AstraZeneca

Revised Clinical Study Protocol	
Drug Substance	Exenatide
Study Code	D5553C00003
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Date	02 September 2015

A 28-week, Multicenter, Randomized, Double-Blind, Active-Controlled, Phase 3 Study with a 24-week Extension Phase Followed by a 52-week Extension Phase to Evaluate the Efficacy and Safety of Simultaneous Administration of Exenatide Once Weekly 2 mg and Dapagliflozin Once Daily 10 mg Compared to Exenatide Once Weekly 2 mg Alone and Dapagliflozin Once Daily 10 mg Alone in Patients with Type 2 Diabetes who have Inadequate Glycemic Control on Metformin

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The following Amendment(s) and Administrative Changes are included in this revised protocol:

Amendment No.	Date of Amendment	Local Amendment No.	Date of local Amendment
1	03 October 2014		
2	20 February 2015		
3	02 September 2015		

Administrative change No.	Date of Administrative Change	Local Administrative change No.	Date of local Administrative Change

AstraZeneca

PROTOCOL SYNOPSIS

A 28-week, Multicenter, Randomized, Double-Blind, Active-Controlled, Phase 3 Study with a 24-week Extension Phase Followed by a 52-week Extension Phase to Evaluate the Efficacy and Safety of Simultaneous Administration of Exenatide Once Weekly 2 mg and Dapagliflozin Once Daily 10 mg Compared to Exenatide Once Weekly 2 mg Alone and Dapagliflozin Once Daily 10 mg Alone in Patients with Type 2 Diabetes who have Inadequate Glycemic Control on Metformin

International Co-ordinating Investigator

[redacted]

Study site(s) and number of subjects planned

This will be a global, multicenter study conducted at approximately 100 sites in the United States (US) and in other countries. Approximately 1100 patients will be screened, and 660 randomized.

Study period		Phase of development
Estimated date of first patient enrolled	3Q 2014	3
Estimated date of last patient completed	4Q 2017	3

Study design

Study D5553C0003 is a 28-week, randomized, double-blind, active-controlled, multicenter, Phase 3 efficacy and safety study with 24-week and 52-week extension phases of simultaneous administration of exenatide once weekly (EQW) 2 mg and dapagliflozin 10 mg once daily (QD) compared to EQW 2 mg alone and dapagliflozin 10 mg QD alone in patients with Type 2 diabetes who have inadequate glycemic control on metformin.

All potentially eligible patients will provide informed consent and undergo screening for all applicable inclusion/exclusion criteria, and submit laboratory samples at Screening (Visit 1, 2 weeks prior to randomization). Patients should be treated with a stable dose of metformin ≥1500 mg/day for at least 2 months prior to Screening, and remain on the same type and dose of metformin therapy for the duration of the study. Eligible patients will enter a 1-week placebo lead-in period, and then be randomized at Visit 3 (Day 0) to receive EQW 2 mg added to metformin, dapagliflozin 10 mg QD added to metformin, or EQW 2 mg + dapagliflozin 10 mg QD added to metformin during the 28-week treatment period. Randomization will be stratified by glycated hemoglobin A1c (HbA1c) at baseline (<9.0% or ≥9.0%). Patients will attend study Visits 4 to 12 at Weeks 1, 2, 4, 8, 12, 16, 20, 24, and 28 during the treatment period. At the end of treatment, eligible patients will enter a 24-week extension period (Extension Period 1), with 3 further visits at Weeks 36, 44, and 52. Following this 24-week extension period, eligible patients will enter an additional 52-week extension period (Extension Period 2), with additional visits at Weeks 65, 78, 91, and 104. A follow-up visit (Visit 20) will be conducted 10 weeks after the last dose of study medication.

Objectives

Primary Objective:	**Outcome Measure:**
To compare the change from baseline in HbA1c at 28 weeks between EQW 2 mg and dapagliflozin 10 mg administered simultaneously compared to EQW 2 mg alone and dapagliflozin 10 mg alone.	The primary efficacy measure is the change in HbA1c from baseline to Week 28.

Secondary Objective:	**Outcome Measure:**
To compare the effect of EQW + dapagliflozin to EQW + placebo and/or to dapagliflozin + placebo, on changes in glycemic control and anthropometric measures.	• Change in total body weight from baseline to Week 28. • Change in fasting plasma glucose (FPG) from baseline to Week 28. • Change in 2-hour postprandial glucose (PPG) after a standardized meal tolerance test at Week 28. • Proportion of patients achieving HbA1c <7.0% at Week 28. • Proportion of patients achieving weight loss ≥5.0% at Week 28. • Change in FPG from baseline to Week 2. • Change in seated systolic BP from baseline to Week 28.

Exploratory Objective:	**Outcome Measure:**
To compare the effect of treatment with EQW +	• Proportion of patients rescued or discontinued

Exploratory Objective:	Outcome Measure:
dapagliflozin versus EQW + placebo and dapagliflozin + placebo, on additional measures of changes in glycemic control, anthropometric measures and lipid profiles.	for lack of glycemic control at Week 28. • Proportion of patients achieving HbA1c ≤6.5% at Week 28. • Change in self-monitored 6-point blood glucose from baseline to Week 28. • Proportion of patients with HbA1c reduction of ≥1.0% at Week 28. • Proportion of patients with HbA1c reduction of ≥1.0% and weight reduction of ≥3.0% at Week 28. • Change in waist circumference compared to baseline at Week 28. • Change in homeostasis Model Assessment (HOMA) B (beta cell function) and HOMA S (insulin sensitivity) scores at Week 28. • Proportion of patients with a reduction in both HbA1c and weight at Week 28. • Change in diastolic BP from baseline to Week 28. • Change in total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, non-HDL cholesterol, and fasting triglycerides from baseline to Week 28. • Diabetes Treatment Satisfaction Questionnaire, status version (DTSQ-s) and Study to Help Improve Early evaluation and management of risk factors Leading to Diabetes (SHIELD)-WQ-9 questionnaire at Week 28. • Change in total body weight in patients without an adverse event (AE) of nausea from baseline to Week 28.
To evaluate exenatide and dapagliflozin pharmacokinetics (PK) in the EQW + dapagliflozin, dapagliflozin + placebo, and EQW + placebo treatment groups.	PK profiles

Safety Objective:	**Outcome Measure :**
To evaluate the safety and tolerability of simultaneous administration of EQW and dapagliflozin 10 mg QD compared to EQW 2 mg alone and dapagliflozin 10 mg QD.	• Incidence, duration, and time course of AEs • Clinical laboratory tests • Physical examination • Vital signs.

Extension Period 1 Objectives	
Exploratory Objective:	**Outcome Measure :**
To assess the safety and tolerability of EQW + dapagliflozin over 52 weeks of treatment.	• Incidence, duration, and time course of AEs • Clinical laboratory tests • Physical examination • Vital signs.
To assess the maintenance of efficacy of EQW 2 mg and dapagliflozin 10 mg QD compared to EQW 2 mg alone and dapagliflozin 10 mg QD over 52 weeks of treatment.	• Change in HbA1c from baseline to Week 52. • Change in total body weight from baseline to Week 52. • Change in FPG from baseline to Week 52. • Change in 2-hour PPG after a standardized meal tolerance test at Week 52. • Proportion of patients achieving HbA1c <7.0% at Week 52. • Proportion of patients achieving weight loss ≥5.0% at Week 52. • Change in seated systolic BP from baseline to Week 52. • Proportion of patients rescued or discontinued for lack of glycemic control at Week 52. • Proportion of patients achieving HbA1c ≤6.5% at Week 52. • Change in self-monitored 6-point blood glucose from baseline to Week 52. • Proportion of patients with HbA1c reduction of ≥1.0% at Week 52. • Proportion of patients with HbA1c reduction of ≥1.0% and weight reduction of ≥3.0% at Week 52. • Change in waist circumference compared to baseline at Week 52. • Change in HOMA B (beta cell function) and HOMA S (insulin sensitivity) scores at

Extension Period 1 Objectives	
Exploratory Objective:	**Outcome Measure :**
	Week 52. • Proportion of patients with a reduction in both HbA1c and weight at Week 52. • Change in diastolic BP from baseline to Week 52. • Change in total cholesterol, LDL cholesterol, HDL cholesterol, non-HDL cholesterol, and fasting triglycerides from baseline to Week 52. • DTSQ-s and SHIELD-WQ-9 questionnaires at Week 52. • Change in total body weight in patients without an AE of nausea from baseline to Week 52.

Extension Period 2 Objectives	
Exploratory Objective:	**Outcome Measure :**
To assess the safety and tolerability of EQW + dapagliflozin over 104 weeks of treatment.	• Incidence, duration, and time course of AEs • Clinical laboratory tests • Physical examination • Vital signs.
To assess the maintenance of efficacy of EQW 2 mg and dapagliflozin 10 mg QD compared to EQW 2 mg alone and dapagliflozin 10 mg QD over 104 weeks of treatment.	• Change in HbA1c from baseline to Week 104. • Change in total body weight from baseline to Week 104. • Change in FPG from baseline to Week 104. • Change in 2-hour PPG after a standardized meal tolerance test at Week 104. • Proportion of patients achieving HbA1c <7.0% at Week 104. • Proportion of patients achieving weight loss ≥5.0% at Week 104. • Change in seated systolic BP from baseline to Week 104. • Proportion of patients rescued or discontinued for lack of glycemic control at Week 104. • Proportion of patients achieving HbA1c ≤6.5% at Week 104. • Change in self-monitored 6-point blood

Extension Period 2 Objectives	
Exploratory Objective:	**Outcome Measure :**
	glucose from baseline to Week 104. • Proportion of patients with HbA1c reduction of ≥1.0% at Week 104. • Proportion of patients with HbA1c reduction of ≥1.0% and weight reduction of ≥3.0% at Week 104. • Change in waist circumference compared to baseline at Week 104. • Change in HOMA B (beta cell function) and HOMA S (insulin sensitivity) scores at Week 104. • Proportion of patients with a reduction in both HbA1c and weight at Week 104. • Change in diastolic BP from baseline to Week 104. • Change in total cholesterol, LDL cholesterol, HDL cholesterol, non-HDL cholesterol, and fasting triglycerides from baseline to Week 104. • DTSQ-s and SHIELD-WQ-9 questionnaires at Week 104. • Change in total body weight in patients without an AE of nausea from baseline to Week 104.

Target patient population

Approximately 660 patients with Type 2 diabetes mellitus (T2DM) with inadequate glycemic control receiving metformin at a dose of≥1500 mg/day for at least 2 months prior to screening, will be randomized to 1 of 3 treatment groups.

Duration of treatment

Study duration will be at least 116 weeks, including a 1-week screening period, a 1-week placebo lead-in period, a 28-week double-blind treatment period, a 24-week double-blind extension period (Extension Period 1), an additional 52-week double-blind extension period (Extension Period 2), and a 10-week safety follow-up period.

Investigational product, dosage and mode of administration

Exenatide once weekly and matching placebo:

Exenatide once weekly or matching placebo will be administered using a 2-mg vial with adaptor, a syringe containing diluent, and a 23-Gauge x 5/16 inch needle. Doses of EQW or matching placebo are to be administered by subcutaneous (SC) injection in the abdomen, thigh, or upper arm once weekly for the 28-week double-blind treatment period and for Extension Periods 1 and 2.

Dapagliflozin and matching placebo:

Dapagliflozin 10 mg tablets or matching placebo will be administered orally once daily for the 28-week double-blind treatment period and for Extension Periods 1 and 2.

Other Treatments

Metformin:
Up to Visit 20 (Week 114), patients should continue to administer the same type and dose of metformin therapy they were using at study entry. Metformin should be administered and stored according to product and country specific labelling.

Rescue therapy:
Patients who require rescue therapy will receive open-label titrated basal insulin.

Statistical methods

Populations for analyses

There will be 2 analysis sets for the efficacy evaluation:

- Intent-to-treat (ITT), the primary analysis set, will include randomized patients who receive at least 1 dose of study medication and have at least 1 post-baseline HbA1c assessment.

- Per-protocol (PP), the secondary analysis set, will be a subset of the ITT population through the exclusion of those with important protocol violation(s). Important protocol violations are those that have the potential to affect the result of the primary analysis. Detailed exclusion criteria for the PP population will be specified in the SAP. Patients excluded from the PP analysis will be identified before database lock.

All randomized patients receiving at least 1 dose of study treatment will be considered in the safety population and included in the safety analysis.

Sample size estimation

A total of 209 patients per treatment group are required, assuming:

- Mean difference of 0.35% in HbA1c change from baseline with EQW + dapagliflozin versus each monotherapy

- Standard deviation of 1.1% and 90% power (based on a 2-sample t-test at a 0.05 significance level)

Assuming a 5% drop-out rate prior to Week 4 (Visit 6), the first visit where HbA1c is tested, 220 patients per treatment arm (a total of approximately 660 patients) would have post-baseline measurements of HbA1c and thus be included in the ITT analysis of the primary objective. Assuming 40% screen failure, a total of 1100 patients will be screened.

Statistical analysis methods

The primary analysis will assess the benefit (superiority) of the combination of EQW + dapagliflozin over the individual components (ie, over EQW and over dapagliflozin) for the change in HbA1c from baseline to Week 28 of the short-term double-blind treatment period for the ITT population.

The mixed model for the repeated measures (MMRM) will include change from baseline to Week 28 in HbA1c as the dependent variable, treatment, region, baseline HbA1c stratum (<9.0% or ≥9.0%), week, and treatment by week interaction as fixed factors. Baseline measurement of HbA1c will be included as a continuous covariate. All observed HbA1c values from post-baseline (including early dropouts, but excluding those data points after glycemic rescue therapy or post-treatment follow-up) will be included in the MMRM analysis. Since MMRM will be used for the primary analysis of primary endpoint, there will be no need to impute missing data. Consequently, no Last Observation Carried Forward or other imputation technique will be required or used for the primary analysis. An unstructured covariance matrix will be used for the MMRM analysis, unless the model does not converge, in which case the covariance structure will be decided based on model convergence status and the Akaike information criterion. The least-squares (LS) means, standard errors, and 2-sided 95% confidence intervals, as well as the mean difference between treatment groups (EQW + dapagliflozin compared to EQW and compared to dapagliflozin) will be presented.

The treatment comparison of the primary efficacy endpoint (HbA1c change from baseline) will be considered significant if and only if the comparisons of the combination treatment group (EQW + dapagliflozin) against both of the 2 active-control groups (dapagliflozin 10 mg QD and EQW 2 mg) are significant. Due to this specific criterion for showing superiority of the combination treatment group over the individual treatment groups in primary endpoint, no multiplicity adjustment for the primary analysis will be required to control the overall type-I error, which is considered to be 0.05; consequently, both of the individual treatment comparisons will be performed at 5% level of significance (ie, alpha = 0.05 2-sided).

For the secondary efficacy endpoints, a Cochran-Mantel-Haenszel (CMH) test stratified by baseline HbA1c stratum (<9.0% or ≥9.0%) will be applied to the categorical variables, and a MMRM model or analysis of covariance (ANCOVA) model will be applied to the continuous variables.

The significance or non-significance of the treatment comparisons for the primary efficacy endpoint will determine whether or not the statistical tests are to be performed to compare treatments for the secondary efficacy endpoints. In other words, if and only if the superiority of the combination treatment group is established simultaneously over both the individual treatment groups in primary endpoint at 5% level of significance, only then can the analyses of the set of 7 secondary endpoints be performed at 5% level of significance. In order to control the overall type-I error rate at 5% level of significance, multiplicity adjustment will be applied while analyzing the set of secondary endpoints, details of which will be provided in the SAP prior to unblinding of treatment assignments.

All safety and tolerability variables (including AEs, laboratory parameters, vital signs) will be summarized descriptively for each treatment group for the Safety population. Safety data collected prior to and after a patient initiates glycemic rescue therapy will be summarized together, as the patients are still on study medication after initiating the rescue therapy. Details on the safety analyses will be provided in the statistical analysis plan (SAP).

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Appendix D Diabetes Treatment Satisfaction Questionnaire

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ANCOVA	Analysis of co-variance
Anti-HBc	Antibody to hepatitis B core antigen
AUA	American Urological Association
AZDD	AstraZeneca Drug Dictionary
βhCG	Human chorionic gonadotropin, beta subunit
BID	Twice-daily
BP	Blood pressure
CK-MB	Creatine kinase, muscle and brain
CMH	Cochran-Mantel-Haenszel
CPK	Creatine phosphokinase
CSA	Clinical Study Agreement
CRO	Contract research organization
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CSRAF	Clinical supplies return authorization form
CV	Cardiovascular
DILI	Drug-induced liver injury
DM	Data Management
DPP-4	Dipeptidyl peptidase-IV
DTSQ-s	Diabetes Treatment Satisfaction Questionnaire, status version
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram

Abbreviation or special term	Explanation
eCRF	Electronic Case Report Form
eDC	Electronic data capture
EQW	Exenatide once weekly
EU	European Commission
FDA	Food and Drug Administration
FPG	Fasting plasma glucose
GCP	Good Clinical Practice
GLP-1	Glucagon-like peptide-1
GI	Gastrointestinal
GMP	Good Manufacturing Practice
HbA1c	Hemoglobin A1c
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
HOMA	Homeostasis Model Assessment
HR	Heart rate
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IgM	Immunoglobulin M
International Co-ordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-to-treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LDL	Low-density lipoprotein
LS	Least-squares
MTT	Meal Tolerance Test
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation or special term	Explanation
MEN 2	Multiple endocrine neoplasia type 2
MMRM	Mixed model for the repeated measures
OAD	Oral anti-diabetes drug
PK	Pharmacokinetic
PP	Per-protocol
PPG	Postprandial glucose
PRO	Patient reported outcome
QC	Once daily
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SDV	Study data verification
SGLT2	Sodium glucose cotransporter 2
SHIELD	Study to Help Improve Early evaluation and management of risk factors Leading to Diabetes
SMBG	Self-monitored blood glucose
SPC	Summary of Product Characteristics
SU	Sulfonylurea
T2DM	Type 2 diabetes mellitus
TB	Total bilirubin
TSH	Thyroid stimulating hormone
TZD	Thiazolidinedione
ULN	Upper limit of normal
WBDC	Web Based Data Capture

1. INTRODUCTION

1.1 Background and rationale for conducting this study

Exenatide once weekly (BYDUREON™) is an extended-release formulation of exenatide, a glucagon-like peptide-1 (GLP-1) receptor agonist, designed to provide continuous therapeutic concentrations of exenatide and offer patients the option of a weekly dosing regimen. 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. BYDUREON is approved by the US Food and Drug Administration (FDA) as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM), and in the European Commission (EU) as an adjunct to metformin, a sulfonylurea (SU), a (thiazolidinedione) TZD, a combination of metformin and SU, or a combination of metformin and TZD to improve glycemic control in adults with T2DM. BYDUREON consists of exenatide-containing polymeric microspheres for reconstitution in an aqueous vehicle. The biodegradable microspheres provide a gradual release of exenatide over predictable periods of time. Once weekly dosing with BYDUREON results in sustained steady-state plasma exenatide concentrations in a range known to be therapeutically effective based on the exenatide BID clinical development program. BYDUREON has demonstrated robust glucose-lowering effects in the fasting, preprandial, and postprandial states, resulting in improvement in 24-hour glucose control in patients with T2DM.

Dapagliflozin (Farxiga) is a potent and selective inhibitor of sodium glucose cotransporter 2 (SGLT2) and is approved by the FDA as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. Dapagliflozin (Forxiga) is also approved in the EU as an adjunct to diet and exercise to improve glycaemic control in patients with T2DM for whom metformin use is considered inappropriate due to intolerance, and in combination with other glucose-lowering medicinal products when these, in combination with diet and exercise do not provide adequate glycemic control. Dapagliflozin is in a new class of compounds referred to as SGLT2 inhibitors. SGLT2 is localized to the renal proximal tubule where it reabsorbs most of the ~180 g of glucose normally filtered through the glomeruli each day. SGLT2 inhibition therefore leads to pharmacologically controlled glucosuria. Dapagliflozin is a highly selective and reversible inhibitor of SGLT2. A pharmacokinetic (PK) half-life of 12.5 hours, due to the C-aryl glucoside-derived chemical structure, allows for the oral administration of dapagliflozin once daily. Inhibition of glucose reabsorption leads to subsequent glycemic effects, including fasting plasma glucose (FPG) lowering and ultimately, effects on hemoglobin A1c (HbA1c). The HbA1c- and weight-lowering efficacy of dapagliflozin has been demonstrated in an extensive development program including more than 10,000 patients. The glycemic-lowering effect induced by SGLT2 inhibition is independent of the presence of insulin. Because of this insulin-independent mechanism of action, dapagliflozin has consistent effects on glycemic control in a wide spectrum of patients with T2DM, whether used as monotherapy at an early stage of disease or in combination with other oral anti-diabetes drugs (OADs) and/or insulin at a later stage, and may also be more likely to maintain its efficacy over time.

The combination of dapagliflozin and exenatide has not previously been studied. Because the 2 agents exert their glycemic and weight-lowering effects via different mechanisms, the simultaneous administration of the 2 compounds is expected to show additive effects on HbA1c and body weight.

