COVER PAGE FOR PROTOCOL AND STATISTICAL ANALYSIS PLAN

Official Study Title: **A 16-week, Single Center, Randomized, Double-Blind, Active Controlled, Parallel Group, Phase 3b Trial to Evaluate the Efficacy of Saxagliptin Co-administered with Dapagliflozin Compared to Dapagliflozin with Regard to Endogenous Glucose Production in Adult Patients with Type 2 Diabetes Who Have Insufficient Glycemic Control on Metformin or Metformin/Sulfonylurea Therapy**

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A 16-week, Single Center, Randomized, Double-Blind, Active Controlled, Parallel Group, Phase 3b Trial to Evaluate the Efficacy of Saxagliptin Co-administered with Dapagliflozin Compared to Dapagliflozin with Regard to Endogenous Glucose Production in Adult Patients with Type 2 Diabetes Who Have Insufficient Glycemic Control on Metformin or Metformin/Sulfonylurea Therapy

PROTOCOL SYNOPSIS

A 16-week, Single, Randomized, Double-Blind, Active-Controlled, Parallel Group, Phase 3b Trial to Evaluate the Efficacy of Saxagliptin Co-administered with Dapagliflozin Compared to Dapagliflozin with Regard to Endogenous Glucose Production in Adult Patients with Type 2 Diabetes Who Have Insufficient Glycemic Control on Metformin or Metformin/Sulfonylurea Therapy

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Study site(s) and number of subjects planned

This will be a single center study conducted at the University of Texas Health Science Center/Texas Diabetes Institute in San Antonio, Texas. Approximately 177 patients will be screened, and 53 randomized.

Study period		Phase of development
Estimated date of first patient enrolled	3Q 2015	3b
Estimated date of last patient completed	1Q 2017	3b

Study design

This is a 16-week, single center, randomized, double-blind, active-controlled, parallel-group, Phase 3b efficacy and safety study of simultaneous administration of saxagliptin 5 mg plus dapagliflozin 10 mg once daily (QD) compared with dapagliflozin plus placebo for saxagliptin, and placebo for saxagliptin plus placebo for dapagliflozin in patients with Type 2 diabetes who have inadequate glycemic control on metformin or metformin/sulfonylurea.

All potentially eligible patients will provide informed consent, undergo screening for all applicable inclusion/exclusion criteria, and submit laboratory samples at Screening (Visit 1, 2 weeks prior to randomization). Patients in all treatment arms should be treated with a stable dose of metformin (≥1000 mg/day) or metformin (≥1000 mg/day) plus sulfonylurea (glipizide, ≥ 5 mg/day or glyburide, ≥ 5 mg/day or glimepiride, ≥4 mg/day) for at least 8 weeks prior to Screening. Subjects will remain on the same type and dose of background therapy for the duration of the study. Eligible patients will be randomized at Visit 3 (Week 0) to receive saxagliptin 5 mg plus dapagliflozin 10 mg, dapagliflozin 10 mg plus placebo for saxagliptin, or placebo for saxagliptin plus placebo for dapagliflozin during the 16-week treatment period. Patients will attend study Visits 4 to 8 at Weeks 4, 8, 12, 15, and 16 during the treatment period.

Note for objectives: The term "Pre-investigational product (IP)" refers to the timepoints collected before IP administration during the glucose turnover study and "post-IP" refers to the timepoints collected after IP administration. The term "pre-glucose load" refers to the timepoints collected before glucose challenge during the oral glucose tolerance test (OGTT) and "post-glucose load" refers to the timepoints collected after glucose challenge.

Objectives

Primary Objective:	**Outcome Measure:**
To compare the post-IP minus pre-IP endogenous glucose production (EGP) during the glucose turnover study in saxagliptin 5 mg plus dapagliflozin 10 mg vs dapagliflozin at Week 15.	• Post-IP minus pre-IP EGP (mg/kg/min) during the glucose turnover study at Week 15.

