough	0	0	1 (5.9%)	1	0	0
Pharyngeal disorder	1 (5.9%)	1	0	0	0	0
Rhinitis allergic	1 (5.9%)	1	0	0	0	0
Gastrointestinal disorders	13 (76.5%)	19	1 (5.9%)	3	0	0
Abdominal distension	2 (11.8%)	3	0	0	0	0
Abdominal pain upper	4 (23.5%)	4	0	0	0	0
Constipation	2 (11.8%)	2	0	0	0	0
Diarrhoea	2 (11.8%)	2	1 (5.9%)	1	0	0
Dry mouth	1 (5.9%)	1	0	0	0	0
Gastrooesophageal reflux disease	1 (5.9%)	1	1 (5.9%)	1	0	0
Haemorrhoids	1 (5.9%)	1	0	0	0	0
Nausea	4 (23.5%)	4	0	0	0	0
Vomiting	1 (5.9%)	1	1 (5.9%)	1	0	0
Skin and subcutaneous tissue disorders	3 (17.6%)	3	0	0	0	0
Hyperhidrosis	2 (11.8%)	2	0	0	0	0
Rash	1 (5.9%)	1	0	0	0	0
Musculoskeletal and connective tissue disorders	3 (17.6%)	4	5 (29.4%)	8	0	0
Arthralgia	0	0	4 (23.5%)	4	0	0
Back pain	1 (5.9%)	2	1 (5.9%)	1	0	0
Muscle spasms	0	0	1 (5.9%)	1	0	0
Osteitis	1 (5.9%)	1	0	0	0	0
Pain in extremity	0	0	1 (5.9%)	1	0	0

System organ class/Preferred term	MILD n (%)	MILD m	MODERATE n (%)	MODERATE m	SEVERE n (%)	SEVERE m
Spinal column stenosis	0	0	1 (5.9%)	1	0	0
Synovial cyst	1 (5.9%)	1	0	0	0	0
Renal and urinary disorders	12 (70.6%)	12	0	0	0	0
Pollakiuria	11 (64.7%)	11	0	0	0	0
Urinary incontinence	1 (5.9%)	1	0	0	0	0
General disorders and administration site conditions	12 (70.6%)	25	4 (23.5%)	4	0	0
Chest pain	0	0	1 (5.9%)	1	0	0
Early satiety	1 (5.9%)	1	0	0	0	0
Fatigue	6 (35.3%)	6	0	0	0	0
Feeling hot	2 (11.8%)	2	0	0	0	0
Hunger	2 (11.8%)	2	0	0	0	0
Injection site erythema	1 (5.9%)	1	0	0	0	0
Injection site mass	4 (23.5%)	4	2 (11.8%)	2	0	0
Injection site pruritus	2 (11.8%)	2	0	0	0	0
Injection site rash	1 (5.9%)	1	0	0	0	0
Injection site swelling	1 (5.9%)	1	0	0	0	0
Peripheral swelling	2 (11.8%)	2	0	0	0	0
Pyrexia	0	0	1 (5.9%)	1	0	0
Thirst	3 (17.6%)	3	0	0	0	0
Investigations	1 (5.9%)	1	0	0	0	0
General physical condition abnormal	1 (5.9%)	1	0	0	0	0
Injury, poisoning and procedural complications	1 (5.9%)	1	3 (17.6%)	4	0	0
Ligament sprain	0	0	1 (5.9%)	2	0	0
Meniscus injury	1 (5.9%)	1	0	0	0	0
Radius fracture	0	0	1 (5.9%)	1	0	0
Upper limb fracture	0	0	1 (5.9%)	1	0	0
Surgical and medical procedures	1 (5.9%)	1	1 (5.9%)	1	2 (11.8%)	2
Meniscus operation	0	0	0	0	1 (5.9%)	1
Skin neoplasm excision	1 (5.9%)	1	0	0	1 (5.9%)	1

	MILD		MODERATE		SEVERE	
System organ class/Preferred term	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**
Spinal laminectomy	0	0	1 (5.9%)	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 extension safety analysis set.