1.2 Rationale for study design, doses and control groups

This study will compare the dual combination of exenatide and dapagliflozin with each individual component in patients with T2DM who are inadequately controlled on metformin monotherapy. Because most diabetes agents reduce HbA1c by an average of 0.5 to 1.5%, many patients with T2DM and poor glycemic control are unlikely to reach HbA1c targets with a single agent alone. In the standard treatment paradigm, patients with poor glycemic control are prescribed oral agents sequentially, a process that results in significant delays in achieving optimal treatment. Combination insulin therapy is also an effective option in patients with very poor glycemic control, though at the cost of weight gain and hypoglycemia. Simultaneous administration of 2 effective glycemic-lowering agents that do not intrinsically increase weight or hypoglycemia is a potential alternative to sequential oral agent administration or insulin in patients with T2DM and poor glycemic control.

The combination of dapagliflozin and exenatide is expected to have additive glucose- and weight-lowering effects due to complimentary mechanisms of action. Dapagliflozin reduces plasma glucose and body weight in an insulin-independent fashion by causing excretion of urinary glucose and associated calories, whereas exenatide reduces glucose in an insulin-dependent fashion by stimulating insulin secretion, inhibiting glucagon release, delaying gastric emptying and promoting satiety via gastrointestinal (GI) and central mechanisms. Both agents act via a glucose-dependent mechanism and do not intrinsically increase the risk of hypoglycemia. The combination of the 2 drugs is thus expected to result in substantial HbA1c lowering, thus potentially decreasing the time to achieving glycemic targets in patients with very high HbA1c values while reducing the risks of weight gain or hypoglycemia.

Study design and regulatory requirement

The current study is designed to demonstrate the efficacy and safety of dapagliflozin plus exenatide versus each individual therapy in patients with inadequate glycemic control on metformin monotherapy. The study has standard design features for a confirmatory Phase III diabetes study (eg, multi-center, randomized, double-blind, parallel group) and incorporates the relevant features with regard to duration of treatment, choice of study population, and choice of outcome variables recommended by the Committee for Proprietary Medicinal Products' guidance for investigations of diabetes (CHMP 2012) and the Food and Drug Administration's draft guidance for industry on diabetes mellitus (FDA 2008).

Study doses and control groups

Control group

This is a double-blind, active-controlled study. The comparison of the combination of dapagliflozin and exenatide with its individual components is consistent with regulatory guidance regarding the investigation of combination products (CHMP 2009).

Background therapy

Metformin is a biguanide; its major effect is to decrease hepatic glucose output and lower fasting glucose. It is recommended as the initial pharmacological therapy in both the US and the EU because of its glycemic efficacy, weight neutrality, low risk of hypoglycemia, good tolerability, and relatively low cost (Inzucchi et al 2012).

Dapagliflozin

Dapagliflozin (Farxiga) is approved by the FDA as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. Dapagliflozin (Forxiga) is also approved in the EU as an adjunct to diet and exercise to improve glycemic control in patients with T2DM for whom metformin use is considered inappropriate due to intolerance, and in combination with other glucose-lowering medicinal products when these, in combination with diet and exercise do not provide adequate glycemic control. The 10 mg dose was chosen for this study as it has been extensively studied in Phase III trials and has demonstrated a favorable benefit-risk profile. In addition, it is the most effective approved dose and therefore the most appropriate option for patients with very poor glycemic control.

Exenatide

Exenatide once weekly (BYDUREON™) is approved by the US FDA as an adjunct to diet and exercise to improve glycemic control in adults with T2DM, and in the EU as an adjunct to metformin, a SU, a TZD, a combination of metformin and SU, or a combination of metformin and TZD to improve glycemic control in adults with T2DM. The 2 mg dose will be used for this study as it is the dose that was studied in the Phase III program, and is the only approved dose of exenatide once weekly.

Choice of outcome variables

The primary endpoint is change in HbA1c, the variable of choice for assessment of long-term glycemic control (FDA 2008, CHMP 2012). HbA1c is considered a well-validated surrogate marker for the microvascular complications of diabetes.

The rationale for selection of the secondary variables is provided below:

- Weight: More than 85% of patients with type 2 diabetes are overweight or obese (CDC 2004). Weight loss is a fundamental goal for the majority

of patients with T2DM as it has been shown to improve comorbid conditions such as hypertension, dyslipidemia, heart disease, osteoarthritis, and sleep apnea (NHLBI 1998).

- Fasting plasma glucose and postprandial glucose after a standard meal: These are well established measures of short-term glycemic efficacy (FDA 2008, CHMP 2012).

- Proportion achieving HbA1c <7.0%: The target HbA1c for most patients with T2DM is <7.0% (Inzucchi et al 2012).

- Proportion achieving weight loss ≥5.0%: A weight loss of ≥5.0% in patients with type 2 diabetes has been associated with decreased insulin resistance, improved measures of glycemia and lipemia, and reduced blood pressure (BP) (Klein et al 2004).

- Systolic BP: Hypertension is a common comorbidity in patients with T2DM. Lowering BP in patients with T2DM has been associated with a significantly lower rate of stroke, heart failure, diabetes-related endpoints, and deaths related to diabetes.

Choice of study population

Age

The prevalence of T2DM increases with age; it is therefore important to assess antidiabetic agents in elderly patients. In this study, because metformin is used as a background therapy, the upper age limit will be based on local metformin prescribing guidelines.

HbA1c

The HbA1c inclusion criterion at randomization (ie, 8.0% to 12.0%, inclusive) was selected to include patients with poor glycemic control, a population that would potentially achieve the greatest benefit from simultaneous addition of 2 anti-diabetic agents.

Kidney Function

The exclusion criteria that relate to creatinine and creatinine clearance are consistent with prescribing guidelines for metformin, dapagliflozin, and exenatide once weekly (EQW).

Pregnancy or breastfeeding

Neither dapagliflozin nor exenatide have been tested in pregnant women and the risks to embryo, fetus, and infant are unknown. For this reason, women who are pregnant or breastfeeding are excluded and women of childbearing age are instructed to take precautions to avoid becoming pregnant during the study.

Other

The purpose of the majority of the inclusion and exclusion criteria is to limit confounding factors that may complicate the interpretation of the study results (eg, corticosteroid-induced T2DM, hemoglobinopathies that would interfere with the HbA1c analyses) or to exclude patients whose safety could be compromised by participation in the study.

The purpose of Extension 1 and Extension 2 is to evaluate the safety and long term durability of treatment with exenatide in combination with dapagliflozin.

1.3 Benefit/risk and ethical assessment

Details regarding potential risks associated with administration of EQW and dapagliflozin are provided in the Investigator's Brochure (IB) for each medication.

The study will provide efficacy and safety information for EQW with or without dapagliflozin, compared with dapagliflozin alone in patients with T2DM who are taking metformin. Patients in the EQW + placebo group will receive dapagliflozin matching placebo with metformin and patients in the dapagliflozin + placebo group will receive EQW matching placebo with metformin. All patients will be monitored throughout the study to ensure adequate glycemic control.

1.3.1 Ethical Safety Considerations

EQW has not previously been studied in combination with dapagliflozin. EQW may cause nausea due to delayed gastric emptying, an effect that tends to resolve over time, and dapagliflozin results in a mild osmotic diuresis. Both agents are associated with a modest systolic blood-pressure-lowering effect of approximately 2 to 4 mmHg. In addition, there have been reports of hypovolemia and prerenal azotemia with both agents, though the incidence of these events has been low. Since the combination of the 2 agents may potentially increase the risk of these events, investigators should be alert to signs or symptoms of these conditions. Blood pressure and renal function will be monitored at each study visit.

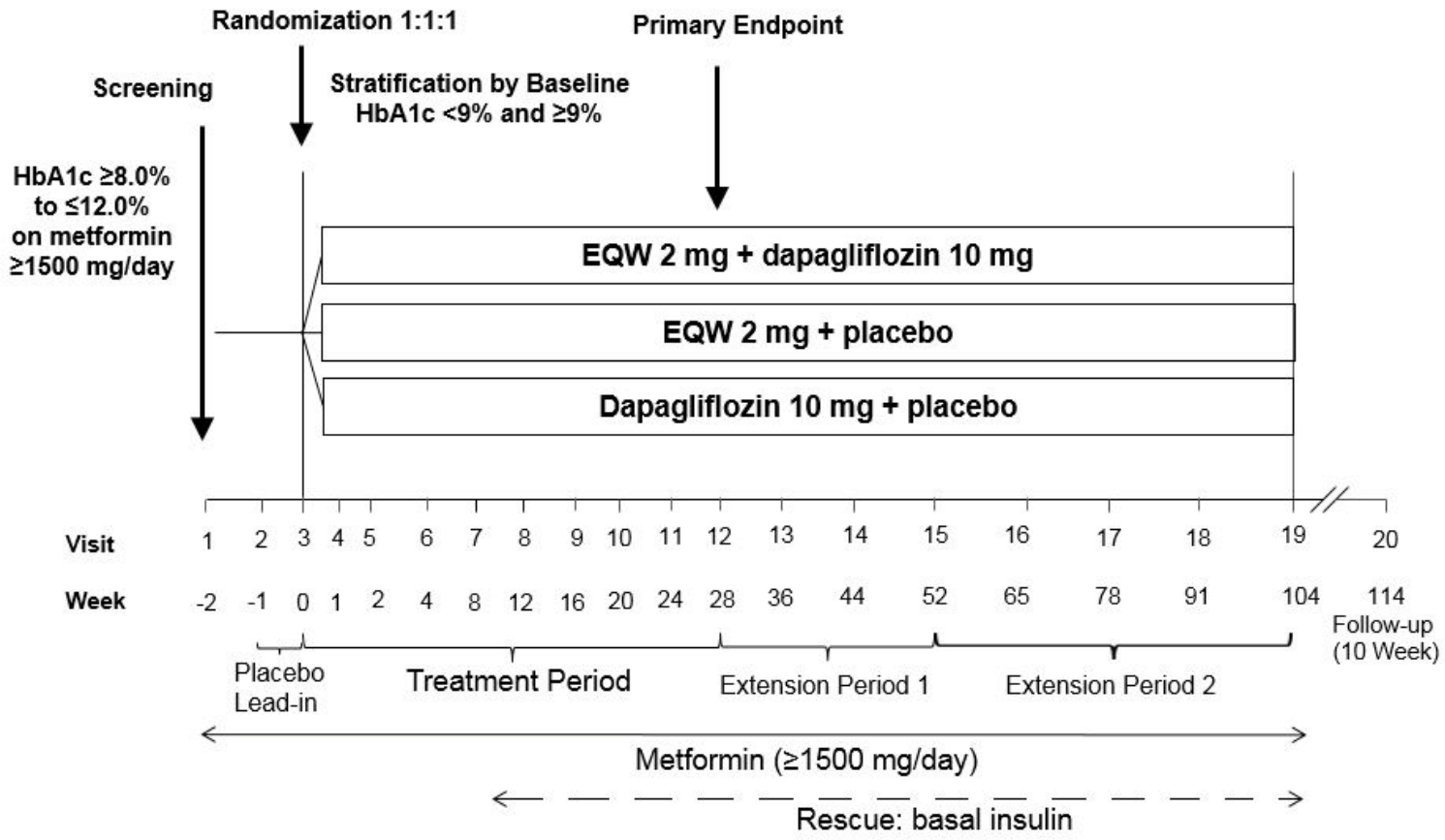
1.4 Study design

Figure 1 presents the overall design of the study.

This is a 28-week, randomized, double-blind, active-controlled, multicenter, Phase III efficacy and safety study of simultaneous administration of EQW 2 mg and dapagliflozin 10 mg QD compared to EQW 2 mg alone and dapagliflozin 10 mg QD alone in patients with T2DM who have inadequate glycemic control on metformin. The primary outcome is change from baseline in HbA1c.

The study consists of a screening visit (Visit 1), a 1-week placebo lead-in period, a randomization visit (Visit 3), and 9 further visits at 1- to 4-week intervals during a treatment period of 28 weeks. At the end of treatment, patients will enter a 24-week extension period (Extension Period 1), with 3 further visits at 8-week intervals and a subsequent 52-week

extension period (Extension Period 2) with 4 further visits at 13-week intervals. A follow-up visit will be conducted 10 weeks after the last dose of study medication in Extension Period 2.



EQW exenatide once weekly.

Figure 1 Study design

2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	Outcome Measure:
To compare the change from baseline in HbA1c at 28 weeks between EQW 2 mg and dapagliflozin 10 mg administered simultaneously compared to EQW 2 mg alone and dapagliflozin 10 mg alone.	The primary efficacy measure is the change in HbA1c from baseline to Week 28.

2.2 Secondary objectives

Secondary Objective:	Outcome Measure:
To compare the effect of EQW + dapagliflozin to EQW + placebo and/or to dapagliflozin + placebo, on changes in glycemic control and anthropometric measures.	• Change in total body weight from baseline to Week 28. • Change in FPG from baseline to Week 28. • Change in 2-hour PPG after a standardized meal tolerance test at Week 28. • Proportion of patients achieving HbA1c <7.0% at Week 28. • Proportion of patients achieving weight loss ≥5.0% at Week 28. • Change in FPG from baseline to Week 2. • Change in seated systolic BP from baseline to Week 28.

2.3 Exploratory objectives

Exploratory Objective:	Outcome Measure:
To compare the effect of treatment with EQW + dapagliflozin versus EQW + placebo and dapagliflozin + placebo, on additional measures of changes in glycemic control, anthropometric measures and lipid profiles.	• Proportion of patients rescued or discontinued for lack of glycemic control at Week 28. • Proportion of patients achieving HbA1c ≤6.5% from baseline at Week 28. • Change in self-monitored 6-point blood glucose from baseline to Week 28. • Proportion of patients with HbA1c reduction of ≥1.0% at Week 28. • Proportion of patients with HbA1c reduction of ≥1.0% and weight reduction of ≥3.0% at Week 28. • Change in waist circumference compared to baseline at Week 28. • Change in homeostasis Model Assessment

Exploratory Objective:	Outcome Measure:
	(HOMA) B (beta cell function) and HOMA S (insulin sensitivity) scores at Week 28. • Proportion of patients with a reduction in both HbA1c and weight at Week 28. • Change in diastolic BP from baseline to Week 28. • Change in total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, non-HDL cholesterol, and fasting triglycerides from baseline to Week 28. • Diabetes Treatment Satisfaction Questionnaire, status version (DTSQ-s) and Study to Help Improve Early evaluation and management of risk factors Leading to Diabetes (SHIELD)-WQ-9 questionnaire at Week 28. • Change in total body weight in patients without an adverse event (AE) of nausea from baseline to Week 28.
To evaluate exenatide and dapagliflozin pharmacokinetics (PK) in the EQW + dapagliflozin, dapagliflozin + placebo, and EQW + placebo treatment groups.	Exenatide and dapagliflozin PK profiles

2.4 Safety objectives

Safety Objective:	Outcome Measure :
To evaluate the safety and tolerability of simultaneous administration of EQW 2 mg and dapagliflozin 10 mg QD compared to EQW 2 mg alone and dapagliflozin 10 mg QD.	• Incidence, duration, and time course of AEs • Clinical laboratory tests • Physical examination • Vital signs.

2.5 Extension Period 1 objectives

Exploratory Objective:	Outcome Measure :
To assess the safety and tolerability of EQW + dapagliflozin over 52 weeks of treatment.	• Incidence, duration, and time course of AEs • Clinical laboratory tests • Physical examination • Vital signs.

Exploratory Objective:	**Outcome Measure :**
To assess the maintenance of efficacy of EQW 2 mg and dapagliflozin 10 mg QD compared to EQW 2 mg alone and dapagliflozin 10 mg QD over 52 weeks of treatment.	• Change in HbA1c from baseline to Week 52. • Change in total body weight from baseline to Week 52. • Change in FPG from baseline to Week 52. • Change in 2-hour PPG after a standardized meal tolerance test at Week 52. • Proportion of patients achieving HbA1c <7.0% at Week 52. • Proportion of patients achieving weight loss ≥5.0% at Week 52. • Change in seated systolic BP from baseline to Week 52. • Proportion of patients rescued or discontinued for lack of glycemic control at Week 52. • Proportion of patients achieving HbA1c ≤6.5% at Week 52. • Change in self-monitored 6-point blood glucose from baseline to Week 52. • Proportion of patients with HbA1c reduction of ≥1.0% at Week 52. • Proportion of patients with HbA1c reduction of ≥1.0% and weight reduction of ≥3.0% at Week 52. • Change in waist circumference compared to baseline at Week 52. • Change in HOMA B (beta cell function) and HOMA S (insulin sensitivity) scores at Week 52. • Proportion of patients with a reduction in both HbA1c and weight at Week 52. • Change in diastolic BP from baseline to Week 52. • Change in total cholesterol, LDL cholesterol, HDL cholesterol, non-HDL cholesterol, and fasting triglycerides from baseline to Week 52. • DTSQ-s and SHIELD-WQ-9 questionnaires at Week 52. • Change in total body weight in patients without an AE of nausea from baseline to Week 52.

2.6 Extension Period 2 objectives

Exploratory Objective:	**Outcome Measure :**
To assess the safety and tolerability of EQW + dapagliflozin over 104 weeks of treatment.	• Incidence, duration, and time course of AEs • Clinical laboratory tests • Physical examination • Vital signs.
To assess the maintenance of efficacy of EQW 2 mg and dapagliflozin 10 mg QD compared to EQW 2 mg alone and dapagliflozin 10 mg QD over 104 weeks of treatment.	• Change in HbA1c from baseline to Week 104. • Change in total body weight from baseline to Week 104. • Change in FPG from baseline to Week 104. • Change in 2-hour PPG after a standardized meal tolerance test at Week 104. • Proportion of patients achieving HbA1c <7.0% at Week 104. • Proportion of patients achieving weight loss ≥5.0% at Week 104. • Change in seated systolic BP from baseline to Week 104. • Proportion of patients rescued or discontinued for lack of glycemic control at Week 104. • Proportion of patients achieving HbA1c ≤6.5% at Week 104. • Change in self-monitored 6-point blood glucose from baseline to Week 104. • Proportion of patients with HbA1c reduction of ≥1.0% at Week 104. • Proportion of patients with HbA1c reduction of ≥1.0% and weight reduction of ≥3.0% at Week 104. • Change in waist circumference compared to baseline at Week 104. • Change in HOMA B (beta cell function) and HOMA S (insulin sensitivity) scores at Week 104. • Proportion of patients with a reduction in both HbA1c and weight at Week 104. • Change in diastolic BP from baseline to Week 104. • Change in total cholesterol, LDL cholesterol, HDL cholesterol, non-HDL cholesterol, and fasting triglycerides from baseline to Week 104.

Exploratory Objective:	Outcome Measure :
	• DTSQ-s and SHIELD-WQ-9 questionnaires at Week 104. • Change in total body weight in patients without an AE of nausea from baseline to Week 104.

3. SUBJECT SELECTION, ENROLLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

3.1 Inclusion criteria

For inclusion in the study patients should fulfill the following criteria:

1. Provision of informed consent prior to any study specific procedures.

2. Is able to read, understand, and sign the Informed Consent Forms (ICFs) and, if applicable, an Authorization to Use and Disclose Protected Health Information form (consistent with Health Insurance Portability and Accountability Act of 1996 [HIPAA] legislation), communicate with the investigator, and understand and comply with protocol requirements.

3. Is at least 18 years old at Screening; the upper age limit should be based on local metformin label restrictions.

4. Has a diagnosis of T2DM.

5. Has HbA1c of 8.0% to 12.0%, inclusive, at Visit 1 and Visit 2.

6. Treated with a stable dose of metformin ≥1500 mg/day for at least 2 months prior to Screening.

7. Is male, or is female and meets all the following criteria:

   - Not breastfeeding.

   - Negative pregnancy test result (human chorionic gonadotropin, beta subunit [βhCG]) at Visit 1 (Screening) (not applicable to hysterectomized females).

   - 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 appropriate birth control (defined as a method which results in a low failure rate, ie, less than 1% per year, when used consistently and correctly, such as implants, injectables, hormonal contraceptives [pills, vaginal rings, or patches], some intrauterine contraceptive devices [levonorgestrel-releasing or copper-T], tubal ligation or occlusion, or a vasectomized partner) during the entire duration of the study. As applicable, all methods must be in effect prior to receiving the first dose of study medication.

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

8. Patients who are receiving the following medications must be on a stable treatment regimen for a minimum of 2 months prior to Visit 1 (Screening):

   - Antihypertensive agents
   - Thyroid replacement therapy
   - Antidepressant agents.

3.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

Endocrine and Metabolic Conditions

1. FPG ≥280 mg/dL (15.6 mmol/L).
2. Serum calcitonin concentration ≥ 40 pg/mL (≥40 ng/L) at Visit 1 (Screening).
3. Clinically significant abnormal free T4 values or patients needing initiation or adjustment of thyroid treatment according to the investigator. Abnormal thyroid stimulating hormone (TSH) value at Screening will be further evaluated by free T4. Patients with clinically significant abnormal free T4 values will be excluded.
4. Known active proliferative retinopathy.

Gastrointestinal/Hepatic Conditions

5. History of, or currently have, acute or chronic pancreatitis, or have triglyceride concentrations ≥500 mg/dL (≥5.65 mmol/L) at Visit 1 (Screening).
6. History or presence of inflammatory bowel disease or other severe GI diseases, particularly those which may impact gastric emptying, such as gastroparesis or pyloric stenosis.