Secondary Objectives:	**Outcome Measures:**
To compare the post-IP minus pre-IP EGP during the glucose turnover study in saxagliptin plus dapagliflozin vs dapagliflozin at Week 0.	• Post-IP minus pre-IP EGP (mg/kg/min) during the glucose turnover study at Week 0.
To compare the change from Week 0 to Week 15 in post-IP minus pre-IP EGP during the glucose turnover study in saxagliptin plus dapagliflozin vs dapagliflozin.	• Change from Week 0 to Week 15 in post-IP minus pre-IP EGP (mg/kg/min) during the glucose turnover study.

Secondary Objectives:	**Outcome Measures:**
To compare pre-IP EGP during the glucose turnover study in saxagliptin plus dapagliflozin vs dapagliflozin at Week 15.	• Pre-IP EGP (mg/kg/min) during the glucose turnover study at Week 15.
To compare the change from Week 0 to Week 15 in pre-IP EGP during the glucose turnover study in saxagliptin plus dapagliflozin mg vs dapagliflozin.	• Change from Week 0 to Week 15 in pre-IP EGP (mg/kg/min) during the glucose turnover study.
To compare pre-glucose load EGP during the OGTT at Week 16 in saxagliptin plus dapagliflozin vs dapagliflozin.	• Pre-glucose load EGP (mg/kg/min) during the OGTT at Week 16.
To compare the change from Week -1 to Week 16 in pre-glucose load EGP during the OGTT in saxagliptin plus dapagliflozin vs dapagliflozin.	• Change from Week -1 to Week 16 in pre-glucose load EGP (mg/kg/min) during the OGTT.
To compare the change from Week -1 to Week 16 in post-glucose load EGP during the OGTT in saxagliptin plus dapagliflozin vs dapagliflozin.	• Change from Week -1 to Week 16 in post-glucose load EGP during OGTT.
To compare the Week -1 in post-glucose load EGP during the OGTT in saxagliptin plus dapagliflozin vs dapagliflozin.	• Post-glucose load EGP during OGTT in saxagliptin/dapagliflozin vs dapagliflozin during week 1
To compare the Week 16 in post-glucose load EGP during the OGTT in saxagliptin plus dapagliflozin vs dapagliflozin.	• Post-glucose load EGP during OGTT in saxagliptin/dapagliflozin vs dapagliflozin during week 16
To compare the change from Week -1 to Week 16 in the rate of glucose disposal (Rd) and rate of glucose appearance (Ra) during OGTT in saxagliptin plus dapagliflozin vs dapagliflozin.	• Change from Week -1 to Week 16 in Rd and Ra during OGTT.
To compare at week -1 and also Week 16 the rate of glucose disposal (Rd) and glucose appearance (Ra) during OGTT in saxagliptin plus dapagliflozin vs dapagliflozin.	• Ra and Rd during OGTT in saxagliptin/dapagliflozin vs dapagliflozin at week -1 and week 16
To compare the mean change from Week 0 to Week 16 in hemoglobin A1c (HbA1c) in saxagliptin plus dapagliflozin vs dapagliflozin.	• Change from Week 0 to Week 16 in HbA1c (% and mmol/mol).
To compare the mean change from Week 0 to Week 15 in pre-IP fasting plasma glucose (FPG) during glucose turnover study in saxagliptin plus dapagliflozin vs dapagliflozin.	• Change from Week 0 to Week 15 in pre-IP plasma glucose (mmol/L) during glucose turnover study.