14.3.2.5 Adverse Events by Relation to Investigational Product.

Table 243 Adverse events by relation to IP - Baseline to 24 weeks. Extension safety analysis set

	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)				Placebo/Dapa 10mg+Exe 2mg (N=17)			
	Not Related		Related		Not Related		Related	
System organ class/Preferred term	n (%)	m	n (%)	m	n (%)	m	n (%)	m
Infections and infestations	9 (42.9%)	11	2 (9.5%)	2	7 (41.2%)	8	1 (5.9%)	1
Ear infection	1 (4.8%)	1	0	0	0	0	0	0
Gastroenteritis	0	0	0	0	1 (5.9%)	1	0	0
Influenza	0	0	0	0	2 (11.8%)	2	0	0
Localised infection	1 (4.8%)	1	0	0	0	0	0	0
Nasopharyngitis	8 (38.1%)	8	0	0	3 (17.6%)	3	0	0
Oral herpes	0	0	0	0	1 (5.9%)	1	0	0
Pneumonia	1 (4.8%)	1	0	0	1 (5.9%)	1	0	0
Urinary tract infection	0	0	0	0	0	0	1 (5.9%)	1
Urinary tract infection fungal	0	0	1 (4.8%)	1	0	0	0	0
Vaginal infection	0	0	1 (4.8%)	1	0	0	0	0
Blood and lymphatic system disorders	1 (4.8%)	1	0	0	0	0	0	0
Anaemia	1 (4.8%)	1	0	0	0	0	0	0
Metabolism and nutrition disorders	1 (4.8%)	2	7 (33.3%)	7	0	0	3 (17.6%)	3
Decreased appetite	0	0	6 (28.6%)	6	0	0	2 (11.8%)	2
Hyperlipidaemia	0	0	0	0	0	0	1 (5.9%)	1
Hypokalaemia	1 (4.8%)	1	0	0	0	0	0	0
Increased appetite	0	0	1 (4.8%)	1	0	0	0	0
Vitamin B12 deficiency	1 (4.8%)	1	0	0	0	0	0	0
Psychiatric disorders	0	0	1 (4.8%)	2	1 (5.9%)	1	1 (5.9%)	1
Anger	0	0	1 (4.8%)	1	0	0	0	0
Nervousness	0	0	1 (4.8%)	1	0	0	0	0
Restlessness	0	0	0	0	0	0	1 (5.9%)	1
Sleep disorder	0	0	0	0	1 (5.9%)	1	0	0

System organ class/Preferred term	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)				Placebo/Dapa 10mg+Exe 2mg (N=17)			
	Not Related		Related		Not Related		Related	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m
Nervous system disorders	4 (19.0%)	5	8 (38.1%)	14	1 (5.9%)	1	5 (29.4%)	7
Dizziness	0	0	5 (23.8%)	5	0	0	2 (11.8%)	2
Head discomfort	1 (4.8%)	1	0	0	0	0	0	0
Headache	3 (14.3%)	3	4 (19.0%)	7	0	0	4 (23.5%)	4
Hypoaesthesia	1 (4.8%)	1	0	0	0	0	0	0
Migraine	0	0	0	0	1 (5.9%)	1	0	0
Tremor	0	0	2 (9.5%)	2	0	0	1 (5.9%)	1
Eye disorders	1 (4.8%)	1	0	0	0	0	0	0
Eye allergy	1 (4.8%)	1	0	0	0	0	0	0
Cardiac disorders	1 (4.8%)	1	0	0	0	0	0	0
Arrhythmia	1 (4.8%)	1	0	0	0	0	0	0
Vascular disorders	2 (9.5%)	2	0	0	3 (17.6%)	3	1 (5.9%)	1
Flushing	0	0	0	0	1 (5.9%)	1	0	0
Hypertension	1 (4.8%)	1	0	0	2 (11.8%)	2	0	0
Hypotension	0	0	0	0	0	0	1 (5.9%)	1
Varicose vein	1 (4.8%)	1	0	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders	4 (19.0%)	6	0	0	3 (17.6%)	3	0	0
Cough	1 (4.8%)	1	0	0	1 (5.9%)	1	0	0
Dyspnoea	1 (4.8%)	1	0	0	0	0	0	0
Oropharyngeal pain	3 (14.3%)	4	0	0	0	0	0	0
Pharyngeal disorder	0	0	0	0	1 (5.9%)	1	0	0
Rhinitis allergic	0	0	0	0	1 (5.9%)	1	0	0
Gastrointestinal disorders	3 (14.3%)	3	13 (61.9%)	28	3 (17.6%)	3	8 (47.1%)	9
Abdominal discomfort	0	0	1 (4.8%)	1	0	0	0	0
Abdominal distension	0	0	2 (9.5%)	2	0	0	2 (11.8%)	2
Abdominal pain upper	0	0	3 (14.3%)	4	0	0	2 (11.8%)	2