7. History of gastric bypass surgery or gastric banding surgery, or either procedure is planned during the time period of the study. Current use of gastric balloons is also excluded.

8. Significant hepatic disease, including, but not limited to, acute hepatitis, chronic active hepatitis, or severe hepatic insufficiency, including patients with alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >3x upper limit of normal (ULN) and/or total bilirubin (TB) >2 mg/dL (>34.2 µmol/L) (patients with TB >2 mg/dL [>34.2 µmol/L] and documented Gilbert's syndrome will be allowed to participate).

9. Known history of hepatotoxicity with any medication.

10. Known history of severe hepatobiliary disease.

11. Positive serological test for hepatitis B or hepatitis C.

Cardiovascular Conditions

12. Clinically significant cardiovascular disease or procedure within 3 months of Visit 1, including but not limited to myocardial infarction, clinically significant arrhythmia, unstable angina, coronary artery bypass surgery, or angioplasty; or are expected to require coronary artery bypass surgery or angioplasty during the course of the study.

13. Presence or history of severe congestive heart failure (New York Heart Association Class IV [CCNYHA 1994]).

14. Severe uncontrolled hypertension defined as systolic BP ≥180 mmHg and/or diastolic BP ≥110 mmHg.

Kidney Conditions

15. Creatinine clearance <60 mL/min (1 mL/s) (calculated by Cockcroft-Gault formula) or a measured serum creatinine value of ≥1.5 mg/dL (133 µmol/L) for male patients and ≥1.4 mg/dL (124 µmol/L) for female patients.

16. Congenital renal glucosuria.

17. History of unstable or rapidly progressing renal disease.

18. History of unexplained microscopic or gross hematuria, or microscopic hematuria at Visit 1, confirmed by a follow-up sample at next scheduled visit, where according to the investigator a satisfactory evaluation of hematuria has not been conducted based on guidance in Section 6.3.9.

Infection Disease/Immunologic Conditions

19. Known or suspected human immunodeficiency virus (HIV) infection.

20. History of organ transplantation.

Hematologic/Oncologic Conditions

21. Presence or history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 (MEN 2) OR a family history of medullary thyroid carcinoma or MEN 2.

22. Malignancy (with the exception of basal and squamous cell carcinoma of the skin) within 5 years of Visit 1 (Screening).

23. Hemoglobinopathy, hemolytic anemia, or chronic anemia (hemoglobin concentration <11.5 g/dL [115 g/L] for males, <10.5 g/dL [105 g/L] for females) or any other condition known to interfere with the HbA1c methodology.

24. Has donated blood or had a significant blood loss within 2 months of first dose of study medication or is planning to donate blood during the study.

25. Has donated plasma within 7 days prior to first dose of study medication.

Prohibited Medications

26. Any exposure to exenatide (including BYETTA®, BYDUREON™, or exenatide suspension) or any GLP-1 analog.

27. Any exposure to dapagliflozin (Forxiga®, Farxiga®) or any SGLT-2 inhibitor.

28. Administration of any antihyperglycemic therapy, other than metformin, for more than 14 days (consecutive or not) during the 12 weeks prior to Visit 1 (Screening). In addition, administration of any antihyperglycemic therapy, other than metformin, at any dose, at any time during the 4 weeks prior to Visit 1 (Screening).

29. Has been treated, is currently being treated, or is expected to require or undergo treatment with any of the following treatment excluded medications:

    - Any DPP-4 inhibitor within 3 months prior to Visit 1 (Screening).

    - Systemic corticosteroids within 3 months prior to Visit 1 (Screening) by oral, intravenous, intra-articular, or intramuscular route; or potent, inhaled, or intrapulmonary (including ADVAIR®) steroids known to have a high rate of systemic absorption. For examples of excluded steroids, refer to Section 7.7.

    - Prescription or over-the-counter weight loss medications within 3 months prior to Visit 1 (Screening).

Other

30. Has a clinically significant medical condition that could potentially affect study participation and/or personal well-being, as judged by the investigator.

31. Has clinically significant abnormal laboratory test values (clinical chemistry, hematology, urinalysis) as judged by the investigator at Visit 1 (Screening).

32. Has known contraindication, allergies, or hypersensitivity to any component of EQW or to dapagliflozin.

33. Has a contraindication to metformin use, including known metabolic or lactic acidosis, or any condition associated with hypoperfusion, hypoxemia, dehydration, or sepsis.

34. Patients who, in the judgment of the investigator, may be a risk for dehydration or volume depletion that may affect the patient's safety and/or the interpretation of efficacy or safety data.

35. Has evidence of current abuse of drugs or alcohol or a history of abuse that, in the investigator's opinion, would cause the individual to be noncompliant.

36. Previous randomization in the present study.

37. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site) or is employed by Amylin, Bristol-Myers Squibb, or AstraZeneca (ie, an employee, temporary contract worker, or designee responsible for the conduct of the study).

38. Is an immediate family member (spouse, parent, child, or sibling; biological or legally adopted) of personnel directly affiliated with the study at the clinical study site, or is directly affiliated with the study at the clinical study site.

39. Administration of any other investigational drug or participation in an interventional clinical research trial within 30 days prior to Visit 1 (or 5 half-lives of the previous investigational drug, whichever is greater).

Procedures for withdrawal of incorrectly enrolled patients see Section 3.4.

3.3 Patient enrollment and randomization

Investigators should keep a record, the patient screening log, of patients who entered pre-study screening.

The investigators will:

1. Obtain signed informed consent from the potential patient before any study specific procedures are performed.

2. Assign potential patient a unique enrollment number, beginning with 'E#'.

3. Determine patient eligibility in accordance with inclusion/exclusion criteria.

4. The Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS) will assign an eligible patient unique randomization code (patient number), beginning with "#".

As patients are enrolled for the study, they must be allocated an E-code via IVRS. The E-code is a 7-digit number made up of the center number and the patient number within that particular center.

If a patient withdraws from participation in the study, then his/her enrollment/randomization code cannot be reused.

3.3.1 Procedures for randomization

Patients who meet all study requirements based on inclusion and exclusion criteria will be centrally randomized (ie, not at the site level or not in a block-stratified fashion) to 1 of 3 treatment groups in a 1:1:1 ratio at Visit 3 (Randomization visit) by the IVRS/IWRS:

- EQW 2 mg + dapagliflozin 10 mg
- EQW 2 mg + placebo
- Dapagliflozin 10 mg + placebo.

Randomization will be stratified by baseline HbA1c stratum (<9.0% or ≥9.0%) (refer to Section 3.5); the randomization schedule will be generated according to the stratifying factor. Randomization codes will be assigned strictly sequentially as patients become eligible for randomization.

Specific information concerning the use of the IVRS/IWRS will be provided to the investigators. If a patient is discontinued from the study, his/her randomization or enrollment number will not be reused, and the patient will not be allowed to re-enter the study. Randomized patients who discontinue early from the study will not be replaced.

If a randomization number is allocated incorrectly, no attempt should be made to remedy the error once study material has been dispensed. The patient will continue with the allocated number and study material. AstraZeneca or representative should be notified as soon as the error is discovered. Subsequent patients will continue using the first unallocated randomization number in the original numbering sequence.

3.4 Procedures for handling incorrectly enrolled or randomized subjects

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Patients who are screened, but subsequently found not to meet all the eligibility criteria must not be randomized or initiated on treatment, and must be withdrawn from the study.

Where a patient does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the investigator should inform the study physician immediately, and a discussion should occur between the study physician and the investigator regarding whether to continue or discontinue the patient from treatment. The study physician must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment groups

Patients who meet all criteria for this study will be randomized to double-blinded treatment at Visit 3. Assignment to treatment groups will be determined by a computer-generated random sequence using an IVRS. Random assignment to study treatment will be stratified by HbA1c stratum (<9.0% or≥9.0%) based on the HbA1c (%) value of individual patients that was measured at a visit immediately preceding the randomization visit (which is Visit 2 at Week -1 in this study) and is available at the time of randomization. However, throughout the protocol, this is referred to as the baseline HbA1c stratum.

3.6 Methods for ensuring blinding

During the Lead-in Period, patients will be treated with single-blinded placebo (tablets and injection). Patients, the investigator, study site personnel, and Sponsor personnel involved with data review and analysis will be blinded starting at Visit 3 (randomization), and will remain blinded to study treatment throughout the 28-week randomized treatment period. Only patients and investigators will remain blinded during the 24-week extension period. To preserve the blinding, access to the treatment codes will be limited to personnel not involved in the daily conduct of the trial or data review and analysis.

No member of the study team in AstraZeneca, at study sites, or any contract research organization (CRO) handling data will have access to the randomization scheme during the conduct of the study with the exception of AstraZeneca's Investigational Product Services and Patient Safety.

The randomization schedule for blinding of randomized treatment will be maintained by AstraZeneca or representative and will not be disclosed until after the first database lock at the end of the initial 28-week treatment period. AstraZeneca and its applicable representative(s) will be unblinded in Extension Periods 1 and 2 (ie, from Week 28 onwards). Sites and patients will remain blinded during Extension Periods 1 and 2.

The results for FPG, HbA1c, urine glucose/creatinine ratio, urine glucose, and urine creatinine are blinded to the investigator for all visits except Visits 1 to 3. FPG and HbA1c values are

blinded to the investigator site until the unblinding criteria for rescue therapy are met. Once the criteria are met, fasting plasma glucose and HbA1c will be reported to the site for an individual patient (ie, if FPG >270 mg/dL from Week 8 to Week 12 [excluding Week 12], or FPG >240 mg/ dL from Week 12 to Week 20 [excluding Week 20], or FPG >200 mg/dL from Week 20 to Week 28 [including Week 28]). Previous values will remain blinded and the site will only receive the values going forward from the point the criteria were met.

3.7 Methods for unblinding

Individual treatment codes, indicating the treatment randomization for each randomized patient, will be available to the investigator(s) or pharmacists from the IVRS/IWRS. Routines for this will be described in the IVRS/IWRS user manual that will be provided to each center.

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomization. The investigator documents and reports the action to AstraZeneca, without revealing the treatment given to patient to the AstraZeneca staff.

AstraZeneca and the safety data entry site retain the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

The exception to the above is for those personnel analyzing the PK and antibody samples. The randomization code will be provided to ensure that only samples from patients who were on active study treatment are analyzed.

Samples from patients not dosed with the relevant active study treatment will only be analyzed on a 'for cause' basis, for example, if there is suspicion that a patient has been dosed incorrectly.

The treatment allocation information will be kept in a secure location until the end of the study.

3.8 Restrictions

Once screened and qualified for entry, patients will be instructed as follows:

- Any new prescription medications or over the counter preparations must be reported to study site staff. For restrictions on concomitant medications, refer to Sections 3.1 and 3.2.
- Continue metformin therapy at current dosage and at approximately the same time each day, except that any morning dose of metformin should be delayed on the morning of study-site visits.

- Fast overnight for at least 8 hours prior to each study-site visit, ie, no food or beverage except water.
- Withhold alcohol, tobacco, and caffeine and refrain from intense exercise 24 hours prior to each study-site visit.
- Do not donate blood for the duration of the study.
- Delay administering the morning dose of metformin therapy (if applicable) and study medication (as applicable) on the morning of each study-site visit and bring metformin and study medication to each study-site visit.
- Patients should not be prescribed GLP-1 receptor agonists (BYETTA, BYDUREON, or Victoza®) or SGLT-2 inhibitors (Farxiga, Forxiga, or Invokana), or any other GLP-1 analogues or SGLT2 inhibitors during the 10-week safety follow-up period.

The Sponsor or designee should be contacted if the investigator is informed of any restriction violations. The Sponsor will decide whether a patient with restriction violations will be allowed to continue study participation.

3.9 Discontinuation of investigational product

Patients may be discontinued from the study medication in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment.
- Patient experiences an AE that, in the investigator's opinion, necessitates discontinuation from study medication.
- The investigator decides that the patient should discontinue study medication. If this decision is made because of a serious adverse event (SAE) or a clinically significant abnormal laboratory value, appropriate measures are to be taken. The Sponsor or its designee is to be alerted immediately. Refer to Section 6.4, Reporting of SAEs.
- Severe non-compliance with the study protocol.
- Calculated creatinine clearance <45 mL/min confirmed by repeat testing or a decrease in renal function that would preclude continued treatment with metformin according to local guidance.
- Loss of glucose control. If any patient experiences a loss of glucose control, in addition to study medication, the investigator should initiate rescue therapy and the patient may continue study participation. The

investigator should follow local prescribing information for the rescue therapy and may discuss appropriate rescue therapy with the AstraZeneca Medical Monitor if needed. Patients must first complete the Rescue visit procedures before receiving open-label rescue therapy. Rescued patients with central laboratory HbA1c values >8.0% despite a maximum tolerated dose of rescue therapy for 12 weeks will be discontinued from the study and referred for additional anti-hyperglycemic therapy (see Section 4.2).

- Patients with a central laboratory ALT and/or AST >3x ULN will be scheduled for a follow-up visit within 3 days following the receipt of the result (see Appendix C, "Algorithm on Management of Sustained Elevated Liver Safety Abnormalities"). Patients should be discontinued from study medication if the initial and repeat laboratory tests meet any of the following criteria:

  - ALT and/or AST are >3x ULN **and** TB >2x ULN.
  - ALT and/or AST are >5x ULN for ≥14 consecutive days, at any time after initial confirmatory results.
  - ALT and /or AST are >8x ULN.

3.9.1 Procedures for discontinuation of a patient from investigational product

If deemed necessary by the investigator, study medication can be stopped temporarily and then re-started after discussion with the medical monitor. These situations will be handled on a case by case basis and all decisions will be documented in the patient's study file.

At any time, patients are free to discontinue study medication or withdraw from the study (ie, study medication and assessments – see Section 3.10), without prejudice to further treatment. A patient that decides to discontinue study medication will always be asked about the reason(s) and the presence of any AEs. AEs will be followed up (see Section 6); patient diaries and all study medications should be returned by the patient.

Patients who discontinue permanently from the study medication will have an Early Termination Visit equivalent to the Week 28 assessments at the time of study medication discontinuation (see Section 4.2.2). Discontinued patients will then be contacted via telephone according to the visit schedule in the Study Plan (Table 1 and Table 2), ie, during the time windows during which the scheduled clinic visits would have been conducted. At these contacts, the following data will be collected and entered onto the clinical database:

- Concomitant medication
- AEs

Discontinued patients should return to the study site and complete assessments required for Visit 12 (Week 28), Visit 15 (Week 52), and Visit 19 (Week 104) as appropriate and outlined in the Study Plan (Table 1 and Table 2). These patients will also be contacted via telephone according to the visit schedule in the Study Plan (Table 1 and Table 2).

Discontinued patients should also return to the study site to complete the Follow-up visit (Visit 20) 10 weeks after the Visit 19 (Week 104) assessments.

Patients who permanently discontinue study medication should retain their patient diaries and glucose meters. They do not have to continue to record their daily blood glucose in the patient diary, and instructions on future self-monitored blood glucose testing will be according to the providing physician. However, discontinued patients who have symptoms suggestive of hypoglycemia should use the glucose meter to measure their blood glucose during the episode, and should record the measurements and details regarding the episode, including symptoms of hypoglycemia, in the patient diary. The 6-point SMBG testing should be performed prior to discontinuation of study medication, but does not have to be repeated at later visits.

If a patient is withdrawn from study, see Section 3.10.

3.10 Criteria for withdrawal

Every reasonable effort should be made to conduct all protocol-required procedures to complete the study. Patients may be removed from the study for the following reasons:

1. Screen failures: see Section 3.10.1.

2. Withdrawal by patient: see Section 3.10.2.

3. Adverse Event: Patient experiences an AE that, in the investigator's opinion, necessitates withdrawal from the study.

4. Investigator Decision: Investigator feels it is in the patient's best interest to terminate participation for reasons other than an AE.

5. Protocol Violation: Patient is noncompliant with protocol procedures, becomes pregnant, violates study entry criteria, or starts an exclusionary concomitant medication.

6. Lost to Follow-Up: Patient fails to return for study visits and cannot be reached with reasonable, repeated attempts.

7. Study Terminated by Sponsor: The Sponsor discontinues the study protocol.

8. Administrative Reasons: The FDA or other regulatory authority discontinues the study protocol or the clinical study site discontinues participation.

Any withdrawal must be fully documented in the patient's source records and recorded on the Disposition page of the electronic case report form (eCRF). The documentation must include the reason for the withdrawal and details of any sequelae (followed until symptoms resolve or improve, as appropriate). Withdrawals due to an AE must be documented on the eCRF.

If a patient is withdrawn from the study, they must complete the procedures outlined in Section 3.9.1, Procedures for discontinuation of a patient from investigational product.

When a patient is lost to follow-up (ie, fails to return for study visits), a reasonable effort (eg, a documented minimum of 2 calls and a certified letter) will be made to contact the patient to determine why the patient failed to return and to attempt to schedule the Early Termination Visit (refer to Table 1 and Table 2).

3.10.1 Screen failures

Screening failures are patients who do not fulfill the eligibility criteria for the study, and therefore must not be randomized. These patients should have the reason for study withdrawal recorded as 'Eligibility Criteria Not Fulfilled' (ie, patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not randomized patients).

3.10.2 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (study medication and assessments), without prejudice to further treatment.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any AEs. The investigator will follow up AEs outside of the clinical study.

If a patient withdraws from participation in the study, then his/her enrollment/randomization code cannot be reused. Withdrawn patients will not be replaced.

3.11 Discontinuation of the study

The study may be stopped if, in the judgment of AstraZeneca, trial patients are placed at undue risk because of clinically significant findings that:

- are assessed as causally related to study medication
- are not considered to be consistent with continuation of the study

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded in the CRF. All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the patients' interests.

4. STUDY PLAN AND TIMING OF PROCEDURES

Table 1 (Study Plan [Part 1] – 28-week Treatment Period) and Table 2 (Study Plan [Part 2] – Extension Period 1, Extension Period 2, and Follow-up) present the schedule of assessments for this study.

Table 1 Study Plan (Part 1) – 28-week Treatment Period

Evaluation	Screening Visit	Lead-in Visit	28-week Treatment Period									End of Treatment Period	Treatment Period: Early Termination	Treatment Period: Rescue
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**ET - TX**	**Rescue - TX**
Week	**-2**	**-1**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**		
Relative to Randomization (days)	**-14**	**-7**	**R**	**7**	**14**	**28**	**56**	**84**	**112**	**140**	**168**	**196**		
Visit Window (days)	**0**	**(±7)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**		
Informed Consent	X													
Medical History	X													
Verify Inclusion/Exclusion Criteria	X		X											
Verify patient has fasted 8 hours	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Contact IVRS	X	X	X	X	X	X	X	X	X	X	X	X	X	
Randomization			X											
Complete Physical Examination	X											X	X	X
Brief Physical Examination		X	X	X	X	X	X	X	X	X	X			
Body weight	X		X	X	X	X	X	X	X	X	X	X	X	X
Waist Circumference			X									X	X	X
Height	X													
Body Mass Index	X		X									X	X	X
Vital signs (seated BP and HR)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X											X	X	X
AEs/potential CV event triggers		X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess hypoglycemia episodes		X	X	X	X	X	X	X	X	X	X	X	X	X
Serum βhCG Test	X											X	X	X
Urine βhCG Test		X	X	X	X	X	X	X	X	X	X			
Urine glucose/creatinine ratio			X	X	X	X	X	X	X	X	X	X	X	X
Chemistry, hematology, urinalysis	X		X	X	X	X	X	X	X	X	X	X	X	X
Serum calcitonin	X											X	X	X
HbA1c	X	X	X			X	X	X	X	X	X	X	X	X
Fasting plasma glucose	X	X	X[b]	X	X	X	X	X	X	X	X	X[b]	X[b]	X[b]
Fasting insulin			X[b]									X[b]	X[b]	X[b]

Evaluation	Screening Visit	Lead-in Visit	28-week Treatment Period									End of Treatment Period	Treatment Period: Early Termination	Treatment Period: Rescue
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**ET - TX**	**Rescue - TX**
Week	**-2**	**-1**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**		
Relative to Randomization (days)	**-14**	**-7**	**R**	**7**	**14**	**28**	**56**	**84**	**112**	**140**	**168**	**196**		
Visit Window (days)	**0**	**(±7)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**		
Fasting C-peptide			X[b]									X[b]	X[b]	X[b]
Fasting glucagon			X[b]									X[b]	X[b]	X[b]
Serum Creatinine (Screening), creatinine clearance (Cockcroft-gault)	X		X	X	X	X	X	X	X	X	X	X	X	X
Fasting Serum Lipids[c]	X		X									X	X	X
Hepatitis screen[d] **and TSH**	X													
Plasma exenatide			X			X	X	X		X		X	X	X
Plasma dapagliflozin			X			X	X	X		X		X	X	X
Antibodies to exenatide			X			X	X	X		X		X	X	X
Blood sample for archiving			X									X	X[h]	X[h]
Meal tolerance test[b]			X									X	X	X
Provide diet and exercise counseling		X	X	X	X	X	X	X	X	X	X	X	X	X
Provide glucose meter/supplies/ instructions		X	X	X	X	X	X	X	X	X	X	X	X	X
Provide patient diary/instructions		X												
Review patient diary and collect pages since last visit			X	X	X	X	X	X	X	X	X	X	X	X
Collect patient diary and glucose meter/supplies (as applicable)														
Instruct patient on 6-point SMBG[e]		X									X			
6-point SMBG			X									X	X	X
Patient reported outcome: DTSQ-s			X									X	X	X
Patient reported outcome: SHIELD-WQ-9 questionnaire												X	X	X
Training on study drug administration		X	X											
Dispense Study Medication and Transport Procedure Review[f]		X	X			X	X	X	X	X	X	X		X

Evaluation	**Screening Visit**	**Lead-in Visit**	28-week Treatment Period									End of Treatment Period	Treatment Period: Early Termination	Treatment Period: Rescue
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**ET - TX**	**Rescue - TX**
Week	**-2**	**-1**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**		
Relative to Randomization (days)	**-14**	**-7**	**R**	**7**	**14**	**28**	**56**	**84**	**112**	**140**	**168**	**196**		
Visit Window (days)	**0**	**(±7)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**		
Collect Used/Unused Study Medication						X	X	X	X	X	X	X	X	X
Dispense rescue medication (if needed)							X	X	X	X	X	X	X	X
Study Medication Compliance Review			X	X	X	X	X	X	X	X	X	X	X	X

Note: See footnotes below Table 2.