Secondary Objectives:	**Outcome Measures:**
To compare the mean change from Week -1 to Week 16 in pre-glucose load FPG and post-glucose load postprandial glucose (PPG) during OGTT in saxagliptin plus dapagliflozin vs dapagliflozin.	• Change from Week -1 to Week 16 in pre-glucose load FPG and post-glucose load PPG (mean and area under the curve [AUC] [mg/mL·time]).
To compare the mean change from Week -1/0 to Week 15/16 in fasting (pre-IP during glucose turnover study/pre-glucose load during OGTT) plasma glucagon, plasma C-peptide, and plasma insulin in saxagliptin plus dapagliflozin vs dapagliflozin.	• Change from Week -1/0 to Week 15/16 in fasting plasma glucagon (pg/mL) during the glucose turnover study and OGTT.. • Change from Week -1/0 to Week 15/16 in fasting plasma C-peptide (ng/mL) during the glucose turnover study and OGTT.. • Change from Week -1/0 to Week 15/16 in fasting plasma insulin (µU/mL) during the glucose turnover study and OGTT..
To explore the mean change from Week -1/0 to Week 15/16 in post-IP (during glucose turnover study) and post-glucose load (during OGTT) plasma glucagon, plasma C-peptide, and plasma insulin in saxagliptin plus dapagliflozin vs dapagliflozin.	• Change from Week -1/0 to Week 15/16 in plasma glucagon (mean [pg/mL] during the glucose turnover study and mean and AUC [pg/mL·time]) during OGTT. • Change from Week -1/0 to Week 15/16 in plasma C-peptide (mean [ng/mL] during the glucose turnover study and mean and AUC [µU/m·time]) during OGTT. • Change from Week -1/0 to Week 15/16 in plasma insulin (mean [µU/mL] during the glucose turnover study and mean and AUC [µU/m·time]) during OGTT.
To compare the mean change from Week 0 to Week 15 in post-IP minus pre-IP plasma glucagon, plasma C-peptide, and plasma insulin during glucose turnover study in saxagliptin plus dapagliflozin vs dapagliflozin.	• Change from Week 0 to Week 15 in post-IP minus pre-IP plasma glucagon (pg/mL), C-peptide (ng/mL), and insulin (µU/mL) during the glucose turnover study.
To compare the mean change and absolute values from Week -1 to Week 16 in insulin secretion, beta cell function, and insulin sensitivity during the OGTT in saxagliptin plus dapagliflozin vs dapagliflozin.	• Change from Week -1 to Week 16 in insulin secretion (change in C-peptide or insulin and change in C-peptide/change in glucose or change in insulin/change in glucose, as mean and AUC). • Change from Week -1 to Week 16 in beta cell function (as change in C-peptide [ng/mL] or insulin/change in glucose [mg/dL] ÷ insulin resistance). • Change from Week -1 to Week 16 in insulin sensitivity (mg/kg·min per µU/mL).

Secondary Objectives:	Outcome Measures:
To compare the mean change from Week 0 to Week 15 in pre-IP, post-IP, and post-IP minus pre-IP counterregulatory hormones during glucose turnover study achieved with saxagliptin plus dapagliflozin vs dapagliflozin.	• Change from Week 0 to Week 15 in pre-IP cortisol (ng/mL). • Change from Week 0 to Week 15 in post-IP cortisol (ng/mL). • Change from Week 0 to Week 15 in post-IP minus pre-IP cortisol (ng/mL). • Change from Week 0 to Week 15 in pre-IP epinephrine, norepinephrine, and growth hormone (pg/mL). • Change from Week 0 to Week 15 in post-IP epinephrine, norepinephrine, and growth hormone (pg/mL). • Change from Week 0 to Week 15 in post-IP minus pre-IP epinephrine, norepinephrine, and growth hormone (pg/mL).
To compare the mean change from Week -2 to Week 16 in body weight, body mass index (BMI), percent body fat, and fat distribution in saxagliptin plus dapagliflozin vs dapagliflozin.	• Change from Week -2 to Week 16 in body weight (kg). • Change from Week -2 to Week 16 in BMI. • Change from Week -2 to Week 16 in percent body fat and fat distribution (per Dual Energy X-ray Absorption [DEXA] scan).

Safety Objective:	Outcome Measures:
To evaluate the safety and tolerability of saxagliptin plus dapagliflozin (plus metformin) vs dapagliflozin, and vs. placebo at Week 16.	• Adverse events (AEs)/Serious AEs (SAEs) • Vital signs • Clinical laboratory tests • Electrocardiogram (ECG; including date and time, and normal/abnormal) • Physical examinations

Exploratory Objectives:	Outcome Measures:
To compare post-IP minus pre-IP EGP during the glucose turnover study at Week 15 in: - saxagliptin plus dapagliflozin vs placebo - dapagliflozin vs placebo.	• Post-IP minus pre-IP EGP (mg/kg) during glucose turnover study at Week 15.
For each secondary outcome measure, the comparisons between the following groups will be explored as exploratory objectives: - saxagliptin plus dapagliflozin vs placebo - dapagliflozin vs placebo	(as indicated in secondary measures)