	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)				Placebo/Dapa 10mg+Exe 2mg (N=17)			
	Not Related		Related		Not Related		Related	
System organ class/Preferred term	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**
Constipation	0	0	2 (9.5%)	2	0	0	1 (5.9%)	1
Diarrhoea	0	0	2 (9.5%)	2	0	0	2 (11.8%)	2
Dry mouth	0	0	1 (4.8%)	1	0	0	0	0
Dyspepsia	0	0	2 (9.5%)	2	0	0	0	0
Gastritis	0	0	1 (4.8%)	1	0	0	0	0
Gastrooesophageal reflux disease	1 (4.8%)	1	1 (4.8%)	1	1 (5.9%)	1	0	0
Lip swelling	0	0	1 (4.8%)	1	0	0	0	0
Nausea	2 (9.5%)	2	5 (23.8%)	6	1 (5.9%)	1	2 (11.8%)	2
Oesophagitis	0	0	1 (4.8%)	1	0	0	0	0
Oral pain	0	0	1 (4.8%)	1	0	0	0	0
Vomiting	0	0	2 (9.5%)	3	1 (5.9%)	1	0	0
Hepatobiliary disorders	2 (9.5%)	2	0	0	0	0	0	0
Cholelithiasis	1 (4.8%)	1	0	0	0	0	0	0
Hyperbilirubinaemia	1 (4.8%)	1	0	0	0	0	0	0
Skin and subcutaneous tissue disorders	1 (4.8%)	1	6 (28.6%)	8	0	0	1 (5.9%)	1
Blister	0	0	1 (4.8%)	1	0	0	0	0
Cold sweat	0	0	2 (9.5%)	2	0	0	0	0
Erythema	0	0	1 (4.8%)	1	0	0	0	0
Hyperhidrosis	1 (4.8%)	1	2 (9.5%)	2	0	0	1 (5.9%)	1
Rash pruritic	0	0	1 (4.8%)	1	0	0	0	0
Skin mass	0	0	1 (4.8%)	1	0	0	0	0
Musculoskeletal and connective tissue disorders	6 (28.6%)	8	4 (19.0%)	5	4 (23.5%)	5	3 (17.6%)	5
Arthralgia	2 (9.5%)	2	1 (4.8%)	1	2 (11.8%)	2	1 (5.9%)	1
Back pain	1 (4.8%)	1	2 (9.5%)	2	0	0	2 (11.8%)	3
Joint swelling	1 (4.8%)	1	1 (4.8%)	2	0	0	0	0
Muscle spasms	0	0	0	0	0	0	1 (5.9%)	1
Myalgia	1 (4.8%)	2	0	0	0	0	0	0
Osteitis	0	0	0	0	1 (5.9%)	1	0	0
Pain in extremity	1 (4.8%)	1	0	0	0	0	0	0

	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)				Placebo/Dapa 10mg+Exe 2mg (N=17)			
	Not Related		Related		Not Related		Related	
System organ class/Preferred term	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**
Spinal column stenosis	0	0	0	0	1 (5.9%)	1	0	0
Synovial cyst	0	0	0	0	1 (5.9%)	1	0	0
Tendon pain	1 (4.8%)	1	0	0	0	0	0	0
Renal and urinary disorders	0	0	4 (19.0%)	4	1 (5.9%)	1	5 (29.4%)	5
Pollakiuria	0	0	4 (19.0%)	4	0	0	5 (29.4%)	5
Urinary incontinence	0	0	0	0	1 (5.9%)	1	0	0
Congenital, familial and genetic disorders	1 (4.8%)	1	0	0	0	0	0	0
Polycystic liver disease	1 (4.8%)	1	0	0	0	0	0	0
General disorders and administration site conditions	5 (23.8%)	6	12 (57.1%)	24	4 (23.5%)	4	12 (70.6%)	22
Asthenia	1 (4.8%)	1	1 (4.8%)	1	0	0	0	0
Chest pain	1 (4.8%)	1	0	0	1 (5.9%)	1	0	0
Early satiety	0	0	1 (4.8%)	1	0	0	1 (5.9%)	1
Fatigue	1 (4.8%)	1	2 (9.5%)	2	0	0	5 (29.4%)	5
Feeling hot	0	0	1 (4.8%)	1	0	0	2 (11.8%)	2
Hunger	0	0	1 (4.8%)	1	1 (5.9%)	1	1 (5.9%)	1
Inflammation	1 (4.8%)	1	1 (4.8%)	1	0	0	0	0
Injection site erythema	0	0	2 (9.5%)	2	0	0	1 (5.9%)	1
Injection site mass	0	0	6 (28.6%)	6	0	0	5 (29.4%)	5
Injection site nodule	0	0	2 (9.5%)	2	0	0	0	0
Injection site pruritus	0	0	6 (28.6%)	6	0	0	2 (11.8%)	2
Injection site rash	0	0	0	0	0	0	1 (5.9%)	1
Injection site swelling	0	0	0	0	0	0	1 (5.9%)	1
Peripheral swelling	0	0	0	0	1 (5.9%)	1	1 (5.9%)	1
Pyrexia	2 (9.5%)	2	0	0	1 (5.9%)	1	0	0
Thirst	0	0	1 (4.8%)	1	0	0	2 (11.8%)	2
Investigations	0	0	0	0	0	0	1 (5.9%)	1
General physical condition abnormal	0	0	0	0	0	0	1 (5.9%)	1