Table 2 Study Plan (Part 2) – 24-week Extension Period 1, 52-week Extension Period 2, and Follow-up

Evaluation	24-week Extension Period 1 Treatment Period					End of Extension Period 1	52-week Extension Period 2 Treatment Period							End of Extension Period 2	Extension Period 1 or 2: Early Termination[a]	Extension Period 1 or 2: Rescue[a]	10-week Follow-up Visit
Visit Number	Monthly Phone Call in-between clinic visits	13	Monthly Phone Call in-between clinic visits	14	Monthly Phone Call in-between clinic visits	15	Monthly Phone Call in-between clinic visits	16	Monthly Phone Call in-between clinic visits	17	Monthly Phone Call in-between clinic visits	18	Monthly Phone Call in-between clinic visits	19	ET – EXT 1 or ET – EXT 2	Rescue – EXT 1 or Rescue – EXT 2	20
Week	32	36	40	44	48	52	56,60	65	69, 73	78	82, 86	91	95, 99	104			114
Relative to Randomization (days)		252		308		364		455		546		637		728			798
Visit Window (days)	(±7)	(±3)	(±7)	(±3)	(±7)	(±3)	(±7)	(±3)	(±7)	(±3)	(±7)	(±3)	(±7)	(±3)			(±3)
Verify patient has fasted 8 hours		X		X		X		X		X		X		X	X	X	
Contact IVRS		X		X		X		X		X		X		X	X		X
Complete Physical Examination						X								X	X	X	X
Brief Physical Examination		X		X				X		X		X					
Body weight		X		X		X		X		X		X		X	X	X	X
Waist Circumference						X								X	X	X	
Body Mass Index						X								X	X	X	X
Vital signs (seated BP and HR)		X		X		X		X		X		X		X	X	X	X
12-lead ECG						X								X	X	X	X
AEs/potential CV event triggers	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Evaluation	24-week Extension Period 1 Treatment Period					End of Extension Period 1	52-week Extension Period 2 Treatment Period							End of Extension Period 2	Extension Period 1 or 2: Early Termination[a]	Extension Period 1 or 2: Rescue[a]	10-week Follow-up Visit
Visit Number	**Monthly Phone Call in-between clinic visits**	**13**	**Monthly Phone Call in-between clinic visits**	**14**	**Monthly Phone Call in-between clinic visits**	**15**	**Monthly Phone Call in-between clinic visits**	**16**	**Monthly Phone Call in-between clinic visits**	**17**	**Monthly Phone Call in-between clinic visits**	**18**	**Monthly Phone Call in-between clinic visits**	**19**	**ET – EXT 1 or ET – EXT 2**	**Rescue – EXT 1 or Rescue – EXT 2**	**20**
Week	**32**	**36**	**40**	**44**	**48**	**52**	**56,60**	**65**	**69, 73**	**78**	**82, 86**	**91**	**95, 99**	**104**			**114**
Relative to Randomization (days)		**252**		**308**		**364**		**455**		**546**		**637**		**728**			**798**
Visit Window (days)	**(±7)**	**(±3)**	**(±7)**	**(±3)**	**(±7)**	**(±3)**	**(±7)**	**(±3)**	**(±7)**	**(±3)**	**(±7)**	**(±3)**	**(±7)**	**(±3)**			**(±3)**
Assess hypoglycemia episodes	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum βhCG Test						X								X	X	X	X
Urine βhCG Test		X		X				X		X		X					
Urine glucose/creatinine ratio		X		X		X		X		X		X		X	X	X	X
Chemistry, hematology, urinalysis		X		X		X		X		X		X		X	X	X	X
Serum calcitonin						X								X	X	X	X
HbA1c		X		X		X		X		X		X		X	X	X	
Fasting plasma glucose		X		X		X[b]		X		X		X		X[b]	X[b]	X[b]	
Fasting insulin						X[b]								X[b]	X[b]	X[b]	
Fasting C-peptide						X[b]								X[b]	X[b]	X[b]	
Fasting glucagon						X[b]								X[b]	X[b]	X[b]	
Serum Creatinine (Screening), creatinine clearance (Cockcroft-gault)		X		X		X		X		X		X		X	X	X	X

Evaluation	24-week Extension Period 1 Treatment Period					End of Extension Period 1	52-week Extension Period 2 Treatment Period							End of Extension Period 2	Extension Period 1 or 2: Early Termination[a]	Extension Period 1 or 2: Rescue[a]	10-week Follow-up Visit
Visit Number	**Monthly Phone Call in-between clinic visits**	**13**	**Monthly Phone Call in-between clinic visits**	**14**	**Monthly Phone Call in-between clinic visits**	**15**	**Monthly Phone Call in-between clinic visits**	**16**	**Monthly Phone Call in-between clinic visits**	**17**	**Monthly Phone Call in-between clinic visits**	**18**	**Monthly Phone Call in-between clinic visits**	**19**	**ET – EXT 1 or ET – EXT 2**	**Rescue – EXT 1 or Rescue – EXT 2**	**20**
Week	**32**	**36**	**40**	**44**	**48**	**52**	**56,60**	**65**	**69, 73**	**78**	**82, 86**	**91**	**95, 99**	**104**			**114**
Relative to Randomization (days)		**252**		**308**		**364**		**455**		**546**		**637**		**728**			**798**
Visit Window (days)	**(±7)**	**(±3)**	**(±7)**	**(±3)**	**(±7)**	**(±3)**	**(±7)**	**(±3)**	**(±7)**	**(±3)**	**(±7)**	**(±3)**	**(±7)**	**(±3)**			**(±3)**
Fasting Serum Lipids[c]						X								X	X	X	
Plasma exenatide						X								X	X	X	
Antibodies to Exenatide						X								X	X	X	X
Blood sample for archiving						X								X	X[h]	X[h]	
Meal tolerance test[b]						X								X	X	X	
Provide diet and exercise counseling		X		X		X		X		X		X		X	X	X	
Provide glucose meter/supplies/ instructions		X		X		X		X		X		X		X	X	X	
Provide patient diary/instructions						X											
Review patient diary and collect pages since last visit		X		X		X		X		X		X		X	X	X	X
Collect patient diary and glucose meter/supplies (as applicable)																	X

Evaluation	24-week Extension Period 1 Treatment Period					End of Extension Period 1	52-week Extension Period 2 Treatment Period							End of Extension Period 2	Extension Period 1 or 2: Early Termination[a]	Extension Period 1 or 2: Rescue[a]	10-week Follow-up Visit
Visit Number	**Monthly Phone Call in-between clinic visits**	**13**	**Monthly Phone Call in-between clinic visits**	**14**	**Monthly Phone Call in-between clinic visits**	**15**	**Monthly Phone Call in-between clinic visits**	**16**	**Monthly Phone Call in-between clinic visits**	**17**	**Monthly Phone Call in-between clinic visits**	**18**	**Monthly Phone Call in-between clinic visits**	**19**	**ET – EXT 1 or ET – EXT 2**	**Rescue – EXT 1 or Rescue – EXT 2**	**20**
Week	**32**	**36**	**40**	**44**	**48**	**52**	**56,60**	**65**	**69, 73**	**78**	**82, 86**	**91**	**95, 99**	**104**			**114**
Relative to Randomization (days)		**252**		**308**		**364**		**455**		**546**		**637**		**728**			**798**
Visit Window (days)	**(±7)**	**(±3)**	**(±7)**	**(±3)**	**(±7)**	**(±3)**	**(±7)**	**(±3)**	**(±7)**	**(±3)**	**(±7)**	**(±3)**	**(±7)**	**(±3)**			**(±3)**
Instruct patient on 6-point SMBG[e]				X								X					
Patient Performs 6-point SMBG						X								X	X	X	
Patient reported outcome: DTSQ-s						X								X	X	X	
Patient reported outcome: SHIELD-WQ-9 questionnaire						X								X	X	X	
Dispense Study Medication and Transport Procedure Review[f]		X		X		X		X		X		X				X[g]	
Collect Used/Unused Study Medication		X		X		X		X		X		X		X	X	X	
Dispense rescue medication (if needed)		X		X		X		X		X		X				X	
Study Medication Compliance Review		X		X		X		X		X		X		X	X	X	

AE adverse event, βhCG beta subunit of human chorionic gonadotropin, BP blood pressure, CV cardiovascular, DTSQ-s Diabetes Treatment Satisfaction Questionnaire, status version, ECG electrocardiogram, HbA1c hemoglobin A1c, HDL high-density lipoprotein, HR heart rate, IgM immunoglobulin M, IVRS Interactive Voice Response System, MTT meal tolerance test, LDL low-density lipoprotein, SHIELD Study to Help Improve Early evaluation and management of risk factors Leading to Diabetes, SMBG self-monitored blood glucose, TSH thyroid stimulating hormone.

[a] Early Termination or Rescue visit procedures are to be completed for all patients who terminate the study or are rescued in the Treatment Period, Extension Period 1 or Extension Period 2, as appropriate. Discontinued patients will be contacted via telephone according to the visit schedule (ie, during the windows that the scheduled clinic visits would have been conducted) for collection of safety information (see Section 3.9.1). At 28, 52, and 104 weeks post-randomization, discontinued patients should return to the study site and complete assessments required for Visit 12 (Week 28), Visit 15 (Week 52), and Visit 19 (Week 104). Discontinued patients should also return to the study site to complete the Follow-up visit (Visit 20) 10 weeks after Visit 19 (Week 104) assessments.

Note: Patients who permanently discontinue study medication do not have to record daily blood glucose in the patient diary but should record symptoms suggestive of hypoglycemia, and should measure and record blood glucose during the episode. The 6-point SMBG testing should be performed prior to discontinuation of study medication, but does not have to be repeated at later visits.

[b] At Visits 3, 12, 15, and 19, the MTT will include blood draws for glucose, insulin, C-peptide, and glucagon at Time 0 and at 120 minutes (see Section 5.1.6). (For patients who receive rescue treatment, the MTT should be performed before the rescue treatment is initiated. Also, for patients who prematurely and permanently discontinue study medication, the MTT should be performed before study medication is discontinued. After rescue therapy is initiated or study medication is discontinued, no further MTTs are required.)

[c] Serum lipids include total-cholesterol, LDL-cholesterol, HDL-cholesterol, non-HDL cholesterol, and triglycerides.

[d] Hepatitis B viral antibody IgM, Hepatitis B surface antigen and Hepatitis C virus antibody.

[e] Patients (or a designated caregiver) will be provided instructions on how to complete a 6-point SMBG profile. 6-point SMBG should be performed on any 3 days in the week prior to Visits 3, 12, 15, and 19.

[f] Placebo lead-in medication will be dispensed at Visit 2. Study medication will be dispensed at Randomization (Visit 3) and every 4 weeks thereafter (Visits 6-11) during the Treatment Period. Study medication will be dispensed every 8 weeks during the Extension Period (Visits 12-14). Patients (or a designated caregiver) will be provided with instructions and supplies (as appropriate) for proper transportation and storage of the study medication.

[g] Study medication will only be dispensed at the Rescue visit if needed.

[h] Archived samples should also be collected at the rescue and early discontinuation visits. People who discontinue early will not have further samples collected for archiving after the early discontinuation visit.

4.1 Screening/Lead-in Period

Procedures will be performed according to the Study Plan (Table 1 and Table 2). Patients will be instructed to arrive in the morning of each scheduled visit. Prior to each study visit, including the Screening Visit, patients are to have fasted overnight for at least 8 hours (no food or beverage except water) (see Section 4.1.1 for information regarding fasting relative to administration of Informed Consent). Patients should delay administering their morning dose of metformin on the morning of the study-site visit. Patients are to abstain from strenuous exercise and alcohol, tobacco, and caffeine for 24 hours before visits.

4.1.1 Screening Visit (Visit 1, Week -2)

The Informed Consent for Protocol D5553C00003 will be signed prior to performing any protocol-required procedures. The Screening period will be a maximum of 14 days (Day -14 [±7] to Day -8), depending on the availability of laboratory data from this visit. Screening procedures should be scheduled for at least 1 day later than the day of Informed Consent signature if the patient is not in a fasting state on the consent date. The following will be performed during this visit:

- IVRS will be contacted to register the patient (IVRS should be called on the day that consent is given).
- The patient's complete medical history will be recorded.
- All prior medications (prescription medications within 3 months) and concomitant medications will be reviewed.
- A complete physical exam will be conducted (refer to Section 5.2.2).
- Vital signs (sitting systolic and diastolic BP and heart rate [HR]) will be measured.
- 12-lead ECG will be performed.
- Body weight and height will be measured.
- BMI will be calculated.
- Inclusion and exclusion criteria will be verified.
- Blood samples will be collected for the following assessments:
    - Serum pregnancy test (βhCG) for all female patients, unless patient has had a hysterectomy
    - Chemistry and hematology

- Serum calcitonin
- HbA1c
- Fasting plasma glucose
- Fasting serum lipid concentrations (total cholesterol, low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol, non-HDL cholesterol, and triglycerides)
- Serum creatinine (calculated creatinine clearance; Cockcroft-Gault formula)
- Hepatitis screening (hepatitis B surface antigen, antibody to hepatitis B core antigen (anti-HBc) IgM, and hepatitis C virus antibody)
- TSH

- Urine will be collected for urinalysis.

Individuals will be disqualified if results of any laboratory test are abnormal and clinically significant as judged by the investigator or medical monitor. Individuals may requalify for study enrollment within 2 weeks of Screening following an abnormal test result by having that test repeated once with acceptable results as judged by the investigator and medical monitor (or designee).

When all of the Screening results are available, individuals will be notified by telephone of their eligibility status.

4.1.2 Rescreening

If a patient was classified as a screen failure, the patient may be rescreened for study inclusion as long as rescreening takes place at least 3 months after the original screening visit. All patients who rescreen will be assigned a new enrollment number. If a patient will be rescreened, they must continue to meet all inclusion/exclusion criteria. They must repeat all study procedures for Visit 1 at the rescreening visit. Only 1 rescreening is permitted. If the patient does not meet all study requirements at the rescreening visit, the patient should be considered a screen failure.

4.1.3 Lead-in Period Visit (Visit 2, Week -1)

The following will be performed during this visit:

- IVRS will be contacted to register the visit.

- AEs, potential CV event triggers (Section 6.8.1), and concomitant medications will be reviewed.
- A brief physical exam will be conducted (refer to Section 5.2.2).
- Vital signs (sitting systolic and diastolic BP and HR) will be measured.
- Blood samples will be collected for the following assessments:
    - HbA1c
    - Fasting plasma glucose
- Urine will be collected for a pregnancy test for all female patients, unless patient has had a hysterectomy.
- Hypoglycemia episodes will be assessed.
- Diet and exercise counseling will be provided.
- Study-related training on use of a glucose meter will be provided. Glucose meter and supplies will be provided.
- Patient diary and instructions for completion will be provided. Patients will monitor their fasting blood glucose levels every other day and will enter the results into the patient diary. If a patient experiences a hypoglycemic episode, details regarding the episode, including symptoms of hypoglycemia, will also be recorded in the patient diary.
- Patients will be instructed on how to complete the 6-point self-monitored blood glucose (SMBG) profile. 6-point SMBG should be performed by the patient on any 3 days in the week prior to Visit 3.
- Patients will receive single-blind placebo tablets to be taken daily for the 1-week placebo lead-in period, as well as the single-blind placebo injection for the placebo lead-in period. Patients (or a designated caregiver) will be trained in administration of the study medication. Patients will be instructed to continue taking metformin as directed during this period.

4.1.4 Randomization and Baseline Visit (Visit 3, Day 0)

Prior to this visit, patients are to have fasted overnight (at least 8 hours), and to have abstained from strenuous exercise, alcohol, tobacco, and caffeine for 24 hours. Patients should delay administering their morning dose of metformin on the morning of the study-site visit. The following will be performed during this visit:

- All inclusion/exclusion criteria will be verified. INDIVIDUALS WHO DO NOT MEET ALL ENTRY CRITERIA MAY NOT BE RANDOMIZED.
- AEs, potential CV event triggers (Section 6.8.1), and concomitant medications will be reviewed.
- IVRS will be contacted for randomization of the patient. Patients will be randomly assigned to 1 of 3 treatment groups: EQW 2 mg + dapagliflozin 10 mg, EQW 2 mg + placebo, or dapagliflozin 10 mg + placebo.
- A brief physical exam will be conducted (refer to Section 5.2.2).
- Vital signs (sitting systolic and diastolic BP and HR) will be assessed.
- Body weight will be measured.
- BMI will be calculated.
- Waist circumference will be measured.
- Urine will be collected for the following assessments (to be collected right before time 0 of the meal tolerance test):
  - Urinalysis
  - Urine glucose/creatinine ratio
  - Pregnancy test for all female patients, unless patient has had a hysterectomy.
- Meal tolerance test will be performed (refer to Section 5.1.6).
- Blood samples will be collected **prior to administration of study medication** for the following assessments:
  - Chemistry and hematology
  - HbA1c
  - Fasting plasma glucose (part of meal tolerance test)
  - Fasting serum lipid concentrations (total cholesterol LDL cholesterol, HDL cholesterol, non-HDL cholesterol, and triglycerides)
  - Fasting glucagon

- Serum creatinine (calculated creatinine clearance; Cockcroft-Gault formula)
- Fasting C-peptide (part of meal tolerance test)
- Fasting insulin (part of meal tolerance test)
- Serum antibodies to exenatide
- Plasma exenatide and dapagliflozin
- Blood sample for archiving.

- DTSQ-s questionnaire will be administered.
- Patient diary will be reviewed.
- Hypoglycemia episodes will be assessed.
- Diet and exercise counseling will be provided.
- Glucose meter and supplies will be provided.
- 6-point SMBG profiles will be reviewed.
- Study medication compliance (placebo lead-in period) will be reviewed.
- Study medication will be dispensed.
- Patients (or a designated caregiver) will be trained in administration of the study medication. Study site personnel will monitor administration of study medication. Metformin should be taken by the patient with the next meal after the study visit.
- Patients (or a designated caregiver) will be provided with instructions and supplies (as appropriate) for proper transportation and storage of the study medication (to ensure temperature control, etc.).

4.2 Treatment period

After the randomization visit (Visit 3), patients will complete study visits at 1- to 4-week intervals until the end of the randomized treatment period (Visit 12, Week 28). Starting at Week 8, patients with inadequate glycemic control based on progressively stricter glycemic criteria as outlined in Table 3 will remain in the study and will receive open-label rescue therapy with basal insulin.

Table 3 Criteria for initiation of rescue therapy during the randomized treatment period

Period	Central laboratory FPG
From Visit 7/Week 8, inclusive, up to and including the day before Visit 8/Week 12	FPG >270 mg/dL (15 mmol/L)
From Visit 8/Week 12, inclusive, up to and including the day before Visit 10/Week 20	FPG >240 mg/dL (13.2 mmol/L)
From Visit 10/Week 20, inclusive, up to and including Visit 12/Week 28 and all unscheduled visits through the day prior to Visit 13/Week 36	FPG >200 mg/dL (11.1 mmol/L)

Note: Repeat FPG testing required for confirmation before rescue initiated.
Abbreviation: FPG fasting plasma glucose

Patients with a central laboratory FPG value meeting the lack of glycemic control criterion at a pre-specified visit will be scheduled for a follow-up visit (within 3 to 5 days) to obtain a second central laboratory FPG value and review the patient's glucose meter readings. If the repeat central laboratory FPG value still meets the criterion, the patient may receive rescue therapy. Patients should continue receiving study medication while receiving rescue therapy. Patients who meet rescue criteria in the double-blind treatment period must first complete the Rescue visit procedures before receiving open-label rescue therapy, to ensure that important trial endpoint measurements are collected.

Patients who receive rescue therapy should be instructed to perform the 6-point SMBG profile before returning to the clinic for the Rescue Visit; see Section 5.1.5 for additional details.