Exploratory Objectives:	Outcome Measures:
To explore the mean change from Week -1 to Week 16 in plasma glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), and free fatty acids (FFA) during fasting and OGTT, mean and AUC in: - saxagliptin plus dapagliflozin (plus metformin) vs dapagliflozin - saxagliptin plus dapagliflozin vs placebo - dapagliflozin vs placebo	• Change from Week -1 to Week 16 in plasma GLP-1 (pM/mL), GIP (pg/mL and AUC [pg/mL·time]), and FFA (mmol/L) during OGTT.
To explore the mean change from Week -2 to Week 16 in fasting and post OGTT mean and AUC FFA in: - saxagliptin plus dapagliflozin vs dapagliflozin - saxagliptin plus dapagliflozin vs placebo - dapagliflozin vs placebo.	• Change from Week -2 to Week 16 in FFA (mmol/L).
To explore the mean change from Week 0 to Week 16 in waist to hip ratio, blood pressure (BP), and lipids within each treatment group and between: - saxagliptin plus dapagliflozin vs dapagliflozin - saxagliptin plus dapagliflozin vs placebo - dapagliflozin vs placebo	• Change from Week 0 to Week 16 in waist to hip ratio (cm), BP (mmHg), and lipids.

Target patient population

Approximately 53 patients with Type 2 diabetes mellitus (T2DM) with inadequate glycemic control receiving metformin at a dose of ≥1000 mg/day for at least 8 weeks prior to screening, will be randomized to 1 of 3 treatment groups.

Duration of treatment

Study duration will be at least 18 weeks, including a 1-week screening period, a 1-week run-in period, and a 16-week double-blind treatment period.

Investigational product, dosage, and mode of administration

Saxagliptin and matching placebo:

Saxagliptin 5 mg tablets or placebo matching saxagliptin will be administered orally QD for the 16-week double-blind treatment period.

Dapagliflozin and matching placebo:

Dapagliflozin 10 mg tablets or placebo matching dapagliflozin will be administered orally QD for the 16-week double-blind treatment period.

Other treatments

Metformin and Sulfonylurea (glipizide, glyburide, glimepiride)

Up to Visit 8 (Week 16), patients should continue to administer the same type and dose of metformin therapy they were using at study entry. Metformin and sulfonylurea will not be provided in pre-packaged kits by the Sponsor and will be sourced locally by the site and in accordance with the approved package labeling. Metformin and sulfonylurea should be administered and stored according to product and country-specific labelling.

Rescue therapy:

Patients who require rescue therapy should receive standard of care treatment; however, Bydureon 2 mg subcutaneously is highly suggested.

Statistical methods

Sample size estimate:

The primary comparison will be comparing EGP for saxagliptin 5 mg plus dapagliflozin 10 mg versus dapagliflozin 10 mg at Week 15.

With 19 patients per treatment group, there will be 90% power to detect a difference in mean EGP of 0.39 mg/kg/min between saxagliptin 5 mg plus dapagliflozin 10 mg and dapagliflozin 10 mg groups assuming a standard deviation of 0.32 using a 2 group t-test with a 0.050 2-sided significance level. Assuming that 10% of subjects in the primary comparison arms early terminate, are rescued, or do not have a Week 16 assessment for any other reason, a total of 21 subjects per treatment arm need to be randomized for each of the saxagliptin 5 mg plus dapagliflozin 10 mg and dapagliflozin 10 mg treatment arms. Approximately 11 subjects will be randomized to the placebo treatment arm for exploratory comparisons of saxagliptin 5 mg plus dapagliflozin 10 mg to placebo (approximately 80% power), for a total of approximately 53 subjects randomized.

Assuming that 70% of screened subjects will fail to meet screening criteria, a total of 177 subjects will need to be screened.

Statistical considerations

Analysis populations:

Classification into Full analysis (FA), Per protocol (PP), and Safety analysis sets will be conducted prior to the database lock.

Primary analyses of efficacy endpoints (primary and secondary) will be performed on the FA set. Supportive analyses will be carried out with the PP analysis set if more than 10% of patients from the FA set are excluded from the PP analysis set for important protocol deviations. All safety analyses will be based on the Safety analysis set.