	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)				Placebo/Dapa 10mg+Exe 2mg (N=17)			
	Not Related		Related		Not Related		Related	
System organ class/Preferred term	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**
Injury, poisoning and procedural complications	2 (9.5%)	3	0	0	3 (17.6%)	4	0	0
Injury	1 (4.8%)	1	0	0	0	0	0	0
Ligament sprain	1 (4.8%)	1	0	0	1 (5.9%)	2	0	0
Meniscus injury	0	0	0	0	1 (5.9%)	1	0	0
Post concussion syndrome	1 (4.8%)	1	0	0	0	0	0	0
Upper limb fracture	0	0	0	0	1 (5.9%)	1	0	0
Surgical and medical procedures	0	0	0	0	2 (11.8%)	2	0	0
Meniscus operation	0	0	0	0	1 (5.9%)	1	0	0
Spinal laminectomy	0	0	0	0	1 (5.9%)	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.
Related= possibly related or related; Not related= unlikely related.
Percentages are based on the number of subjects in the extension safety analysis set.

Table 244 Adverse events by relation to IP - 24 to 52 weeks. Extension safety analysis set

	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)				Placebo/Dapa 10mg+Exe 2mg (N=17)			
	Not Related		Related		Not Related		Related	
System organ class/Preferred term	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**
Infections and infestations	4 (19.0%)	5	2 (9.5%)	5	2 (11.8%)	2	2 (11.8%)	4
Fungal infection	0	0	0	0	0	0	1 (5.9%)	2
Fungal skin infection	0	0	0	0	0	0	1 (5.9%)	1
Gastroenteritis	1 (4.8%)	1	0	0	0	0	0	0
Genital infection fungal	0	0	0	0	0	0	1 (5.9%)	1
Influenza	1 (4.8%)	1	0	0	1 (5.9%)	1	0	0
Pneumonia	1 (4.8%)	1	0	0	0	0	0	0
Post procedural infection	1 (4.8%)	1	0	0	0	0	0	0
Respiratory tract infection viral	1 (4.8%)	1	0	0	0	0	0	0
Upper respiratory tract infection	0	0	0	0	1 (5.9%)	1	0	0
Vaginal infection	0	0	2 (9.5%)	5	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (4.8%)	1	0	0	1 (5.9%)	1	0	0
Adenocarcinoma of colon	1 (4.8%)	1	0	0	0	0	0	0
Lipoma	0	0	0	0	1 (5.9%)	1	0	0
Metabolism and nutrition disorders	1 (4.8%)	1	2 (9.5%)	2	1 (5.9%)	1	2 (11.8%)	2
Decreased appetite	0	0	1 (4.8%)	1	0	0	1 (5.9%)	1
Hypercholesterolaemia	0	0	0	0	1 (5.9%)	1	0	0
Hypokalaemia	1 (4.8%)	1	0	0	0	0	0	0
Increased appetite	0	0	1 (4.8%)	1	0	0	1 (5.9%)	1
Nervous system disorders	2 (9.5%)	4	4 (19.0%)	5	0	0	3 (17.6%)	3
Dizziness	1 (4.8%)	1	2 (9.5%)	2	0	0	1 (5.9%)	1
Headache	1 (4.8%)	2	1 (4.8%)	1	0	0	1 (5.9%)	1
Migraine	1 (4.8%)	1	0	0	0	0	0	0
Tremor	0	0	2 (9.5%)	2	0	0	1 (5.9%)	1
Cardiac disorders	0	0	0	0	1 (5.9%)	1	1 (5.9%)	1