Rescued patients with central laboratory HbA1c values >8.0% despite a maximum tolerated dose of rescue therapy for 12 weeks will be discontinued from the study and referred for additional antihyperglycemic therapy.

4.2.1 Treatment Period Visits (Visits 4 to 11, Weeks 1, 2, 4, 8, 12, 16, 20, and 24)

Prior to these visits, patients are to have fasted overnight (at least 8 hours). Patients should delay administering their morning dose of metformin and study medication on the morning of the study-site visit.

The following will be performed during these visits:

- IVRS will be contacted to register the visit.
- AEs, potential CV event triggers (Section 6.8.1), and concomitant medications will be reviewed.
- A brief physical exam will be conducted (refer to Section 5.2.2).

- Vital signs (sitting systolic and diastolic BP and HR) will be assessed.
- Body weight will be measured.
- Blood samples will be collected **prior to administration of study medication** for the following assessments:
  - Chemistry and hematology
  - HbA1c (Visits 6, 7, 8, 9, 10, and 11 only)
  - Fasting plasma glucose will be collected at all treatment visits (need for rescue will be evaluated at Visits 7 to 11 only)
  - Serum creatinine (calculated creatinine clearance; Cockcroft-Gault formula)
  - Serum antibodies to exenatide (Visits 6, 7, 8, and 10 only)
  - Plasma exenatide and dapagliflozin (Visits 6, 7, 8, and 10 only).
- Urine will be collected for the following assessments:
  - Urinalysis
  - Urine glucose/creatinine ratio
  - Pregnancy test for all female patients, unless patient has had a hysterectomy.
- Patient diary will be reviewed.
- Visit 11 only: Patients will be instructed to perform 6-point SMBG on any 3 days in the week prior to Visit 12.
- Hypoglycemia episodes will be assessed.
- Diet and exercise counseling will be provided.
- Glucose meter and supplies will be provided.
- Study medication compliance will be reviewed.
- Study medication will be dispensed every 4 weeks during the treatment period: Visits 6 to 11. Study site personnel will monitor administration of injectable study medication (if the patient is due for an injection at the time of the visit).

- Instructions, reminders, and supplies (as appropriate) will be given to the patient (or designated caregiver) for proper transportation and storage of the study medication (to ensure temperature control, etc.).
- Rescue medication will be dispensed at Visits 7 to 11 if criteria for rescue medication are met (refer to Table 3).
- Used/unused study medication will be collected every 4 weeks (Visits 6 to 11).

4.2.2 End of Treatment Period Visit (Visit 12, Week 28) or Early Termination or Rescue during Treatment Period

Prior to this visit, patients are to have fasted overnight (at least 8 hours), and to have abstained from strenuous exercise, alcohol, tobacco, and caffeine for 24 hours. Patients should delay administering the morning dose of metformin and study medication on the morning of the visit and bring OAD medication and study medication to the study-site visit.

The following procedures will be conducted:

- IVRS will be contacted to register an End of Treatment Period Visit or Early Termination visit; the IVRS will not be contacted for a Rescue visit.
- AEs, potential CV event triggers (Section 6.8.1), and concomitant medications will be reviewed.
- A complete physical exam will be conducted (refer to Section 5.2.2).
- Vital signs (sitting systolic and diastolic BP and HR) will be assessed.
- 12-lead ECG will be performed **prior to administration of study medication**.
- Body weight will be measured.
- BMI will be calculated.
- Waist circumference will be measured.
- Urine will be collected for the following assessments (to be collected right before time 0 of the meal tolerance test):
  - Urinalysis
  - Urine glucose/creatinine ratio.

- Meal tolerance test will be performed (refer to Section 5.1.6). (For patients who receive rescue treatment, the MTT should be performed before the rescue treatment is initiated. Also, for patients who prematurely and permanently discontinue study medication, the MTT should be performed before study medication is discontinued. After rescue therapy is initiated or study medication is discontinued, no further MTTs are required.)

- Blood samples will be collected after **administration of dapagliflozin** for the following assessments:

  - Serum pregnancy test (βhCG) for all female patients, unless patient has had a hysterectomy
  - Chemistry and hematology
  - Serum calcitonin
  - HbA1c
  - Fasting plasma glucose (need for rescue will be evaluated; part of meal tolerance test)
  - Fasting serum lipid concentrations (total cholesterol, LDL cholesterol, HDL cholesterol, non-HDL cholesterol, and triglycerides)
  - Fasting glucagon
  - Serum creatinine (calculated creatinine clearance; Cockcroft-Gault formula)
  - Fasting C-peptide (part of meal tolerance test)
  - Fasting insulin (part of meal tolerance test)
  - Serum antibodies to exenatide
  - Plasma exenatide and dapagliflozin. Samples for plasma dapagliflozin will be drawn 1 hour after administration of study medication as part of the meal tolerance test (refer to Section 5.1.6).
  - Blood sample for archiving.

- DTSQ-s questionnaire will be administered.

- SHIELD-WQ-9 questionnaire will be administered.
- Patient diary will be reviewed.
- 6-point SMBG profiles will be reviewed.
- Hypoglycemia episodes will be assessed.
- Diet and exercise counseling will be provided.
- Glucose meter and supplies will be provided (or collected).
- Study medication compliance will be reviewed.
- Study medication will be dispensed for the Extension Period if this is an End of Treatment Visit. If this is a Rescue visit, study medication for the treatment period will be dispensed if needed. Study site personnel will monitor administration of injectable study medication (if the patient is due for an injection at the time of the visit).
- Instructions, reminders, and supplies (as appropriate) will be given to the patient (or designated caregiver) for proper transportation and storage of the study medication (to ensure temperature control, etc.).
- Rescue medication will be dispensed if criteria for rescue medication are met (refer to Table 3).
- Used/unused study medication will be collected.
- A between-visit telephone contact will take place between Visits 12 to 13 for collection of safety information.

4.3 Extension Period 1 (24-week Extension period)

Patients will return for follow-up visits every 8 weeks during the long-term site-and patient-blinded Extension Period 1. Patients will monitor their fasting blood glucose levels at least once a week and will continue to enter the results into the patient diary. Diet and lifestyle modification will be reinforced at each visit during this period. Patients will be contacted approximately monthly between visits (as described in Table 2).

The need for initiation of rescue therapy will be assessed based on criteria in Table 4. Patients must first complete the Rescue visit procedures before receiving open-label rescue therapy.

Table 4 Criteria for initiation of rescue therapy during Extension Period 1

Period	Central Laboratory HbA1c
From the day of Visit 13/Week 36 up to and including Visit 15/Week 52 and all unscheduled visits through the day prior to Visit 16/Week 65	HbA1c >8.0%

Note: Rescue upon receipt of HbA1c results. No repeat testing required for confirmation.

4.3.1 Extension Period 1 Visits (Visits 13 and 14, Weeks 36 and 44)

Prior to these visits, patients are to have fasted overnight (at least 8 hours). Patients should delay administering their morning dose of metformin and study medication on the morning of the study-site visit.

The following will be performed during these visits:

- IVRS will be contacted to register the visit.
- AEs, potential CV event triggers (Section 6.8.1), and concomitant medications will be reviewed.
- A brief physical exam will be conducted (refer to Section 5.2.2).
- Vital signs (sitting systolic and diastolic BP and HR) will be assessed.
- Body weight will be measured.
- Blood samples will be collected **prior to administration of study medication** for the following assessments:
  - Chemistry and hematology
  - HbA1c (need for rescue will be evaluated)
  - Fasting plasma glucose
  - Serum creatinine (calculated creatinine clearance; Cockcroft-Gault formula).
- Urine will be collected for the following assessments:
  - Urinalysis
  - Urine glucose/creatinine ratio

- Pregnancy test for all female patients, unless patient has had a hysterectomy.

- Patient diary will be reviewed.
- Visit 14 only: Patients will be instructed to complete 6-point SMBG profiles on any 3 days in the week prior to Visit 15.
- Hypoglycemia episodes will be assessed.
- Diet and exercise counseling will be provided.
- Glucose meter and supplies will be provided.
- Study medication compliance will be reviewed.
- Study medication will be dispensed every 8 weeks during Extension Period 1: Visits 13 and 14. Study site personnel will monitor administration of injectable study medication (if the patient is due for an injection at the time of the visit).
- Instructions, reminders, and supplies (as appropriate) will be given to the patient (or designated caregiver) for proper transportation and storage of the study medication (to ensure temperature control, etc.).
- Rescue medication will be dispensed at Visits 13 and 14 if criteria for rescue medication are met (refer to Table 2).
- Used/unused study medication will be collected.
- Between-visit telephone contacts will take place between Visits 13 to 16 for collection of safety information.

4.4 52-week Extension Period (Extension Period 2)

Patients will return for follow-up visits every 3 months (13 weeks) during the long-term site- and patient-blinded Extension Period 2. Patients will monitor their fasting blood glucose levels at least once a week and will continue to enter the results into the patient diary. Diet and lifestyle modification will be reinforced at each visit during this period. Patients will be contacted via telephone approximately monthly between visits (as described in Table 2).

The need for initiation of rescue therapy will be assessed based on criteria in Table 5. Patients must first complete the Rescue Visit procedures before receiving open-label rescue therapy.

Table 5 Criteria for initiation of rescue therapy during Extension Period 2

Period	Central Laboratory HbA1c
From the day of Visit 16/Week 65 up to and including Visit 17/Week 78 and all unscheduled visits through the day prior to Visit 18/Week 91	HbA1c >7.5%
From the day of Visit 18/Week 91 up to and including the day **before** Visit 19/Week 104	HbA1c >7.0%

Note: Rescue upon receipt of HbA1c results. No repeat testing required for confirmation.
Patients will discontinue study medication at the end of this treatment period (Visit 19, Week 104).

4.4.1 Extension Period 2 Visits (Visits 16, 17, and 18, Weeks 65, 78, and 91)

Prior to these visits, patients are to have fasted overnight (at least 8 hours). Patients should delay administering their morning dose of metformin and study medication on the morning of the study-site visit.

The following will be performed during these visits:

- IVRS will be contacted to register the visit.
- AEs, potential CV event triggers (Section 6.8.1), and concomitant medications will be reviewed.
- A brief physical exam will be conducted (refer to Section 5.2.2).
- Vital signs (sitting systolic and diastolic BP and HR) will be assessed.
- Body weight will be measured.
- Blood samples will be collected **prior to administration of study medication** for the following assessments:
  - Chemistry and hematology
  - HbA1c (need for rescue will be evaluated)
  - Fasting plasma glucose
  - Serum creatinine (calculated creatinine clearance; Cockcroft-Gault formula).
- Urine will be collected for the following assessments:

- Urinalysis
- Urine glucose/creatinine ratio
- Pregnancy test for all female patients, unless patient has had a hysterectomy.

- Patient diary will be reviewed.
- Visit 18 only: Patients will be instructed to complete 6-point SMBG profiles on any 3 days in the week prior to Visit 19.
- Hypoglycemia episodes will be assessed.
- Diet and exercise counseling will be provided.
- Glucose meter and supplies will be provided.
- Study medication compliance will be reviewed.
- Study medication will be dispensed every 13 weeks during Extension Period 2: Visits 16 to 18. Study site personnel will monitor administration of injectable study medication (if the patient is due for an injection at the time of the visit).
- Instructions, reminders, and supplies (as appropriate) will be given to the patient (or designated caregiver) for proper transportation and storage of the study medication (to ensure temperature control, etc.).
- Rescue medication will be dispensed at Visits 16 to 18 if criteria for rescue medication are met (refer to Table 5).
- Used/unused study medication will be collected.
- Between-visit telephone contacts will take place between Visits 16 to 19 for collection of safety information.

4.5 End of Extension Period 1 Visit (Visit 15, Week 52), End of Extension Period 2 Visit (Visit 19, Week 104), or Early Termination or Rescue Visit during Extension Period 1 or Extension Period 2

Prior to this visit, patients are to have fasted overnight (at least 8 hours), and to have abstained from strenuous exercise, alcohol, tobacco, and caffeine for 24 hours. Patients should delay administering the morning dose of metformin and study medication on the morning of the visit and bring oral antidiabetes medication and study medication to the study-site visit.

The following procedures will be conducted:

- IVRS will be contacted to register an End of Treatment Period Visit or Early Termination visit; the IVRS will not be contacted for a Rescue visit.
- AEs, potential CV event triggers (Section 6.8.1), and concomitant medications will be reviewed.
- A complete physical exam will be conducted (refer to Section 5.2.2).
- Vital signs (sitting systolic and diastolic BP and HR) will be assessed.
- 12-lead ECG will be performed.
- Body weight will be measured.
- BMI will be calculated.
- Waist circumference will be measured.
- Urine will be collected for the following assessments (to be collected right before time 0 of the meal tolerance test):
  - Urinalysis
  - Urine glucose/creatinine ratio.
- Meal tolerance test (MTT) will be performed (refer to Section 5.1.6).
- Blood samples will be collected **after administration of dapagliflozin** for the following assessments:
  - Serum pregnancy test (βhCG) for all female patients, unless patient has had a hysterectomy
  - Chemistry and hematology
  - Serum calcitonin
  - HbA1c
  - Fasting plasma glucose (need for rescue will be evaluated; part of meal tolerance test)

- Fasting serum lipid concentrations (total cholesterol, LDL cholesterol, HDL cholesterol, non-HDL cholesterol, and triglycerides)
- Fasting glucagon
- Serum creatinine (calculated creatinine clearance; Cockcroft-Gault formula)
- Fasting C-peptide (part of meal tolerance test)
- Fasting insulin (part of meal tolerance test)
- Serum antibodies to exenatide
- Plasma exenatide
- Blood sample for archiving.

- DTSQ-s questionnaire will be administered.
- SHIELD-WQ-9 questionnaire will be administered.
- Patient diary will be reviewed.
- 6-point SMBG profiles will be reviewed.
- Hypoglycemia episodes will be assessed.
- Diet and exercise counseling will be provided.
- Glucose meter and supplies may be provided (if needed) at Visits 15 and 19 and at a Rescue visit.
- Study medication compliance will be reviewed.
- Study medication will be dispensed at Visit 15 and (if needed) may be dispensed at a Rescue visit. At Visit 19 or an Early Termination visit, study medication will not be dispensed but a treatment regimen judged to be appropriate by the investigator may be initiated. However, patients should not be prescribed GLP-1 receptor agonists (BYETTA, BYDUREON or Victoza®) or SGLT-2 inhibitors (Farxiga, Forxiga, or Invokana), or any other GLP-1 analogues or SGLT2 inhibitors during the 10-week safety Follow-up Period.
- Used/unused study medication will be collected.

4.6 Follow-up Period

Patients will stop taking investigational medications at Visit 19 (Week 104) and will be re-evaluated 10 weeks later.

The following procedures will be conducted:

- IVRS will be contacted to register the visit.
- AEs, potential CV event triggers (Section 6.8.1), and concomitant medications will be reviewed.
- A complete physical exam will be conducted (refer to Section 5.2.2).
- Vital signs (sitting systolic and diastolic BP and HR) will be assessed.
- 12-lead ECG will be performed.
- Body weight will be measured.
- BMI will be calculated.
- Blood samples will be collected for the following assessments:
  - Serum pregnancy test (βhCG) for all female patients, unless patient has had a hysterectomy
  - Chemistry and hematology
  - Serum calcitonin
  - Serum creatinine
  - Serum antibodies to exenatide.
- Urine will be collected for the following assessments:
  - Urinalysis
  - Urine glucose/creatinine ratio.
- Hypoglycemia episodes will be assessed.
- Patient diary will be reviewed and collected.
- Glucose meter and supplies will be collected.

5. STUDY ASSESSMENTS

The Inform Web Based Data Capture (WBDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded on the eCRFs as specified in the study protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

5.1 Efficacy assessments

Study outcome measures are summarized in Section 8.4.

5.1.1 HbA1c

Blood samples for measurement of HbA1c will be collected according to the schedule presented in the Study Plan (Table 1 and Table 2). The instructions for collection, processing, packaging and shipping of the samples will be detailed in the lab manual.

5.1.2 Body weight

Body weight will be measured according to the schedule presented in the Study Plan (Table 1 and Table 2). The study-site staff should use a digital precision scale if possible, and record the weight in kilograms or pounds to the first decimal point (eg, 95.3 kg). The same scale should be used and the patient should wear a standard hospital-type gown or equivalent light clothing and no shoes for the body weight measurement at each visit.

5.1.3 Waist circumference

For waist circumference measurement, the study-site personnel must ensure that:

- The patient stands and the examiner places a measuring tape in a horizontal plane around the abdomen at the level of the umbilicus.
- The measuring tape is snug, but does not compress the skin, is parallel to the floor, and is not twisted.
- The measurement is taken at the end of a normal respiratory expiration.
- The measurement is recorded in centimeters to the first decimal point.
- Waist circumference will be measured according to the schedules presented in the Study Plan (Table 1 and Table 2).

5.1.4 Fasting plasma glucose

Blood samples for measurement of FPG will be collected according to the schedules presented in the Study Plan (Table 1 and Table 2). The instructions for collection, processing, packaging and shipping of the samples will be detailed in the lab manual.

5.1.5 6-point SMBG profiles

Patients will be instructed to perform 6-point SMBG profiles according to the schedule presented in the Study Plan (Table 1 and Table 2). Each separate 6-point SMBG profile encompasses 3 days, with 3 glucose measurements obtained preprandially (within 15 minutes prior to the meal) and 3 glucose measurements obtained postprandially (1.5 to 2 hours after the meal) for the 3 main meals of the day on each of the 3 days.

Patients who receive rescue therapy should be instructed to perform the 6-point SMBG after repeat FPG results confirm that rescue therapy is needed (see Section 4.2 for additional details on rescue criteria and therapy). However, the 6-point SMBG may be omitted at investigator discretion, if the investigator determines that it will be in the subject's best interest to begin rescue therapy sooner than 3 days after the confirmatory results are received.

5.1.6 Meal Tolerance Test

Liquid Meal Tolerance Tests (MTTs) are scheduled to occur at Week 0 (Visit 3), Week 28 (Visit 12) or Early Termination or Rescue, Week 52 (Visit 15), Week 104 (Visit 19) or Early Termination or Rescue. (For patients who receive rescue therapy, the MTT should be performed before the rescue treatment is initiated. Also, for patients who prematurely and permanently discontinue study medication, the MTT should be performed before study medication is discontinued. After rescue therapy is initiated or study medication is discontinued, no further MTTs are required.) A nutritional drink (eg, Ensure) will be used as a liquid meal supplement for the MTT.

The MTT visit should be rescheduled within 3 days of the visit if any of the following apply:

- Patient did not fast for at least 8 hours prior to the visit.
- Patient did not abstain from tobacco, alcohol, and caffeine for 24 hours prior to the MTT.

At Week 0/Randomization (Visit 3), study medication is to be given **AFTER** MTT is complete.

Please follow the steps below for MTT at Visit 3:

Step	Description	Starting Time Point	Ending Time Point
1	Collect urine for urinalysis.	-15 minutes	0 minutes
2	Draw the Time 0 blood sample for glucose, insulin, C-peptide, glucagon, and other laboratory tests due at the visit.	0 minutes	5 minutes
3	Administer the liquid meal supplement, starting immediately after the blood sample is drawn. Liquid meal should be consumed over 10 minutes.	5 minutes	15 minutes
4	Draw specimens for post-liquid meal glucose, C-peptide, glucagon, and insulin at 120 minutes from Time 0 blood draw.	120 minutes	125 minutes
5	Give study medication AFTER 120-minute blood draw is complete. Metformin should be taken by the subject at the next meal following completion of the MTT.	125 minutes	130 minutes

At Week 28 (Visit 12) or Early Termination or Rescue, patients should delay administering oral study medication (dapagliflozin/placebo) on the morning of the visit and bring it to the study site visit. Dapagliflozin/placebo is given BEFORE administration of the liquid meal supplement. Exenatide/placebo is taken by the patient at the usual weekly scheduled time prior to the visit (or can be taken at the site if the patient is due for a dose at the time of the visit). Metformin should be taken by the subject at the next meal following completion of the MTT.

Please follow the steps below for MTT at Visit 12:

Step	Description	Starting Time Point	Ending Time Point
1	Give dapagliflozin/placebo (and exenatide/placebo, if applicable) 1 hour BEFORE drawing the blood sample.	-60 minutes	-55 minutes
2	Collect urine for urinalysis.	-15 minutes	0 minutes
3	Draw the Time 0 blood sample 60 minutes AFTER administration of dapagliflozin/placebo. Samples should be drawn for glucose, insulin, C-peptide, glucagon, plasma dapagliflozin/placebo, and other laboratory tests due at the visit.	0 minutes	5 minutes
4	Administer the liquid meal supplement, starting immediately after the Time 0 blood samples are drawn. Liquid meal should be consumed over 10 minutes.	5 minutes	15 minutes
5	Draw specimens for post-liquid meal glucose, C-peptide, glucagon, and insulin at 120 minutes after Time 0 (Step 3).	120 minutes	125 minutes

At Week 52 (Visit 15), Week 104 (Visit 19), or Early Termination or Rescue, patients should delay administering oral study medication (dapagliflozin/placebo) on the morning of the visit and bring it to the study site visit. Dapagliflozin/placebo is given BEFORE administration of the liquid meal supplement. Exenatide/placebo is taken by the patient at the usual weekly scheduled time prior to the visit (or can be taken at the site if the patient is due for a dose at the time of the visit). Metformin should be taken by the subject at the next meal following completion of the MTT. The MTT at Week 52 (Visit 15)/Week 104 (Visit 19)/Early Termination/Rescue will only be done on patients who have not received rescue medication.