Efficacy analysis set

Full analysis set

The FA set will be defined as all randomized patients with a baseline and a post baseline efficacy assessment value. Patients will be analyzed according to the treatment assigned.

Per protocol analysis set

The PP analysis set will be defined as all FA patients without an important protocol deviation that might affect the primary analyses. The criteria for important protocol deviations will be defined in the statistical analysis plan. Patients will be analyzed according to the treatment randomized/received.

Safety analysis set

The Safety analysis set will be defined as all randomized patients who received at least 1 dose of study medication. Patients will be analyzed according to the actual treatment randomized/received.

Analysis of the primary variable:

The primary endpoint (EGP) will be tested in a confirmatory fashion for saxagliptin 5 mg plus dapagliflozin 10 mg versus dapagliflozin 10 mg at the α=0.05 (2-sided) level. The other comparisons (contrasts) will be tested in an exploratory sense at the α=0.05 (2-sided) level. No multiplicity control is required.

The primary efficacy analysis will be performed using an analysis of covariance (ANCOVA) method for the change from baseline at Week 16, with terms for treatment group and baseline HbA1c subgroup ($\leq$8.5% versus >8.5%), and baseline EGP value in the model. Point estimates and 95% confidence intervals will be calculated for the adjusted mean changes within each treatment group as well as for the differences in adjusted mean changes between treatment groups. A subject who terminates from the study early, is rescued, or does not have a Week 16 assessment for any other reason will not contribute to the primary analysis.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
ADA	American Diabetes Association
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under the curve
DD	Drug Dictionary
β-hCG	Human chorionic gonadotropin, beta subunit
BMI	Body mass index
BP	Blood pressure
CR	Counter-regulatory
CrCl	Creatinine clearance
CRF	Case Report Form (electronic/paper)
CRO	Contract research organization
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CSRAF	Clinical supplies return authorization form
CV	Cardiovascular
DEXA	Dual Energy X-ray Absorption
DILI	Drug-induced liver injury
DM	Data Management
DPP-4	Dipeptidyl peptidase-4
EC	Ethics Committee (synonymous to [IRB] and Independent Ethics Committee [IEC])
ECG	Electrocardiogram
eDC	Electronic data capture
EGP	Endogenous glucose production

Abbreviation or special term	Explanation
EU	European Union
FA	Full analysis
FDA	Food and Drug Administration
FFA	Free fatty acids
FPG	Fasting plasma glucose
GAD	Glutamate decarboxylase
GCP	Good Clinical Practice
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1	Glucagon-like peptide-1
GMP	Good manufacturing practice
GPV&E	Global Pharmacovigilance & Epidemiology
Hb	Hemoglobin
HbA1c	Hemoglobin A1c
HDL	High-density lipoprotein
HL	Hy's Law
HR	Heart rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IP	Investigational Product
IRB	Institutional Review Board
LDL	Low-density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
NGT	Normal glucose tolerant
OGTT	Oral glucose tolerance test
PHL	Potential Hy's Law
PP	Per protocol
PPG	Postprandial glucose
QD	Once daily
SAE	Serious adverse event

Abbreviation or special term	Explanation
SAP	Statistical Analysis Plan
SCSM	Supply Chain Study Management
SDV	Study data verification
SGLT2	Sodium glucose cotransporter 2
SMBG	Self-monitored blood glucose
SU	Sulfonylurea
T4	Thyroxine
T2DM	Type 2 diabetes mellitus
TB	Total bilirubin
TSH	Thyroid stimulating hormone
TZD	Thiazolidinedione
µCi	Microcurie
UKPDS	United Kingdom Prospective Diabetes Study Group
ULN	Upper limit of normal
US	United States
WBDC	Web Based Data Capture
WOCBP	Women of childbearing potential

1. INTRODUCTION

1.1 Background and rationale for conducting this study

Hyperglycemia is the major risk factor for microvascular complications, and many studies have documented that correction of the hyperglycemia reduces the risk of microvascular complications. Every 1% decrease in hemoglobin A1c (HbA1c) is associated with an approximate 35% reduction in microvascular complications (DCCT 1993, UKPDS 1998, UKPDS 1998b).