	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)				Placebo/Dapa 10mg+Exe 2mg (N=17)			
	Not Related		Related		Not Related		Related	
System organ class/Preferred term	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**
Arrhythmia	0	0	0	0	0	0	1 (5.9%)	1
Ventricular extrasystoles	0	0	0	0	1 (5.9%)	1	0	0
Vascular disorders	0	0	0	0	0	0	1 (5.9%)	1
Hypertension	0	0	0	0	0	0	1 (5.9%)	1
Respiratory, thoracic and mediastinal disorders	1 (4.8%)	2	0	0	0	0	0	0
Epistaxis	1 (4.8%)	2	0	0	0	0	0	0
Gastrointestinal disorders	3 (14.3%)	3	4 (19.0%)	16	3 (17.6%)	3	6 (35.3%)	7
Abdominal distension	0	0	0	0	0	0	1 (5.9%)	1
Abdominal pain upper	0	0	0	0	0	0	2 (11.8%)	2
Constipation	1 (4.8%)	1	0	0	0	0	1 (5.9%)	1
Diarrhoea	0	0	1 (4.8%)	4	0	0	1 (5.9%)	1
Dry mouth	0	0	0	0	0	0	1 (5.9%)	1
Dyspepsia	0	0	1 (4.8%)	1	0	0	0	0
Gastrointestinal haemorrhage	1 (4.8%)	1	0	0	0	0	0	0
Gastrooesophageal reflux disease	0	0	0	0	1 (5.9%)	1	0	0
Haemorrhoids	0	0	0	0	1 (5.9%)	1	0	0
Nausea	1 (4.8%)	1	4 (19.0%)	7	0	0	1 (5.9%)	1
Vomiting	0	0	1 (4.8%)	4	1 (5.9%)	1	0	0
Skin and subcutaneous tissue disorders	1 (4.8%)	1	2 (9.5%)	2	0	0	2 (11.8%)	2
Angioedema	0	0	1 (4.8%)	1	0	0	0	0
Hyperhidrosis	0	0	1 (4.8%)	1	0	0	1 (5.9%)	1
Rash	0	0	0	0	0	0	1 (5.9%)	1
Skin ulcer	1 (4.8%)	1	0	0	0	0	0	0
Musculoskeletal and connective tissue disorders	0	0	0	0	2 (11.8%)	2	0	0
Arthralgia	0	0	0	0	1 (5.9%)	1	0	0
Pain in extremity	0	0	0	0	1 (5.9%)	1	0	0

	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)				Placebo/Dapa 10mg+Exe 2mg (N=17)			
	Not Related		Related		Not Related		Related	
System organ class/Preferred term	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**
Renal and urinary disorders	0	0	2 (9.5%)	2	0	0	6 (35.3%)	6
Nocturia	0	0	1 (4.8%)	1	0	0	0	0
Pollakiuria	0	0	1 (4.8%)	1	0	0	6 (35.3%)	6
General disorders and administration site conditions	1 (4.8%)	1	5 (23.8%)	7	1 (5.9%)	1	2 (11.8%)	2
Fatigue	1 (4.8%)	1	2 (9.5%)	2	1 (5.9%)	1	0	0
Injection site mass	0	0	0	0	0	0	1 (5.9%)	1
Peripheral swelling	0	0	1 (4.8%)	3	0	0	0	0
Pyrexia	0	0	1 (4.8%)	1	0	0	0	0
Thirst	0	0	1 (4.8%)	1	0	0	1 (5.9%)	1
Injury, poisoning and procedural complications	2 (9.5%)	2	0	0	1 (5.9%)	1	0	0
Ligament sprain	1 (4.8%)	1	0	0	0	0	0	0
Procedural haemorrhage	1 (4.8%)	1	0	0	0	0	0	0
Radius fracture	0	0	0	0	1 (5.9%)	1	0	0
Surgical and medical procedures	1 (4.8%)	1	0	0	1 (5.9%)	2	0	0
Hip arthroplasty	1 (4.8%)	1	0	0	0	0	0	0
Skin neoplasm excision	0	0	0	0	1 (5.9%)	2	0	0

Adverse events are coded according to MedDRA version 18.0E.
n is the number of subjects, m is the number of events.
Related= possibly related or related; Not related= unlikely related.
Percentages are based on the number of subjects in the extension safety analysis set.

Table 245 Adverse events by relation to IP - Baseline to 52 weeks. Extension safety analysis set