Please follow the steps below for MTT at Visit 15, Visit 19, or Early Termination or Rescue:

Step	Description	Starting Time Point	Ending Time Point
1	Give dapagliflozin/placebo (and exenatide/placebo, if applicable) 1 hour BEFORE drawing the blood sample.	-60 minutes	-55 minutes
2	Collect urine for urinalysis.	-15 minutes	0 minutes
3	Draw the Time 0 blood sample 60 minutes AFTER administration of dapagliflozin/placebo. Samples should be drawn for glucose, insulin, C-peptide, glucagon, and other laboratory tests due at the visit.	0 minutes	5 minutes
4	Administer the liquid meal supplement, starting immediately after the Time 0 blood samples are drawn. Liquid meal should be consumed over 10 minutes.	5 minutes	15 minutes
5	Draw specimens for post-liquid meal glucose, C-peptide, glucagon, and insulin at 120 minutes after Time 0 (step 3).	120 minutes	125 minutes

5.2 Safety assessments

The investigator will evaluate all Screening and safety laboratory reports and will sign and date the review. Any out of range laboratory results should be assessed for clinical significance, and reported as AEs accordingly. The investigator should follow all clinically significant laboratory abnormalities occurring during the study that were not present at baseline. These abnormalities should be evaluated with additional tests, if necessary, until the underlying cause is diagnosed or resolution occurs. The diagnosis and resolution date must be reported to the Sponsor.

Samples will be collected according to the schedules presented in the Study Plan (Table 1 and Table 2). The instructions for collection, processing, packaging and shipping of the samples will be detailed in the lab manual.

5.2.1 Laboratory safety assessments

5.2.1.1 Hematology

Hematology assessments will include the following: red cell count, hemoglobin, hematocrit, white cell count, platelets, differential count, mean cell volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration (or other routine hematology assessments as approved by the Sponsor).

5.2.1.2 Chemistry

Chemistry assessments will include the following: urea nitrogen, creatinine, total protein, albumin, uric acid, TB, alkaline phosphatase (ALP), ALT, AST, gamma glutamyl transpeptidase, amylase, lipase, creatine phosphokinase (CPK), creatine kinase, muscle and brain (CK-MB) (if CPK is elevated), troponin T (if CK-MB is elevated), sodium, potassium, chloride, bicarbonate, magnesium, phosphorus, and calcium (or other routine chemistry panels as approved by the Sponsor). Fasting C-peptide will be assessed according to the schedule presented in the Study Plan (Table 1 and Table 2).

5.2.1.3 Urinalysis

Urinalysis assessments will include the following: pH, specific gravity, glucose (urine glucose will be blinded throughout the study), blood, ketones, protein, and microscopic analysis (or other routine urinalysis as approved by the Sponsor).

5.2.1.4 Other Clinical Laboratory Evaluations

Fasting lipid panel

Fasting serum lipids (total-cholesterol, LDL-cholesterol, HDL-cholesterol, non-HDL cholesterol, and triglycerides) will be assessed at Screening (Visit 1), Baseline (Visit 3), Week 28 (Visit 12), Week 52 (Visit 15), and Week 104 (Visit 19).

Fasting glucagon

Fasting plasma glucagon will be collected according to the schedule presented in the Study Plan (Table 1 and Table 2).

Calcitonin

Blood samples will be drawn for measurement of calcitonin concentrations according to the schedules presented in the Study Plan (Table 1 and Table 2).

If an elevation of calcitonin is noted and deemed of clinical concern:

- The investigator should assess for factors that could be impacting calcitonin concentrations (ie, concomitant medications) and consider stopping them prior to rechecking calcitonin concentrations.

- If calcitonin concentrations remain elevated upon recheck, the patient should be referred to their healthcare provider for appropriate follow-up.
- Any subsequent testing and interpretation of results should be provided to the study site personnel.
- The investigator should discuss patient continuation in the study with the medical monitor.

The investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at center as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.3.

Thyroid Stimulating Hormone (TSH)

Blood samples will be collected for the measurement of thyroid stimulating hormone (TSH) at Screening, as presented in the Study Plan (Table 1 and Table 2). Abnormal TSH values will be further evaluated by free T4. Patients with abnormal free T4 values will be excluded.

Pregnancy Testing

All female patients, regardless of childbearing status (unless patient has had a hysterectomy), will provide blood or urine samples for pregnancy tests according to the schedules presented in the Study Plan (Table 1 and Table 2). The first dose of study medication or any other in-clinic dose of study medication will not be administered until a negative result is obtained.

Antibodies to Exenatide

Blood samples will be collected for the measurement of antibodies to exenatide according to the schedules presented in the Study Plan (Table 1 and Table 2).

Anti-exenatide antibody samples will be retained at the AZ Biobank or an AZ approved storage facility for up to a maximum of 15 years after the study completion date or according to local legislation. Samples may be destroyed prior to this timeframe if the patient has withdrawn consent or the samples are no longer required. The anti-exenatide antibody samples may be disposed of or destroyed and anonymized by pooling.

Additional analyses for anti-exenatide antibodies may be conducted. In addition, analyses may also be conducted on the anonymized, pooled anti-exenatide antibody samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the clinical study report (CSR).

Biological Samples for Future Research (Samples to Be Archived)

Up to 10 additional blood samples (approximately 5 to 6 mL each) will be collected at up to 5 different time points (ie, up to 2 samples at each time point) according to the schedule

presented in the Study Plan (Table 1 and Table 2) for potential future measurement of other analytes, if indicated upon review of the data.

Biological samples for future research will be retained at the AZ Biobank or an AZ approved storage facility for a maximum of 15 years after the study completion date or according to local legislation. Samples may be destroyed prior to this timeframe if the patient has withdrawn consent.

5.2.2 Physical examination

A complete physical examination should be performed according to the schedules presented in the Study Plan (Table 1 and Table 2). The complete physical examination includes the following: general appearance including skin inspection (including injection site), lymph nodes, thyroid, musculoskeletal/extremities, cardiovascular, lungs, abdomen, and reflexes. Baseline physical examination data are collected at Visit 1, and new findings at the following physical examinations are recorded as change from baseline.

A brief physical examination should be conducted according to the schedules presented in the Study Plan (Table 1 and Table 2). A brief physical examination includes the following: skin (including injection site), extremities, cardiovascular, lungs, and abdomen. Baseline data is collected at Day 0 during the full physical examination, and new findings at the following physical examinations are recorded as change from baseline.

Clinically significant abnormalities in physical examination findings at study termination must be followed up by the investigator and evaluated with additional tests if necessary, until the underlying cause is diagnosed or resolution occurs. As appropriate, the diagnosis and resolution date physical examination abnormalities must be reported as AEs.

Refer to Section 6.1 for reporting AEs.

5.2.3 ECG

A 12-lead ECG will be performed at Visit 1 (Screening), unless the patient has had a satisfactory ECG result in the past 6 months. Additional 12-lead ECGs will be performed according to the schedules presented in the Study Plan (Table 1 and Table 2).

Standard 12-lead ECGs will be performed after approximately 5 minutes of quiet rest with the patient in a supine position. If the ECG must be performed with the patient in another position (sitting, standing, etc), the investigator should record the alternate position. The investigator should date and sign the ECG tracing and record the clinical significance of any abnormal result on the tracing. ECGs will be interpreted by a qualified physician (the investigator or qualified designee) at the clinical study site.

Refer to Section 6.1 for reporting AEs.

5.2.4 Vital signs

Vital sign measurements in this study will include sitting systolic and diastolic BP and pulse. Vital signs should be measured after the patient rests for approximately 5 minutes and with the patient in a sitting position.

BP measurement with a properly calibrated and validated instrument should be used. Patients should be seated quietly for at least 5 minutes in a chair rather than on an examination table, with feet on the floor and arm supported at heart level. An appropriate-sized cuff (cuff bladder encircling at least 80% of the arm) should be used to ensure accuracy. There will be 2 BP measurements made at least 30 seconds apart. Both BP measurements as well as the calculated average will be entered in the eCRF. The same arm should be used for all BP measurements during the study.

BP and pulse measurement must be performed in the seated position.

5.2.5 Other safety assessments

5.2.5.1 Cardiovascular events

Deaths (including cause of death [cardiovascular related vs. noncardiovascular]) and cardiovascular events (including myocardial infarction, stroke, acute coronary syndrome, ventricular fibrillation/tachycardia, and congestive heart failure requiring hospitalization) considered to be SAEs should be reported to the safety data entry site within 24 hours (refer to Section 6.4).

5.2.5.2 Pancreatitis

All SAEs of pancreatitis should be reported to the safety data entry site within 24 hours (refer to Section 6.4).

5.2.5.3 Liver function test abnormalities

Please see Appendix C, 'Algorithm on Management of Sustained Elevated Liver Safety Abnormalities', for further guidance. Investigators should contact the medical monitor if a patient develops a liver function test abnormality.

5.2.5.4 Injection-site adverse events

Small, asymptomatic, SC nodule formation at the injection site is an expected event associated with sustained release delivery systems.

Injection sites should be routinely examined at each study site visit. If any injection-site reaction meets the criteria for an AE (refer to Section 6.1), the event is to be reported on the AE eCRF, with the reaction described as specifically as possible. In the rare event of a severe injection site-related AE, the affected patient may be asked to undergo further evaluation which could include a biopsy of the injection site or nodule, if appropriate.

5.3 Other assessments

5.3.1 Hypoglycemia

Using the plasma equivalent-reporting glucose meters provided, patients should check their glucose levels, whenever possible, if they have symptoms suggestive of hypoglycemia.

For each hypoglycemic episode, patients should record their blood glucose levels, associated symptoms, and treatments in the study diaries.

5.3.2 Patient reported outcomes

The methods for collecting patient reported outcome (PRO) data are presented below. For the timing of individual assessments refer to the Study Plan (Table 1 and Table 2).

5.3.2.1 DTSQ-s

Treatment satisfaction will be assessed using the status version of the DTSQ-s (Appendix D). The DTSQ-s is an 8-item PRO measure consisting of items that assess current satisfaction with treatment as well as concerns about hyperglycemia and hypoglycemia over the past few weeks (Bradley 1994).

5.3.2.2 SHIELD-WQ-9 questionnaire

The SHIELD-WQ-9 measures health-related quality of life in response to self-perceived weight change (Appendix E). It consists of 2 questions where question 1 asks the patient if she/he has gained, lost weight or stayed at the same and question 2 is based on response to question 1 and asks about effects (9 dimensions) due to change or lack of change in body weight using 4 response options: worsen, improved, stayed the same, and not applicable.

The questions have been used in the observational study SHIELD - Study to Help Improve Early evaluation and management of risk factors Leading to Diabetes (Bays et al 2007a, Bays et al 2007b). It is included for exploratory purposes and the questions will be assessed at Weeks 28, 52, and 104.

5.4 Pharmacokinetics

5.4.1 Collection of samples

Blood samples for determination of exenatide and dapagliflozin concentrations in plasma will be taken at the times presented in the Study Plan (Table 1 and Table 2).

Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

5.4.2 Determination of drug concentration

Samples for determination of drug concentration in plasma will be analyzed by an appointed laboratory on behalf of AstraZeneca using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

5.4.3 Storage and destruction of pharmacokinetic samples

PK samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses. If kept for future analysis, the samples will be retained at the AZ Biobank or an AZ approved storage facility for a maximum of 15 years after the study completion date or according to local legislation. Samples may be destroyed prior to this timeframe if the patient has withdrawn consent.

All samples still within the known stability of the analytes of interest at the time of receipt by the bioanalytical laboratory will be analyzed.

PK samples may be disposed of or destroyed and anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the clinical study report (CSR).

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in a Bioanalytical Report.

Any residual sample remaining after PK analysis has been performed may be used for exploratory biomarker research and characterization of metabolites, if consent for this exploratory research has been obtained.

5.5 Pharmacodynamics (not applicable)

5.6 Pharmacogenetics (not applicable)

5.7 Biomarker analysis (not applicable)

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section and all relevant safety reporting procedures and requirements.

6.1 Definition of adverse events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

6.2 Definitions of serious adverse event

An SAE is an AE occurring during any study phase (ie, lead-in, treatment, Extension Period 1, Extension Period 2, follow-up), that fulfills 1 or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent 1 of the outcomes listed above.

Any event of cancer, drug dependency/abuse, laboratory abnormalities fulfilling the Hy's law definition (ALT/AST >3x ULN and total bilirubin >2x ULN) should be reported as an SAE using the most relevant SAE criteria, as judged by the investigator.

For further guidance on the definition of a SAE, see Appendix B, 'Additional Safety Information'.

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

AEs will be collected from time of signature of informed consent, during the lead-in period, throughout the treatment and extension periods and including the follow-up period (Visit 20).

All AEs will be recorded on source documents and the eCRFs.

6.3.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last visit in the study are followed up by the investigator for as long as medically indicated. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

6.3.3 Variables

The following variables will be collect for each AE;

- AE (verbatim)

- The date and time when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the IP (yes or no)
- Action taken with regard to IP
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date investigator became aware of serious AE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Description of AE.

The maximum intensity of an AE will be rated according to the following definition:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities).

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of

disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.2.

6.3.4 Causality collection

The investigator will assess causal relationship between IP and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B, 'Additional Safety Information'.

6.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: 'Have you had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.3.6 Adverse events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarized in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the IP.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible, the reporting investigator should use the clinical rather than the laboratory term (eg, anemia instead of low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

6.3.7 Hy's Law

Cases where a patient shows an AST or ALT > 3x ULN together with total bilirubin > 2x ULN must be reported as SAEs.

Potential Hy's Law cases that meet any of the identification criteria specified in Appendix C will require an unscheduled laboratory draw for assessment by the central laboratory (see central laboratory manual for further instructions on appropriate laboratory kit).

6.3.8 Hypoglycemia

Patients will be asked to test their blood glucose if they develop symptoms suggestive of hypoglycemia and to record specific symptoms in the patient diary. If the investigator determines that a patient experienced symptoms consistent with hypoglycemia, the event should be documented in the patient's source documentation and the hypoglycemia eCRF page (not AE eCRF page) must be completed. If a plasma or capillary glucose value of ≤70 mg/dL (3.9 mmol/L) is noted within the data, and the patient is asymptomatic, the investigator should assess whether the circumstances around the value are consistent with hypoglycemia. If the assessment is that the value is consistent with hypoglycemia, the hypoglycemia eCRF page should be completed. Study site personnel must obtain accurate information for the patient's file and for the hypoglycemia page of the eCRF. If the hypoglycemic episode intensity is judged to be severe, the investigator is required to contact the Sponsor.

The criteria for evaluating the intensity of a hypoglycemic episode are the following:

- MILD: Usually transient, requires no special treatment, and does not interfere with the patient's daily activities.
- MODERATE: Usually causes a low level of inconvenience or concern to the patient and may interfere with daily activities, but is usually ameliorated by simple therapeutic measures.
- SEVERE: Requires the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma.

All hypoglycemia events will be programmatically classified as major, minor, or other hypoglycemia:

- Major hypoglycemia is an event that results in loss of consciousness, seizure or coma (or other mental status change consistent with neuroglycopenia in the judgment of the investigator or physician), which resolves after administration of glucagon or glucose. In addition, any event that requires third party assistance to resolve because of severe impairment in consciousness or behavior (whether or not symptoms of hypoglycemia are detected by patient) and is associated with a plasma or capillary glucose concentration of <3 mmol/L (54 mg/dL) will be classified as major hypoglycemia.

- Minor hypoglycemia is a non-major hypoglycemia event that has symptoms consistent with hypoglycemia and had plasma or capillary glucose value of <3 mmol/L (54 mg/dL) prior to treating the episode.

- If a hypoglycemia event does not meet the criteria for a major or minor event described above, it will be classified as other hypoglycemia.

6.3.9 Microscopic Hematuria

In the event that hematuria is observed during a patient's participation, the sponsors recommend standard of care in diagnosing the cause of the hematuria. This section presents references and an example of standard of care evaluation of microscopic hematuria. Local standards of care should be followed.

Patients with repeated reports of microscopic hematuria in 2 or more properly collected urine samples need to have follow-up for this result according to standard of care. The American Urological Association defines microscopic hematuria as 3 or more red blood cells per high-power microscopic field in urinary sediment from 2 or more properly collected urinalysis specimens (American Urological Association (AUA) website, 2011; Grossfeld et al 2001). These Best Practice guidelines have been evaluated by Jung in 2011 in a study of 772,000 patients (Jung et al 2011).

Patients who show microscopic hematuria that is accompanied by significant proteinuria, red blood cell casts, or dysmorphic red blood cells in the sediment should be evaluated for the presence of primary renal disease and need to be referred to a nephrologist (American Urological Association (AUA) website, 2011; Grossfeld et al 2001).

Patients who lack other explanation for their hematuria, or who have risk factors for significant urologic disease, will need a urological evaluation and should be referred to an urologist. Risk factors for significant urological disease include unexplained microscopic hematuria as well as smoking history, occupational exposure to dyes or chemicals (such as benzenes or aromatic amines), visible hematuria, age >40 years, previous urologic history, history of irritative voiding symptoms, history of urinary tract infection, analgesics or phenacetin abuse, history of pelvic irradiation, or cyclophosphamide use (American Urological Association (AUA) website, 2011; Grossfeld et al 2001). Results from any procedure or investigations should be reported on the eCRF.

6.3.10 Asymptomatic bacteriuria

The following is presented to assist in the classification and management of infections of the urinary and genital tracts in studies with dapagliflozin. It is not intended to supplant investigators' clinical judgment.

During enrollment, treatment, and follow up of patients in this trial, the investigator may discover a patient with asymptomatic bacteriuria. Asymptomatic bacteriuria is defined as the presence of $\geq 10^5$ colony forming units/mL of bacteria in a properly collected voided urine specimen, without signs or symptoms typically attributed to urinary tract infection.

Asymptomatic bacteriuria is prevalent among diabetic women, and is associated with pyuria in 70% of cases. Neither guidelines from the US (Nicolle et al 2005, Lin et al 2008) nor Europe (European Association of Urology 2008) recommend screening for, or treatment of, asymptomatic bacteriuria in non-pregnant diabetic patients. In this study, the central laboratory will report urinary dipstick test results for hemoglobin but will not routinely report the results of urinary dipstick tests for leukocyte esterase as a screening test for pyuria in surveillance urine examinations.

6.3.11 Volume depletion

Dapagliflozin has a modest diuretic effect. The risk of volume depletion is enhanced when 2 diuretics are used in combination and in patients that otherwise are at risk for volume depletion. Therefore, caution should be exercised when administering to patients at risk for volume depletion due to co-existing conditions or concomitant medications, such as loop diuretics. These patients should be carefully monitored for volume status, electrolytes, and renal function.

6.3.12 Malignancy

All cases of malignancies should be reported to the safety data entry site within 24 hours.

6.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the CRF.

If any SAE occurs in the course of the study, then investigators or other site personnel inform the appropriate AstraZeneca representatives within 1 day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all the necessary information is provided to the safety data entry site **within 1 calendar day** of initial receipt for fatal and life threatening events **and within 3 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the investigator or other study site personnel reports a SAE to the appropriate AstraZeneca representative by designated back-up procedures.

The AstraZeneca representative will advise the investigator/study site personnel how to proceed.

The reference document for definition of expectedness/listedness is the Investigator's Brochure (IB) for the AstraZeneca drug and the EU Summary of Product Characteristics (SPC) for the active comparator product (including any AstraZeneca comparator).

6.5 Overdose

Overdose is defined as more than 100 mg (10 tablets) of dapagliflozin per day, or more than 1 dose of EQW within 3 days. 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. EQW has been well-tolerated with no major safety concerns when given in doses of up to 10 mg/day in patients with T2DM. If an overdose is suspected, monitoring of vital functions as well as treatment as appropriate should be performed.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.
- An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on an AstraZeneca study medication occurs in the course of the study, then the investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 6.4. For other overdoses, reporting must occur within 30 days.

6.6 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to the safety data entry site.

6.6.1 Maternal exposure

If a patient becomes pregnant during the course of the study all study medication should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal

birth, or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the safety data entry site within 1 or 3 calendar days for SAEs (see Section 6.4) and within 3 days for all other pregnancies.

The same timelines apply when outcome information is available.

6.6.2 Paternal exposure

There is no restriction on fathering children or donating sperm during the study.

Pregnancy of the subject's partners is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality), occurring from the date of the first dose until 10 weeks after the subject's last dose of the study medications should, if possible, be followed up and documented.

6.7 Management of IP related toxicities

Dose reductions are not permitted in this study.

6.8 Study governance and oversight

6.8.1 Cardiovascular Adjudication Committee

Predefined cardiovascular events (including cause of death [cardiovascular related vs. non-cardiovascular], myocardial infarction, stroke, acute coronary syndrome, ventricular fibrillation/tachycardia, and congestive heart failure requiring hospitalization) will be adjudicated using pre-specified criteria by an adjudication committee composed of independent cardiologists blinded to study treatment. The adjudication committee operations and criteria will be described in a separate charter.