Insulin resistance and progressive beta cell failure represent the core defects that characterize patients with type 2 diabetes mellitus (T2DM) (DeFronzo 2009). Hyperglycemia plays an important role in the pathogenesis of insulin resistance and beta cell failure (i.e., glucotoxicity). Thus, improved glycemic control in diabetic patients would help reduce the risk of microvascular complications and ameliorate the metabolic abnormalities (i.e., insulin resistance and beta cell failure) that contribute to the progressive course of the disease. Tight glycemic control has become the cornerstone of management in patients with T2DM, and professional organizations recommend that the HbA1c should be maintained at ≤6.5% to 7% (Qaseem et al 2007, AACE 2007, Nathan et al 2008).

Despite the irrefutable evidence for the importance of maintaining tight glycemic control, ~50% of T2DM patients fail to achieve the American Diabetes Association (ADA) goal for glycemic control of HbA1c <7.0% (Hoerger et al 2008). Progressive beta cell failure, weight gain, and hypoglycemia are major obstacles for the achievement of optimal glycemic control (DeFronzo 2009). Therefore, the development of novel treatment regimens that effectively lower plasma glucose levels, maintain glycemic control, and are not associated with hypoglycemia and weight gain, are needed for the management of T2DM. Two new classes of antidiabetic agents that have unique properties to help overcome these obstacles have been developed: the dipeptidyl peptidase-4 (DPP-4) inhibitors and the renal sodium glucose cotransporter 2 (SGLT2) inhibitors.

DPP-4 inhibitors approved by the Food and Drug Administration (FDA) for the treatment of T2DM include: saxagliptin, vildagliptin, linagliptin, alogliptin, and sitagliptin (Dicker 2011). In clinical studies, these drugs effectively reduced HbA1c in patients with inadequately controlled T2DM on a stable dose of metformin, sulfonylurea, or thiazolidinedione (Del Prato et al 2011, Gomis et al 2011, Owens et al 2011, Taskinen et al 2011), and the decrease in HbA1c was durable for at least 2 years (Göke et al 2008). DPP-4 inhibitors decrease the plasma glucose concentration by stimulating insulin secretion and suppressing plasma glucagon levels, thus leading to a decrease in endogenous glucose production (EGP) (Balas et al 2007). In Phase 3 studies, saxagliptin demonstrated clinically meaningful reductions in HbA1c (0.5% to 0.8%) and favorable safety and tolerability when given as monotherapy or in combination with metformin, metformin plus sulfonylurea, or pioglitazone (Del Prato et al 2011, Gomis et al 2011, Owens et al 2011,Taskinen et al 2011).

Dapagliflozin (US trade name: Farxiga™) is a potent and selective SGLT2 inhibitor and is approved by the FDA as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. Dapagliflozin (European Union [EU] trade name: 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. Dapagliflozin is in a new class of compounds referred to as SGLT2 inhibitors. SGLT2 is responsible for the resorptions of 80% to 90% (~180 g/day) of glucose normally filtered through the glomeruli daily in a normal glucose tolerant (NGT) individual. SGLT2 inhibition therefore leads to pharmacologically controlled glucosuria and reduces the HbA1c by 0.5% to 0.8% in patients with T2DM (Abdul-Ghani et al 2011). The decrease in HbA1c primarily results from a decrease in the fasting plasma glucose (FPG) concentration (by ~30 mg/dL) and, to a lesser extent, from a decrease in the postprandial plasma glucose concentration (Abdul-Ghani et al 2011).

Unlike diabetic patients, inhibition of SGLT2 in NGT patients produces glucosuria without a significant decrease in the FPG concentration (Komoroski et al 2009). The FPG concentration is determined by the balance between the rate of basal EGP and the rate of basal whole body glucose disposal (Jani et al 2008). Thus, the maintenance of the FPG concentration in NGT individuals following the induction of glucosuria by SGLT2 inhibition suggested that an increase in basal EGP quantitatively offset the increased rate of renal glucose excretion. The increase in EGP in NGT individuals can be viewed as a compensatory mechanism to prevent the development of hypoglycemia by the glucosuria. Because the increase in EGP is the principal factor responsible for the increase in EGP concentration in T2DM individuals, a compensatory increase in EGP following the onset of glucosuria would compromise the clinical efficacy of the SGLT2 inhibitor.