	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)				Placebo/Dapa 10mg+Exe 2mg (N=17)			
	Not Related		Related		Not Related		Related	
System organ class/Preferred term	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**
Infections and infestations	12 (57.1%)	16	3 (14.3%)	7	8 (47.1%)	10	3 (17.6%)	5
Ear infection	1 (4.8%)	1	0	0	0	0	0	0
Fungal infection	0	0	0	0	0	0	1 (5.9%)	2
Fungal skin infection	0	0	0	0	0	0	1 (5.9%)	1
Gastroenteritis	1 (4.8%)	1	0	0	1 (5.9%)	1	0	0
Genital infection fungal	0	0	0	0	0	0	1 (5.9%)	1
Influenza	1 (4.8%)	1	0	0	3 (17.6%)	3	0	0
Localised infection	1 (4.8%)	1	0	0	0	0	0	0
Nasopharyngitis	8 (38.1%)	8	0	0	3 (17.6%)	3	0	0
Oral herpes	0	0	0	0	1 (5.9%)	1	0	0
Pneumonia	2 (9.5%)	2	0	0	1 (5.9%)	1	0	0
Post procedural infection	1 (4.8%)	1	0	0	0	0	0	0
Respiratory tract infection viral	1 (4.8%)	1	0	0	0	0	0	0
Upper respiratory tract infection	0	0	0	0	1 (5.9%)	1	0	0
Urinary tract infection	0	0	0	0	0	0	1 (5.9%)	1
Urinary tract infection fungal	0	0	1 (4.8%)	1	0	0	0	0
Vaginal infection	0	0	2 (9.5%)	6	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (4.8%)	1	0	0	1 (5.9%)	1	0	0
Adenocarcinoma of colon	1 (4.8%)	1	0	0	0	0	0	0
Lipoma	0	0	0	0	1 (5.9%)	1	0	0
Blood and lymphatic system disorders	1 (4.8%)	1	0	0	0	0	0	0
Anaemia	1 (4.8%)	1	0	0	0	0	0	0
Metabolism and nutrition disorders	2 (9.5%)	3	9 (42.9%)	9	1 (5.9%)	1	4 (23.5%)	5
Decreased appetite	0	0	7 (33.3%)	7	0	0	2 (11.8%)	3
Hypercholesterolaemia	0	0	0	0	1 (5.9%)	1	0	0
Hyperlipidaemia	0	0	0	0	0	0	1 (5.9%)	1

	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)				Placebo/Dapa 10mg+Exe 2mg (N=17)			
	Not Related		Related		Not Related		Related	
System organ class/Preferred term	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**
Hypokalaemia	2 (9.5%)	2	0	0	0	0	0	0
Increased appetite	0	0	2 (9.5%)	2	0	0	1 (5.9%)	1
Vitamin B12 deficiency	1 (4.8%)	1	0	0	0	0	0	0
Psychiatric disorders	0	0	1 (4.8%)	2	1 (5.9%)	1	1 (5.9%)	1
Anger	0	0	1 (4.8%)	1	0	0	0	0
Nervousness	0	0	1 (4.8%)	1	0	0	0	0
Restlessness	0	0	0	0	0	0	1 (5.9%)	1
Sleep disorder	0	0	0	0	1 (5.9%)	1	0	0
Nervous system disorders	6 (28.6%)	9	10 (47.6%)	19	1 (5.9%)	1	7 (41.2%)	10
Dizziness	1 (4.8%)	1	6 (28.6%)	7	0	0	3 (17.6%)	3
Head discomfort	1 (4.8%)	1	0	0	0	0	0	0
Headache	4 (19.0%)	5	5 (23.8%)	8	0	0	4 (23.5%)	5
Hypoaesthesia	1 (4.8%)	1	0	0	0	0	0	0
Migraine	1 (4.8%)	1	0	0	1 (5.9%)	1	0	0
Tremor	0	0	3 (14.3%)	4	0	0	2 (11.8%)	2
Eye disorders	1 (4.8%)	1	0	0	0	0	0	0
Eye allergy	1 (4.8%)	1	0	0	0	0	0	0
Cardiac disorders	1 (4.8%)	1	0	0	1 (5.9%)	1	1 (5.9%)	1
Arrhythmia	1 (4.8%)	1	0	0	0	0	1 (5.9%)	1
Ventricular extrasystoles	0	0	0	0	1 (5.9%)	1	0	0
Vascular disorders	2 (9.5%)	2	0	0	3 (17.6%)	3	2 (11.8%)	2
Flushing	0	0	0	0	1 (5.9%)	1	0	0
Hypertension	1 (4.8%)	1	0	0	2 (11.8%)	2	1 (5.9%)	1
Hypotension	0	0	0	0	0	0	1 (5.9%)	1
Varicose vein	1 (4.8%)	1	0	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders	5 (23.8%)	8	0	0	3 (17.6%)	3	0	0