6.8.2 Hepatic Adjudication Committee

An independent Hepatic Adjudication Committee, blinded to the treatment of the patients, will determine the probability that drug-induced liver injury (DILI) is the cause of liver-related abnormalities, including, but not limited to:

- Hepatic events timely related to death (within 30 days before death)
- AST and/or ALT >3x ULN and TB >2x ULN (within 14 days of the AST and/or ALT elevation)

- AST and/or ALT >10 x ULN

A separate Adjudication Manual will define and describe the procedure for the handling, reporting and classification of these cases.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational products

Investigational product	Dosage form and strength	Manufacturer
Exenatide once weekly (EQW)	2.0 mg powder for injection	AstraZeneca
Placebo to match exenatide once weekly	Placebo powder for injection	AstraZeneca
Dapagliflozin	10 mg tablets	AstraZeneca
Matching placebo for dapagliflozin	Placebo tablets	AstraZeneca

All investigational products will be packed into kits enough for 4-week treatment. The vials containing the exenatide/placebo powder for injections will be packed into a small box containing 4 vials. Four syringes with diluent for suspension of EQW and matching placebo will be packed into another box also containing 6 vial adaptors and 6 23-Gauge x 5/16 inch needles.

Dapagliflozin and matching placebo tablets will be packed in bottles containing 35 tablets.

Exenatide placebo for the single-blind run-in period will be packed into a box containing 1 vial of exenatide placebo powder for injection, 1 syringe with diluents, 2 vial adaptors, and 2 23-Gauge x 5/16 inch needles.

7.2 Dose and treatment regimens

The study consists of a Screening Visit (Visit 1), a Lead-in Period Visit (Visit 2), a single-blind run-in period of 1 week and a randomization visit (Visit 3), followed by a 28-week randomized, double-blind treatment period and a 24-week extension period. Double-blind study medication will be dispensed every 4 weeks during the treatment period and every 8 weeks during Extension Period 1. Double-blind study medication will be dispensed every 3 months (13 weeks) during Extension Period 2. Instructions for dose preparation of the exenatide once weekly injection will be provided in the Instructions for Use.

AstraZeneca or a designated representative will provide all IPs. At each visit, patients will receive sufficient quantity of drug to last the duration of time between visits. In the event the patient loses her/his study medication, the study center should call into the IVRS/IWRS

system in order to allow the system to determine the appropriate alternative kit identification number(s) to be dispensed from the study center's remaining inventory.

Lead-in period (Visit 2, Week -1)

Patients will receive dapagliflozin placebo tablets to be taken daily for the 1-week placebo lead-in period, as well as an exenatide placebo injection to be taken once at the start of the placebo lead-in period. A medically qualified staff member will demonstrate preparing the study medication by reconstitution of the powder in the diluent provided for the patient or a designated caregiver, after which the patient (or designated caregiver) will administer the placebo injection. Patients will be instructed to continue taking metformin as directed during this period.

28-week Treatment period (Visits 3-12)

At Visit 3 patients will be randomly assigned to 1 of the 3 treatment arms and randomized study medication (injection and tablets) will be dispensed. For EQW and matching placebo, the doses of study medication will be taken at the study site. The injection must be administered immediately after preparation of the dose. Patients will subsequently self-administer EQW or matching placebo (or have it administered by a caregiver) once weekly relative to the date of the first dose of EQW (Visit 3 [Day 0]) through Visit 12 (Week 28/Study Termination). Patients will receive dapagliflozin or matching placebo tablets to be taken once daily through Visit 12 (Week 28/Study Termination).

On weeks of scheduled study visits, patients should bring their study medication with them to the study site (patients should be given instructions and supplies as appropriate for study medication transportation to ensure proper temperature control, etc.) and will self-administer EQW as directed by study-site personnel.

If a dose of EQW is missed, it should be administered as soon as noticed, provided the next regularly scheduled dose is due at least 3 days later. Thereafter, patients can resume their usual dosing schedule of once every 7 days (weekly).

If a dose of EQW is missed and the next regularly scheduled dose is due 1 or 2 days later, the patient should not administer the missed dose and instead resume EQW with the next regularly scheduled dose.

Doses of EQW or matching placebo are to be administered by SC injection in the abdomen, thigh, or upper arm. The site of injection should be rotated within or across regions on a regular basis so that the same site is not used repeatedly.

If a dose of dapagliflozin is missed, advise patients to take it as soon as it is remembered unless it is almost time for the next dose, in which case patients should skip the missed dose and take the medicine at the next regularly scheduled time. Advise patients not to take 2 doses of dapagliflozin at the same time.

Extension Period 1 (Visits 12 to 15)

Study medication will be dispensed every 8 weeks during this period.

Extension Period 2 (Visits 16 to 19)

Study medication will be dispensed every 3 months (13 weeks) during this period.

7.3 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

7.4 Storage

All study medications should be kept in a secure place under appropriate storage conditions. The IP label on the study medication kit specifies the appropriate storage.

7.5 Compliance

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

The administration of all study medications (including IPs) should be recorded in the appropriate sections of the eCRF. Treatment compliance (number of doses received relative to doses planned) will be summarized by treatment for the ITT Population.

7.6 Accountability

The study medication provided for this study will be used only as directed in the study protocol.

The study site personnel will account for all study medications dispensed to and returned from the patient.

Study site personnel will account for all study medications received at the site, unused study medications and for appropriate destruction. Certificates of delivery, destruction and return should be signed.

A drug disposition form will be provided to record all study medication dispensed to or returned from each patient. Upon completion of the study, all unused study medication, and copies of completed drug disposition forms should be returned to the Sponsor (or designee).

Used study medication kits may be disposed at study sites after accountability has been verified by the Sponsor (or designee) and will not be returned to the Sponsor (or designee).

For unused study medication, a clinical supplies return authorization form (CSRAF) will be completed by the clinical research associate at the closeout visit. The completed CSRAF should be enclosed with each return drug shipment to the Sponsor (or designee). The study site personnel must maintain documentation of any missing, damaged, or unreturned study medication.

7.7 Concomitant and other treatments

Patients must follow the medication restrictions outlined in the inclusion and exclusion criteria (Section 3.1 and Section 3.2, respectively) during the study. Dosages for certain concomitant medications should 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, must be reported to the Sponsor.

Metformin and rescue therapy will not be provided in pre-packaged kits by the Sponsor and will be sourced locally by the site in cooperation with the CRO and in accordance with the approved package labeling.

The table below lists prohibited medications and the applicable time frames.

Restricted Medication/Class of drug:	**Usage**
Antihypertensive agents	Patient must either not be treated with or has been on a stable treatment regimen for a minimum of 2 months prior to Visit 1 (Screening).
Thyroid replacement therapy	Patient must either not be treated with or has been on a stable treatment regimen for a minimum of 2 months prior to Visit 1 (Screening).
Antidepressant agents	Patient must either not be treated with or has been on a stable treatment regimen for a minimum of 2 months prior to Visit 1 (Screening).
Antihyperglycemic therapy	Administration of any antihyperglycemic therapy, other than metformin, for more than 14 days (consecutive or not) during the 12 weeks prior to enrollment is prohibited.
Antihyperglycemic therapy	Administration of any antihyperglycemic therapy, other than metformin, at any dose, at any time during the 4 weeks prior to the enrollment visit is prohibited.
Exenatide (including BYETTA®, BYDUREON™, or exenatide suspension) or any GLP-1 analog	Any prior exposure is prohibited (or use of non-study products during the study).
Dapagliflozin (FORXIGA, FARXIGA) or any	Any prior exposure is prohibited (or use of non-study

Restricted Medication/Class of drug:	Usage
SGLT-2 inhibitor	products during the study).
Any DPP-4 inhibitor	Prohibited within 3 months prior to Visit 1 (Screening) and during the study.
Systemic corticosteroids by oral, intravenous, intra-articular, or intramuscular route	Prohibited within 3 months prior to Visit 1 (Screening) and during the study.
Potent, inhaled, or intrapulmonary (including ADVAIR®) steroids known to have a high rate of systemic absorption[a]: • beclomethasone dipropionate nasal and oral inhalation (Beclovent, Beclonase, Qnasl, Qvar) • budesonide nasal and oral inhalation (Pulmicort, Symbicort, Rhinocort) • flunisolide oral inhalation aerosol and nasal route (Aerobid, Aerospan, Nasalide, Nasarel) • fluticasone propionate aerosol and powder (Advair, Flovent) • mometasone furoate aerosol and powder inhalation (Asmanex, Dulera)	Prohibited within 3 months prior to Visit 1 (Screening) and during the study.
Prescription or over-the-counter weight loss medications	Prohibited within 3 months prior to Visit 1 (Screening) and during the study.

[a] Not excluded: ciclesonide oral inhalation and nasal spray (Alvesco, Omnaris, Zetonna). This is not a comprehensive listing. If the exclusion status of any concomitant medication is in question, please contact the Medical Monitor for discussion.

The following steroids are permitted during the study: ciclesonide oral inhalation and nasal spray (Alvesco, Omnaris, Zetonna).

7.7.1 Metformin

Up to Visit 20 (Week 114), patients should continue to administer the same type and dose of metformin therapy they were using at study entry. Metformin will be prescribed by the investigator and should be administered and stored according to product and country-specific labeling.

7.7.2 Rescue therapy

Patients who require rescue therapy (ie, FPG rescue criteria met) will receive open-label titrated basal insulin, as prescribed by the investigator (see Section 4.2). Patients should continue receiving study medication while receiving rescue therapy. Patients must first complete the Rescue visit procedures before receiving open-label rescue therapy.

7.7.3 Other concomitant treatment

Other medication other than that described above, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF.

8. STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

All personnel involved with the analysis of the study will remain blinded until database lock and protocol violators identified at the end of the 28-week randomized treatment period. AstraZeneca and its applicable representative(s) will be unblinded in Extension Periods 1 and 2 (ie, from Week 28 onwards). Sites, site monitors, and patients will remain blinded during Extension Periods 1 and 2.

Statistical analysis of this study will be the responsibility of AstraZeneca or its representatives.

All of the data will be entered, verified, and archived by AstraZeneca or its representatives. All data listings, summaries, and analyses will be performed under the guidance and approval of statisticians at AstraZeneca.

Baseline: Baseline refers to the last measurement collected prior to the first dose of study medication at the randomization visit.

All collected data will be listed. A detailed statistical analysis plan (SAP) will be written and approved prior to database lock.

8.2 Sample size estimate

A total of 209 patients per treatment group are required, assuming:

- Mean difference of 0.35% in HbA1c change from baseline with EQW + dapagliflozin versus each monotherapy
- Standard deviation of 1.1% and 90% power (based on a 2-sample t-test at a 0.05 significance level)

Assuming a 5% drop-out rate prior to Week 4 (Visit 6), the first visit where HbA1c is tested, 220 patients per treatment arm (a total of approximately 660 patients) would have post-baseline measurements of HbA1c and thus be included in the ITT analysis of the primary objective. Assuming 40% screen failure, a total of 1100 patients will be screened.

8.3 Definitions of analysis sets

8.3.1 Efficacy analysis set

There will be 2 analysis sets for the efficacy evaluation:

- Intent-to-treat (ITT), the primary analysis set will include randomized patients who receive at least 1 dose of study medication and have at least 1 post-baseline HbA1c assessment.
- Per-protocol (PP), the secondary analysis set, will be a subset of the ITT population through the exclusion of those with important protocol violation(s). Important protocol violations are those that have the potential to affect the result of the primary analysis. Detailed exclusion criteria for the PP population will be specified in the SAP. Patients excluded from the PP analysis will be identified before database lock.

8.3.2 Safety analysis set

All randomized patients receiving at least 1 dose of study treatment will be considered in the safety population and included in the safety analysis.

8.4 Outcome measures for analyses

8.4.1 Primary efficacy endpoint

The primary efficacy endpoint is the change in HbA1c from baseline to Week 28.

8.4.2 Secondary efficacy endpoints

- Change in total body weight from baseline to Week 28
- Change in FPG from baseline to Week 28
- Change from baseline in 2-hour PPG after standardized MTT at Week 28
- Proportion of patients achieving HbA1c <7.0% at Week 28
- Proportion of patients achieving weight loss ≥5 .0% at Week 28
- Change from baseline in FPG to Week 2 (dapagliflozin+exenatide vs exenatide)
- Change from baseline in seated systolic BP from baseline to Week 28

8.4.3 Exploratory endpoints

- Proportion of patients rescued or discontinued for lack of glycemic control at Week 28

- Proportion of patients achieving HbA1c ≤6.5% at Week 28.
- Change in self monitored 6-point blood glucose from baseline to Week 28
- Proportion of patients with HbA1c reduction of ≥1.0% at Week 28
- Proportion of patients with HbA1c reduction of ≥1.0% and weight reduction of ≥3.0% at Week 28
- Change in waist circumference compared to baseline at Week 28
- Change in HOMA B (beta cell function) and HOMA S (insulin sensitivity) scores at Week 28
- Proportion of patients with a reduction in both HbA1c and weight at Week 28
- Change in diastolic BP from baseline to Week 28
- Change in total cholesterol, LDL cholesterol, HDL cholesterol, non-HDL cholesterol, and fasting triglycerides from baseline to Week 28
- DTSQ-s and SHIELD WQ-9 questionnaire at Week 28
- Change in total body weight in patients without an AE of nausea from baseline to Week 28
- Exenatide and dapagliflozin PK profiles

8.4.4 Extension Period 1 exploratory endpoints

- Change in HbA1c from baseline to Week 52.
- Change in total body weight from baseline to Week 52.
- Change in FPG from baseline to Week 52.
- Change in 2-hour PPG after a standardized meal tolerance test at Week 52.
- Proportion of patients achieving HbA1c <7.0% at Week 52.
- Proportion of patients achieving weight loss ≥5.0% at Week 52.
- Change in seated systolic BP from baseline to Week 52.

- Proportion of patients rescued or discontinued for lack of glycemic control at Week 52.
- Proportion of patients achieving HbA1c ≤6.5% at Week 52.
- Change in self-monitored 6-point blood glucose from baseline to Week 52.
- Proportion of patients with HbA1c reduction ≥1.0% at Week 52.
- Proportion of patients with HbA1c reduction ≥1.0% and weight reduction of ≥3.0% at Week 52.
- Change in waist circumference compared to baseline at Week 52.
- Change in HOMA B (beta cell function) and HOMA S (insulin sensitivity) scores at Week 52.
- Proportion of patients with a reduction in both HbA1c and weight at Week 52.
- Change in diastolic BP from baseline to Week 52.
- Change in total cholesterol, LDL cholesterol, HDL cholesterol, non-HDL cholesterol, and fasting triglycerides from baseline to Week 52.
- DTSQ-s and SHIELD-WQ-9 questionnaires at Week 52.
- Change in total body weight in patients without an AE of nausea from baseline to Week 52.

8.4.5 Extension Period 2 exploratory endpoints

- Change in HbA1c from baseline to Week 104.
- Change in total body weight from baseline to Week 104.
- Change in FPG from baseline to Week 104.
- Change in 2-hour PPG after a standardized meal tolerance test at Week 104.
- Proportion of patients achieving HbA1c <7.0% at Week 104.
- Proportion of patients achieving weight loss ≥5.0% at Week 104.
- Change in seated systolic BP from baseline to Week 104.

- Proportion of patients rescued or discontinued for lack of glycemic control at Week 104.
- Proportion of patients achieving HbA1c ≤6.5% at Week 104.
- Change in self-monitored 6-point blood glucose from baseline to Week 104.
- Proportion of patients with HbA1c reduction ≥1.0% at Week 104.
- Proportion of patients with HbA1c reduction ≥1.0% and weight reduction of ≥3.0% at Week 104.
- Change in waist circumference compared to baseline at Week 104.
- Change in HOMA B (beta cell function) and HOMA S (insulin sensitivity) scores at Week 104.
- Proportion of patients with a reduction in both HbA1c and weight at Week 104.
- Change in diastolic BP from baseline to Week 104.
- Change in total cholesterol, LDL cholesterol, HDL cholesterol, non-HDL cholesterol, and fasting triglycerides from baseline to Week 104.
- DTSQ-s and SHIELD-WQ-9 questionnaires at Week 104.
- Change in total body weight in patients without an AE of nausea from baseline to Week 104.

8.5 Methods for statistical analyses

8.5.1 Analysis of the primary variable

The primary analysis will assess the benefit (superiority) of the combination of EQW + dapagliflozin over the individual components (ie, over EQW and over dapagliflozin) for the change in HbA1c from baseline to Week 28 of the short-term double-blind treatment period for the ITT population.

The mixed model for the repeated measures (MMRM) will include change from baseline to Week 28 in HbA1c as the dependent variable, treatment, region, baseline HbA1c stratum (<9.0% or ≥9.0%), week, and treatment by week interaction as fixed factors. Baseline measurement of HbA1c will be included as a continuous covariate. All observed HbA1c values from post-baseline (including early dropouts, but excluding those data points after glycemic rescue therapy or post-treatment follow-up) will be included in the MMRM analysis. Since MMRM will be used for the primary analysis of primary endpoint, there will be no need

to impute missing data. Consequently, no Last Observation Carried Forward or other imputation technique will be required or used for the primary analysis. An unstructured covariance matrix will be used for the MMRM analysis, unless the model does not converge, in which case the covariance structure will be decided based on model convergence status and the Akaike information criterion. The least-squares (LS) means, standard errors, and 2-sided 95% confidence intervals, as well as the mean difference between treatment groups (EQW + dapagliflozin compared to EQW and compared to dapagliflozin) will be presented.

The treatment comparison of the primary efficacy endpoint (HbA1c change from baseline) will be considered significant if and only if the comparisons of the combination treatment group (EQW + dapagliflozin) against both of the 2 active-control groups (dapagliflozin 10 mg QD and EQW 2 mg) are significant. Due to this specific criterion for showing superiority of the combination treatment group over the individual treatment groups in primary endpoint, no multiplicity adjustment for the primary analysis will be required to control the overall type-I error, which is considered to be 0.05; consequently, both of the individual treatment comparisons will be performed at 5% level of significance (ie, alpha = 0.05 2-sided).

The same MMRM analysis will be applied to the PP population as a supportive analysis for the primary efficacy endpoint.

8.5.2 Analysis of the secondary variables

For the secondary efficacy endpoints, a Cochran-Mantel-Haenszel (CMH) test stratified by baseline HbA1c stratum (<9.0% or ≥9.0%) will be applied to the categorical variables, and an MMRM model or analysis of covariance (ANCOVA) model will be applied to the continuous variables.

The significance or non-significance of the treatment comparisons for the primary efficacy endpoint will determine whether or not the statistical tests are to be performed to compare treatments for the secondary efficacy endpoints. In other words, if and only if the superiority of the combination treatment group is established simultaneously over both the individual treatment groups in primary endpoint at 5% level of significance, only then can the analyses of the set of 7 secondary endpoints be performed at 5% level of significance. In order to control the overall type-I error rate at 5% level of significance, multiplicity adjustment will be applied while analyzing the set of secondary endpoints, details of which will be provided in the SAP prior to unblinding of treatment assignments.

The 7 secondary endpoints are listed below:

- Change in total body weight from baseline to Week 28
- Change in FPG from baseline to Week 28
- Change from baseline in 2-hour PPG after standardized MTT at Week 28
- Proportion of patients achieving HbA1c <7.0% at Week 28

- Proportion of patients achieving weight loss ≥5.0% at Week 28
- Change from baseline in FPG to Week 2 (dapagliflozin+exenatide vs exenatide)
- Change from baseline in seated systolic BP from baseline to Week 28

Although the nominal p-values respective to each of the treatment comparisons for all the 7 secondary endpoints will be presented in the report, in order to control the overall type-I rate at 5% level of significance, multiplicity adjustment will be applied while performing the 13 treatment comparisons in the set of 7 secondary endpoints, details of which will be provided in the SAP prior to unblinding of treatment assignments.

8.5.3 Analysis of exploratory variables

For categorical variables, a CMH test, stratified by baseline HbA1c stratum (<9.0% or ≥9.0%) will be applied to compare the differences between treatment groups.

For continuous variables, a MMRM or analysis of co-variance (ANCOVA) model will be applied to compare the differences between treatment groups.

Detailed analysis methodology for the exploratory efficacy endpoints will be provided in the SAP.

8.5.4 Analysis of PK variables

Plasma concentration data will be listed, summarized, and plotted vs time relative to intake of exenatide and dapagliflozin. A population PK analysis of data may be performed as outlined in a population PK analysis plan.

8.5.5 Safety and tolerability analysis

All safety and tolerability variables (including AEs, laboratory parameters, vital signs) will be summarized descriptively for each treatment group for the Safety population. Safety data collected prior to and after the patient initiates glycemic rescue therapy will be summarized together, as the patients are still on study medication after initiating the rescue therapy. Details on the safety analyses will be provided in the SAP.