	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)				Placebo/Dapa 10mg+Exe 2mg (N=17)			
	Not Related		Related		Not Related		Related	
System organ class/Preferred term	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**
Cough	1 (4.8%)	1	0	0	1 (5.9%)	1	0	0
Dyspnoea	1 (4.8%)	1	0	0	0	0	0	0
Epistaxis	1 (4.8%)	2	0	0	0	0	0	0
Oropharyngeal pain	3 (14.3%)	4	0	0	0	0	0	0
Pharyngeal disorder	0	0	0	0	1 (5.9%)	1	0	0
Rhinitis allergic	0	0	0	0	1 (5.9%)	1	0	0
Gastrointestinal disorders	5 (23.8%)	6	14 (66.7%)	44	5 (29.4%)	6	11 (64.7%)	16
Abdominal discomfort	0	0	1 (4.8%)	1	0	0	0	0
Abdominal distension	0	0	2 (9.5%)	2	0	0	2 (11.8%)	3
Abdominal pain upper	0	0	3 (14.3%)	4	0	0	4 (23.5%)	4
Constipation	1 (4.8%)	1	2 (9.5%)	2	0	0	2 (11.8%)	2
Diarrhoea	0	0	3 (14.3%)	6	0	0	3 (17.6%)	3
Dry mouth	0	0	1 (4.8%)	1	0	0	1 (5.9%)	1
Dyspepsia	0	0	3 (14.3%)	3	0	0	0	0
Gastritis	0	0	1 (4.8%)	1	0	0	0	0
Gastrointestinal haemorrhage	1 (4.8%)	1	0	0	0	0	0	0
Gastrooesophageal reflux disease	1 (4.8%)	1	1 (4.8%)	1	2 (11.8%)	2	0	0
Haemorrhoids	0	0	0	0	1 (5.9%)	1	0	0
Lip swelling	0	0	1 (4.8%)	1	0	0	0	0
Nausea	3 (14.3%)	3	6 (28.6%)	13	1 (5.9%)	1	3 (17.6%)	3
Oesophagitis	0	0	1 (4.8%)	1	0	0	0	0
Oral pain	0	0	1 (4.8%)	1	0	0	0	0
Vomiting	0	0	3 (14.3%)	7	2 (11.8%)	2	0	0
Hepatobiliary disorders	2 (9.5%)	2	0	0	0	0	0	0
Cholelithiasis	1 (4.8%)	1	0	0	0	0	0	0
Hyperbilirubinaemia	1 (4.8%)	1	0	0	0	0	0	0
Skin and subcutaneous tissue disorders	2 (9.5%)	2	7 (33.3%)	10	0	0	3 (17.6%)	3
Angioedema	0	0	1 (4.8%)	1	0	0	0	0
Blister	0	0	1 (4.8%)	1	0	0	0	0

	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)				Placebo/Dapa 10mg+Exe 2mg (N=17)			
	Not Related		Related		Not Related		Related	
System organ class/Preferred term	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**
Cold sweat	0	0	2 (9.5%)	2	0	0	0	0
Erythema	0	0	1 (4.8%)	1	0	0	0	0
Hyperhidrosis	1 (4.8%)	1	2 (9.5%)	3	0	0	2 (11.8%)	2
Rash	0	0	0	0	0	0	1 (5.9%)	1
Rash pruritic	0	0	1 (4.8%)	1	0	0	0	0
Skin mass	0	0	1 (4.8%)	1	0	0	0	0
Skin ulcer	1 (4.8%)	1	0	0	0	0	0	0
Musculoskeletal and connective tissue disorders	6 (28.6%)	8	4 (19.0%)	5	5 (29.4%)	7	3 (17.6%)	5
Arthralgia	2 (9.5%)	2	1 (4.8%)	1	3 (17.6%)	3	1 (5.9%)	1
Back pain	1 (4.8%)	1	2 (9.5%)	2	0	0	2 (11.8%)	3
Joint swelling	1 (4.8%)	1	1 (4.8%)	2	0	0	0	0
Muscle spasms	0	0	0	0	0	0	1 (5.9%)	1
Myalgia	1 (4.8%)	2	0	0	0	0	0	0
Osteitis	0	0	0	0	1 (5.9%)	1	0	0
Pain in extremity	1 (4.8%)	1	0	0	1 (5.9%)	1	0	0
Spinal column stenosis	0	0	0	0	1 (5.9%)	1	0	0
Synovial cyst	0	0	0	0	1 (5.9%)	1	0	0
Tendon pain	1 (4.8%)	1	0	0	0	0	0	0
Renal and urinary disorders	0	0	6 (28.6%)	6	1 (5.9%)	1	11 (64.7%)	11
Nocturia	0	0	1 (4.8%)	1	0	0	0	0
Pollakiuria	0	0	5 (23.8%)	5	0	0	11 (64.7%)	11
Urinary incontinence	0	0	0	0	1 (5.9%)	1	0	0
Congenital, familial and genetic disorders	1 (4.8%)	1	0	0	0	0	0	0
Polycystic liver disease	1 (4.8%)	1	0	0	0	0	0	0
General disorders and administration site conditions	6 (28.6%)	7	13 (61.9%)	31	5 (29.4%)	5	12 (70.6%)	24
Asthenia	1 (4.8%)	1	1 (4.8%)	1	0	0	0	0
Chest pain	1 (4.8%)	1	0	0	1 (5.9%)	1	0	0
Early satiety	0	0	1 (4.8%)	1	0	0	1 (5.9%)	1

	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)				Placebo/Dapa 10mg+Exe 2mg (N=17)			
	Not Related		Related		Not Related		Related	
System organ class/Preferred term	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**
Fatigue	2 (9.5%)	2	2 (9.5%)	4	1 (5.9%)	1	5 (29.4%)	5
Feeling hot	0	0	1 (4.8%)	1	0	0	2 (11.8%)	2
Hunger	0	0	1 (4.8%)	1	1 (5.9%)	1	1 (5.9%)	1
Inflammation	1 (4.8%)	1	1 (4.8%)	1	0	0	0	0
Injection site erythema	0	0	2 (9.5%)	2	0	0	1 (5.9%)	1
Injection site mass	0	0	6 (28.6%)	6	0	0	6 (35.3%)	6
Injection site nodule	0	0	2 (9.5%)	2	0	0	0	0
Injection site pruritus	0	0	6 (28.6%)	6	0	0	2 (11.8%)	2
Injection site rash	0	0	0	0	0	0	1 (5.9%)	1
Injection site swelling	0	0	0	0	0	0	1 (5.9%)	1
Peripheral swelling	0	0	1 (4.8%)	3	1 (5.9%)	1	1 (5.9%)	1
Pyrexia	2 (9.5%)	2	1 (4.8%)	1	1 (5.9%)	1	0	0
Thirst	0	0	2 (9.5%)	2	0	0	3 (17.6%)	3
Investigations	0	0	0	0	0	0	1 (5.9%)	1
General physical condition abnormal	0	0	0	0	0	0	1 (5.9%)	1
Injury, poisoning and procedural complications	4 (19.0%)	5	0	0	4 (23.5%)	5	0	0
Injury	1 (4.8%)	1	0	0	0	0	0	0
Ligament sprain	2 (9.5%)	2	0	0	1 (5.9%)	2	0	0
Meniscus injury	0	0	0	0	1 (5.9%)	1	0	0
Post concussion syndrome	1 (4.8%)	1	0	0	0	0	0	0
Procedural haemorrhage	1 (4.8%)	1	0	0	0	0	0	0
Radius fracture	0	0	0	0	1 (5.9%)	1	0	0
Upper limb fracture	0	0	0	0	1 (5.9%)	1	0	0
Surgical and medical procedures	1 (4.8%)	1	0	0	3 (17.6%)	4	0	0
Hip arthroplasty	1 (4.8%)	1	0	0	0	0	0	0
Meniscus operation	0	0	0	0	1 (5.9%)	1	0	0
Skin neoplasm excision	0	0	0	0	1 (5.9%)	2	0	0

System organ class/Preferred term	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)				Placebo/Dapa 10mg+Exe 2mg (N=17)			
	Not Related		Related		Not Related		Related	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m
Spinal laminectomy	0	0	0	0	1 (5.9%)	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.
Related= (Possible related, Related), Not related= (unlikely related).
Percentages are based on the number of subjects in the extension safety analysis set.

14.3.2.6 Adverse Events Leading to Withdrawal of Investigational Product

Table 246 Adverse events leading to withdrawal of IP - Baseline to 52 weeks. Extension safety analysis set

	Dapa 10mg+Exe 2mg/Dapa 10mg+Exe 2mg (N=21)		Placebo/Dapa 10mg+Exe 2mg (N=17)	
System organ class/Preferred term	**n (%)**	**m**	**n (%)**	**m**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (4.8%)	1	0	0
Adenocarcinoma of colon	1 (4.8%)	1	0	0
Nervous system disorders	1 (4.8%)	1	0	0
Dizziness	1 (4.8%)	1	0	0
Eye disorders	1 (4.8%)	1	0	0
Eye allergy	1 (4.8%)	1	0	0
Gastrointestinal disorders	2 (9.5%)	2	0	0
Gastrointestinal haemorrhage	1 (4.8%)	1	0	0
Nausea	1 (4.8%)	1	0	0
Skin and subcutaneous tissue disorders	1 (4.8%)	1	0	0
Angioedema	1 (4.8%)	1	0	0
General disorders and administration site conditions	1 (4.8%)	1	0	0
Fatigue	1 (4.8%)	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 extension 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

Narratives are provided in Section 12.5.2.

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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) (Main study)

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

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 Subjects Excluded From the Efficacy Analysis

16.2.4 Demographic Data

16.2.5 Compliance

16.2.6 Individual Efficacy Response Data

16.2.7 Adverse Event Listings (Each Patient)

16.2.8 Individual Laboratory Measurements by Patient

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)

16.5 CLINICAL TRIAL REPORT FOR THE 24-WEEK SHORT-TERM TREATMENT PERIOD (VERSION 1.1, DATED 11 JAN 2017)

16.6 FULL POPULATIONS TABLES