8.5.5.1 Adverse events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All AEs will be summarized by treatment group. The number and percentages of patients who experienced at least 1 AE will be summarized by system organ class and preferred term. AEs will also be summarized by relationship to the study medication and by severity. Deaths, SAEs, and AEs leading to study discontinuation will be tabulated and presented in data listings. Patient level data listings of all AEs will be presented.

8.5.5.2 Clinical laboratory

Clinical laboratory results (chemistry, hematology, urinalysis, etc.) will be summarized using descriptive statistics for each visit by treatment group. Observed values at each visit and changes from baseline to each post-baseline visit will be presented. Changes from baseline in high/low/normal findings for clinical laboratory parameters for which normal ranges apply will be summarized by treatment group using shift tables. All laboratory data will be provided in patient data listings.

8.5.5.3 Vital signs

Vital signs (BP, pulse) will be summarized by treatment group for each applicable visit. Observed and changes from baseline values will be summarized for each visit where appropriate.

8.5.5.4 Physical examinations

Shift from baseline in physical examination findings will be presented as appropriate.

8.5.5.5 Anti-exenatide antibodies

Antibody to exenatide data will be listed and summarized. A patient is said to have treatment-emergent antibodies to exenatide at a visit if the antibody test is positive after the first dose of randomized study medication following a negative or missing antibody measurement on or before the first dose of randomized study medication, or the titer is increased by at least 3 dilutions from a detectable measurement prior to the first dose of randomized study medication. The incidence of treatment-emergent antibodies to exenatide will be summarized by treatment, study visit, and individual titer, as appropriate. Subgroup analyses such as change in HbA1c and incidence of AEs by antibody response (or titer group) will be explored.

8.5.6 Subgroup analysis

The primary endpoint, change from baseline in HbA1c at Week 28, will be summarized descriptively for subgroups of interest (eg, age group, gender, ethnicity, race, country). Additional subgroup analysis may be performed as appropriate and details will be specified in the SAP.

8.5.7 Interim analysis

No formal interim analysis will be conducted.

The efficacy and safety analyses will be conducted when all the patients complete 28 weeks of treatment. The analyses for the entire 52-week treatment period will be performed when all the patients complete the Extension Period 1. Similar analyses for the entire 104-week treatment period will be performed when all the patients complete the Extension Period 2.

The trial will be on-going at the time of the analyses on data collected from the 28 weeks of treatment. The site and patients will remain blinded to the treatment assignment until the study completion and final database lock.

8.5.8 Sensitivity analysis

Sensitivity analyses will be performed on the primary endpoint (eg, ANCOVA). Details will be specified in the SAP.

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site personnel

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol (CSP) and related documents with the investigational staff and also train them in any study specific procedures and the WBDC system utilized.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.2 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study medication accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

The AstraZeneca representative will be available between visits if the investigator(s) or other staff at the center needs information and advice about the study conduct.

9.2.1 Source data

Refer to the Clinical Study Agreement (CSA) for location of source data.

9.2.2 Study agreements

The Principal Investigator at each/the center should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this CSP and the CSA, the terms of CSP shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the CSA shall prevail.

Agreements between AstraZeneca or representative and the Principal Investigator should be in place before any study-related procedures can take place, or patients are enrolled.

9.2.3 Archiving of study documents

The investigator follows the principles outlined in the CSA.

9.3 Study timetable and end of study

The end of the study is defined as 'the last visit of the last patient undergoing the study'.

The first patient is expected to be enrolled 3rd Quarter of 2014. The study is expected to complete 4th Quarter 2017

The study may be terminated at individual centers if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with EQW or dapagliflozin.

9.4 Data management by AstraZeneca or delegate

Data management will be performed by the CRO, according to the Data Management Plan. AEs and medical/surgical history will be classified according to the terminology of the latest version of the MedDRA. Medications will be classified according to the AstraZeneca Drug Dictionary (AZDD). Classification coding will be performed by the Medical Coding Team at the CRO.

Data entered in the electronic data capture (eDC) system will be immediately saved to a central database and changes tracked to provide an audit trail. When the Principal Investigator has signed the eCRF electronically as per eCRF instructions, then the patient's data will be locked

Electronic case report forms

The eCRF and the protocol are both confidential. The eCRF will be created by Quintiles and programmed into the eDC system. All study centers will need internet access to access the eCRFs and will only have access to data for patients at their own study centers. Data Management (DM) and other coordinator teams will have access to data at all study centers. All eCRFs are to be completed by an authorized member of the study center staff and reviewed and signed by the investigator. All entries, corrections, and alterations are to be made by the responsible investigator or an authorized member of the study center staff. All eCRFs are to be completed in a manner that ensures accurate interpretation of data. It is each investigator's responsibility to ensure that all discontinued orders or changes in the study or other medications entered on the patient's eCRF correspond to the entries on the patient's medical records.

The eCRFs for any patient leaving the study should be completed at the time study medication is terminated or a patient discontinues study participation for whatever reason. The eCRFs must accurately reflect data contained in the patient's records (eg, source).

Dataflow

After the data are entered into the eCRF by study center, auto-queries that are generated by the eDC system should be addressed by the study center. Data queries will be raised for inconsistent, impossible, or missing data. At the monitoring visit, the Study Monitor must perform the study data verification (SDV) of the required fields on completed forms, and if there are no open queries, freeze the form. DM will run manual consistency checks outside of the eDC system and will raise manual queries for study centers to address; if the form is frozen, DM will unfreeze it to allow study centers to amend data. The same process is to be followed by any other groups creating manual queries in the eDC system (eg, for SAE reconciliation). Once all data are entered, SDV complete on required fields, manual queries and electronic data reconciliation complete, and all queries closed, then the casebook can be signed. Once the casebook is signed, DM will then lock the casebook so that no amendments can be made.

Database lock

Once all patient casebooks are locked, the final data transfer can be sent to statistics. A database lock checklist will also be completed by DM and the programmer to confirm all applicable quality control checks were performed. When all data have been coded, validated, and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked

Coding

All AEs and Medical Histories recorded in the eCRF will be classified according to the terminology of the latest version of the MedDRA. Medications will be classified according to

the AZDD. The coding will occur outside of the eDC system and will be merged with the clinical datasets sent to statistics.

The data collected through third party sources will be obtained and reconciled against study data.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

Serious Adverse Event (SAE) Reconciliation

Quintiles will perform SAE reconciliation between the Quintiles clinical study database and the safety data entry site clinical patient safety database.

Data associated with human biological samples

Data associated with biological samples will be transferred from laboratory(ies) internal or external to AstraZeneca.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonization (ICH)/Good Clinical Practice (GCP), applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Subject data protection

The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

10.3 Ethics and regulatory review

An Ethics Committee (EC) should approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the patients. The investigator will ensure the distribution of these documents to the applicable EC, and to the study site staff.

The opinion of the EC should be given in writing. The investigator should submit the written approval to AstraZeneca before enrollment of any patient into the study.

The EC should approve all advertising used to recruit patients for the study.

AstraZeneca or designee should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the EC annually.

Before enrollment of any patient into the study, the final study protocol, including the final version of the ICF, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca or designee will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca or designee will provide Regulatory Authorities, ECs and Principal Investigators with safety updates/reports according to local requirements.

Each Principal Investigator is responsible for providing the EC/Institutional Review Board (IRB) with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. AstraZeneca will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

10.4 Informed consent

The Principal Investigator(s) at each center will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study
- Ensure each patient is notified that they are free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed ICF(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed ICF is given to the patient
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the informed consent form that is approved by an EC.

10.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the International Co-ordinating Investigator and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised CSP).

The amendment is to be approved by the relevant EC and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to EC, see Section 10.3.

If a protocol amendment requires a change to a center's ICF, AstraZeneca and the center's EC are to approve the revised ICF before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each EC.

As a result of Protocol Amendment 3 (31 August 2015), all participating patients at the time of amendment approval will be asked to review and sign a revised ICF that describes the added Extension Period 2 that increases the duration of the study. If a patient does not consent to participate in Extension Period 2, the ICF should still be signed indicating the patient's preference not to continue receiving study drug but the patient will continue to participate in applicable visits and procedures.

10.6 Audits and inspections

Authorized representatives of AstraZeneca, a regulatory authority, or an EC may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The investigator will contact AstraZeneca or representative immediately if contacted by a regulatory agency about an inspection at the center.

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Revised Clinical Study Protocol Appendix B

Drug Substance	Exenatide
Study Code	D5553C00003
Edition Number	1.0
Date	03 October 2014

Appendix B
Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse.

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?

- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?

- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

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Clinical Study Protocol Appendix C	
Drug Substance	Exenatide
Study Code	D5553C00003
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Date	11 July 2014

Appendix C
Algorithm on Management of Sustained Elevated Liver Safety Abnormalities

ALGORITHM ON MANAGEMENT OF SUSTAINED ELEVATED LIVER SAFETY ABNORMALITIES

The monitoring for liver safety will be performed using the serum levels of AST, ALT and TB (see Figure 1 algorithm flow chart).

Patients with a central laboratory ALT and/or AST >3X ULN will be scheduled for a follow-up visit within 3 days following receipt of the initial laboratory results, to obtain repeat central laboratory ALT, AST, TB and Alkaline Phosphatase (ALK-P). In the event that the repeat laboratory assessments cannot be obtained within 3 days, the Investigator is encouraged to discuss possible alternatives with the Sponsor. Patients should remain on study medication until confirmatory results are obtained, unless otherwise contraindicated.

- **If the repeat ALT and AST are ≤3X ULN,** patient should continue double-blind treatment according to their original visit schedule unless otherwise contraindicated.

- **If the repeat ALT and/or AST are >3X ULN but ≤8X ULN and TB ≤1.5X ULN,** the patient's medical history, including details of risk factors for liver diseases, should be evaluated for potential underlying aetiologies. In addition, specialized blood sampling will be performed to evaluate liver function as well as identify potential causes of laboratory elevation(s). The Investigator should continue to monitor the patient's liver tests every 3 days following receipt of the prior laboratory results until the ALT and AST are ≤2X ULN or until ALT and AST are at or below baseline levels. The frequency of retesting can decrease to once a week or less if abnormalities stabilize and the patient is asymptomatic. Patients should remain on study medication unless confirmatory results indicate that a criterion for discontinuation has been met or continuing study medication would be otherwise contraindicated.

Patients must be discontinued from the study if an initial and repeat confirmatory laboratory tests meet any of the following criteria:

- ALT and/or AST are >3x ULN and TB >2x ULN

- ALT and/or AST are >5x ULN for ≥14 consecutive days, at any time after initial confirmatory results

- ALT and/or AST are >8x ULN

In each of these situations, study medication will be discontinued, the Sponsor notified and the End of Treatment Visit performed within 3 days of the confirmed laboratory results (see Section 3.9). At the End of Treatment Visit, medical history including details of risk factors for liver diseases (if not previously assessed) will be requested and additional blood sampling performed (**Specialized Liver Panel** and **Liver Discontinuation Panel**, see detailed below). Patient should also be scheduled for a Follow-up Visit (ie, procedures of Visit 12) 3 weeks

after discontinuation of investigational product. A referral consultation to a hepatologist or gastroenterologist (specializing in liver abnormalities) should be obtained.

Any additional tests and/or examinations should be carried out at the discretion of the Investigator. Any further investigations and laboratory results for patients with abnormal laboratory values at the Follow-up Visit should be made available to the Sponsor upon request.

Additional information, including but not limited to completion of supplemental eCRFs may be requested for certain adverse events and/or laboratory abnormalities which are reported/identified as part of the hepatic safety surveillance.

Following the End of Treatment Visit, the Investigator should continue to monitor the subject's liver tests every 3 days following receipt of the prior laboratory results until the ALT and AST are ≤2x ULN or until ALT and AST are at or below baseline levels. The frequency of retesting can decrease to once a week or less if abnormalities stabilize and the subject is asymptomatic.

Guidance on Assessment of Hepatic Laboratory Abnormalities

The following is presented to assist in the evaluation and management of hepatic laboratory values. It is not intended to supplant Investigators' clinical judgment.

Patients who experience ALT and/or AST values >3x ULN confirmed with a repeated test will have the following performed within 3 days of the confirmed laboratory results:

- AE assessment
- Physical Examination for jaundice and other signs of liver diseases
- Review of relevant risk factors and current history focusing on possible causes of the increased ALT and/or AST and/or TB, including:
  - Use of suspect concomitant medication [including over-the-counter (ie, acetaminophen/paracetamol), herbal and vitamin preparations]
  - Recent alcohol consumption or recreational drug/narcotic use
  - Recent unaccustomed physical exertion
  - Occupational or environmental exposure to hepatotoxins
  - Other conditions which may cause liver diseases or which may cause abnormal test results
- Specialized Liver Laboratory Panel (see below)

Specialized Liver Panel

For patients who are being monitored frequently as a result of confirmed AST and/or ALT >3x ULN, additional central laboratory tests will be performed within 3 days of receipt of confirmatory results. These laboratory tests will study the possible causes of the increased ALT and/or AST and/or TB, and may include, but are not limited to, the following tests:

- Hepatitis A IgM
- Hepatitis BsAg
- Hepatitis B Core Ab IgM
- Hepatitis C virus RNA
- Hepatitis C Ab
- Hepatitis E IgM
- Epstein-Barr Virus (EBV) IgM Ab
- Lactate Dehydrogenase (LDH)
- Gamma-glutamyl-transpeptidase (GGT)
- Carbohydrate deficient transferrin (CDT)
- Prothrombin time (PT/INR)
- Iron Panel - iron, ferritin, total iron binding capacity (TIBC)
- Immunology Panel including Antinuclear Antibody (ANA), Anti-Smooth Muscle Antibody (SMA) and Anti-Liver/Kidney Microsomal Antibody (Anti-LKM)
- Anti-tissue Transglutaminase Antibody

Liver Discontinuation Panel

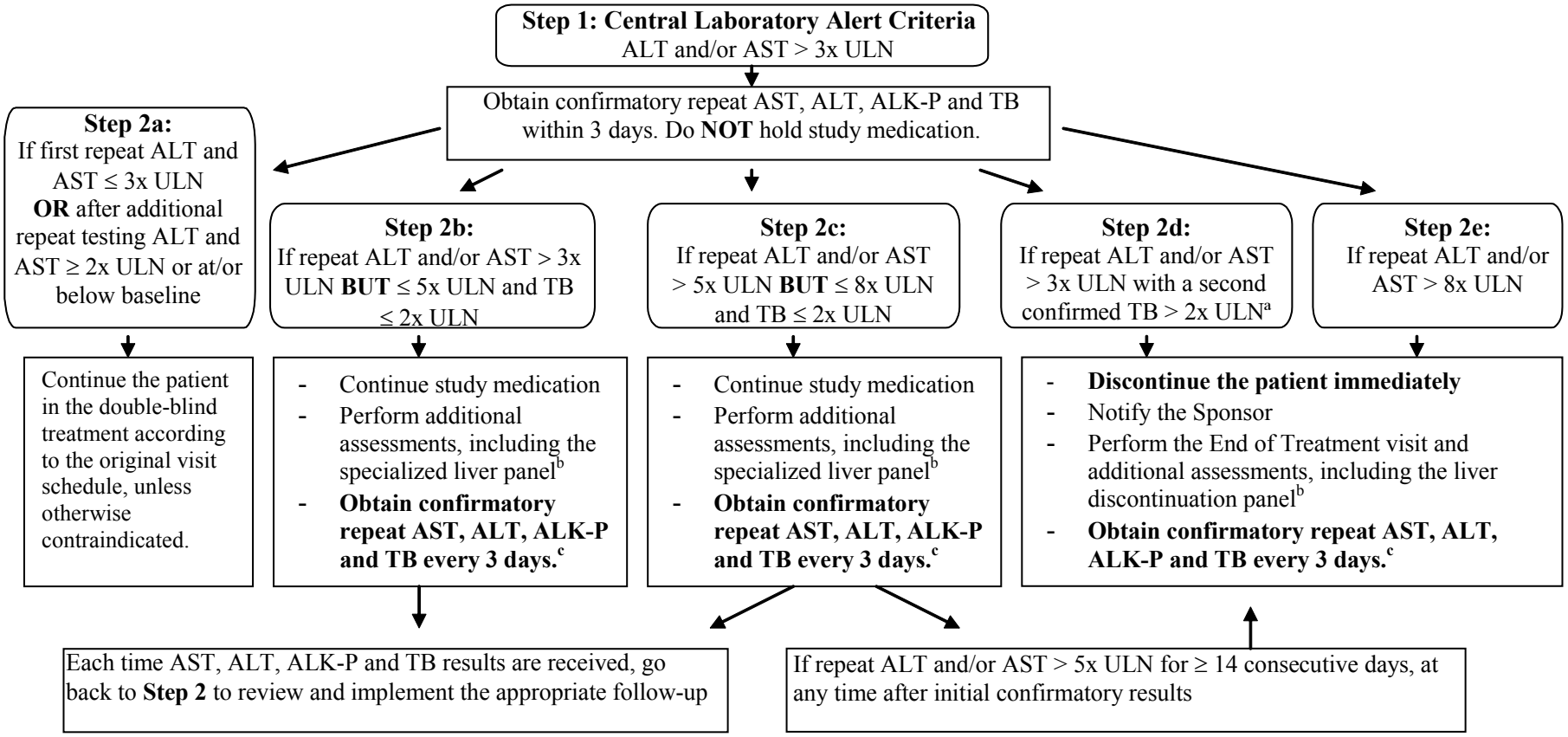
For patients who are discontinued from the study as a result of sustained elevated liver safety abnormalities, additional central laboratory tests will be performed at the time of End of Treatment Visit. Similar to the Specialized Liver Panel, these laboratory tests will study the possible causes of the increased ALT and/or AST and/or TB, and may include, but are not limited to, the following tests:

- Cytomegalovirus (CMV) IgM Ab
- Herpes Simplex Virus (HSV) 1 and 2

- Ceruloplasmin
- Toxoplasmosis
- Alpha-1 antitrypsin

For specific details regarding the Specialized Liver Panel or the Liver Discontinuation Panel laboratory tests, refer to the Central Laboratory Manual for this study.

Figure 1 Sustained elevated liver safety abnormalities flow chart



[a] In patients with repeat ALT or AST > 3x ULN but ≤ 8x ULN, only patients with TB ≤ 2x ULN at Step 1 should be followed according to Step 2b. Patients with an initial TB and confirmatory repeat TB > 2x ULN should be followed according to Step 2d.

[b] Please see text above in the Appendix for details on additional assessments to be performed (AE assessment, PE, review of current medical history including focused review of current medical history including focused review of risk factors for liver diseases and collection of blood samples [specialized liver panel or liver discontinuation panel]).

[c] Confirmatory repeat AST, ALT, ALK-P and TB should be obtained every 3 days following receipt of prior laboratory results, until the ALT and AST are ≤ 2x ULN or until ALT and AST are at or below baseline levels. The frequency of retesting can decrease to once a week or less if abnormalities stabilize and the patient is asymptomatic.

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Clinical Study Protocol Appendix D	
Drug Substance	Exenatide
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Appendix D
Diabetes Treatment Satisfaction Questionnaire, status version

Diabetes Treatment Satisfaction Questionnaire: DTSQs

The following questions are concerned with the treatment for your diabetes (including insulin, tablets and/or diet) and your experience over the past few weeks. Please answer each question by circling a number on each of the scales.

1. How satisfied are you with your current treatment?

very satisfied	6	5	4	3	2	1	0	very dissatisfied

2. How often have you felt that your blood sugars have been unacceptably high recently?

most of the time	6	5	4	3	2	1	0	none of the time

3. How often have you felt that your blood sugars have been unacceptably low recently?

most of the time	6	5	4	3	2	1	0	none of the time

4. How convenient have you been finding your treatment to be recently?

very convenient	6	5	4	3	2	1	0	very inconvenient

5. How flexible have you been finding your treatment to be recently?

very flexible	6	5	4	3	2	1	0	very inflexible

6. How satisfied are you with your understanding of your diabetes?

very satisfied	6	5	4	3	2	1	0	very dissatisfied

7. Would you recommend this form of treatment to someone else with your kind of diabetes?

Yes, I would definitely recommend the treatment	6	5	4	3	2	1	0	No, I would definitely not recommend the treatment

8. How satisfied would you be to continue with your present form of treatment?

very satisfied	6	5	4	3	2	1	0	very dissatisfied

Please make sure that you have circled one number on each of the scales.

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Clinical Study Protocol Appendix E	
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Appendix E
SHIELD-WQ-9 Questionnaire

Questions on weight and health related quality of life

1. **Compared to your first study visit, have you…** (check one box)

☐ Gained weight ☐ Lost weight ☐ Stayed the same

2. **Based on your response to question 1 above, how did your body weight change(s) *or lack of* body weight change affect you in the following areas?**
(check one box for each statement)

My change or lack of change in body weight had the following effects...	**Worsened**	**Improved**	**Stayed the same**	**Not applicable**
How I feel physically - physical health	☐	☐	☐	☐
My interactions with family	☐	☐	☐	☐
My work performance	☐	☐	☐	☐
My interactions with colleagues or friends	☐	☐	☐	☐
My social activities	☐	☐	☐	☐
My daily activities	☐	☐	☐	☐
My self-esteem	☐	☐	☐	☐
How I feel emotionally - emotional health	☐	☐	☐	☐
My overall quality of life	☐	☐	☐	☐