To examine this possibility, we measured the rate of EGP in T2DM patients following dapagliflozin therapy, and verified an increase in the rate of basal EGP (Merovci et al 2014). We hypothesized that inhibition of SGLT2 would have produced a greater decrease in the FPG concentration and HbA1c, if the increase in EGP had been prevented. Because DPP-4 inhibitors decrease FPG concentration by inhibiting EGP (Balas et al 2007), we further hypothesized that the combination of DPP-4 and SGLT2 inhibitors would prevent the compensatory increase in EGP and exert a complimentary effect to decrease FPG concentration and HbA1c. In line with this, in a recent oral glucose tolerance test (OGTT), treatment with saxagliptin and dapagliflozin in addition to metformin resulted in a complementary decrease in HbA1c and plasma glucagon levels (Hansen et al 2014). The aim of this present study is to test the hypothesis that saxagliptin combined with dapagliflozin can modulate EGP in T2DM patients.

1.2 Rationale for study design, doses, and control groups

The study is intended to demonstrate complimentary action of saxagliptin/dapagliflozin added to metformin versus dapagliflozin added to metformin with regard to EGP.

Many medications are approved for the treatment of T2DM; however, the challenge of achieving and maintaining treatment goals within the current sequential therapy approach is linked to shortcomings of older classes of drugs. Metformin is in the biguanide drug class that acts to decrease hepatic glucose output and subsequently, decreases fasting hyperglycemia.

Metformin, the oral first-line gold standard agent, is recommended as the initial pharmacological therapy because of its glycemic efficacy, weight neutrality, low risk of hypoglycemia, and beneficial cardiovascular (CV) profile. Current sequential add-on second- and third-line oral therapy includes oral drugs such as sulfonylureas (SUs) and thiazolidinediones (TZDs). These therapies and insulin are associated with increased risks for weight gain and hypoglycemia; therefore, caution is recommended when using combination therapy with other agents known to cause hypoglycemia. Hypoglycemia is a clinically important issue in optimizing treatment and there is emerging evidence that hypoglycemia is associated with negative CV outcomes. Efforts by patients to lose weight as part of a therapeutic lifestyle program are undermined by therapies that lead to weight gain. The majority of patients with T2DM are overweight or obese, and additional weight gain often results in reduced treatment efficacy.

Over the past few years, it has been widely recognized that the management approach for each T2DM patients' needs to be personalized based on his or her clinical characteristics (e.g., the likelihood of weight gain, risk for hypoglycemia, and lifestyle preferences [e.g., many patients may be reluctant to use injections]) (Inzucchi et al 2012). Based on data from the National Health and Nutrition Examination Survey in 2007 to 2010, HbA1c is not appropriately controlled in approximately one-third of patients using even less stringent targets (Ali et al 2013).

Because of the challenge to achieve glycemic control in patients with T2DM, the progressive nature of the disease, and the limitations of available oral and non-oral therapies, there is a significant medical need for oral combination treatment options and dual add-on therapy in patients with high baseline HbA1c. Expert groups have increasingly suggested making use of combination therapy early after diagnosis to improve glycemic control (Inzucchi et al 2012, Rodbard et al 2009). In a recent study, initiating triple therapy (pathophysiological-based approach) in patients with new onset T2DM versus metformin followed by sequential addition of SUs and basal insulin (treat-to-fail approach) demonstrated a more durable HbA1c reduction over 24 months and less hypoglycemia with initial triple therapy (Abdul-Ghani et al **2014**). Initial combination therapy with saxagliptin and dapagliflozin added to metformin may have similar potential for durable glucose lowering in combination with low risk of hypoglycemia.

Treatment with saxagliptin and dapagliflozin, both individually and in combination with metformin, have demonstrated a favorable safety and tolerability profile. These drugs had a low propensity for hypoglycemia, therefore addressing a potential key concern when adding 2 glucose lowering agents simultaneously. These drugs have demonstrated weight neutrality (saxagliptin) or moderate weight reduction (dapagliflozin). Dapagliflozin has also been shown to cause a persistent reduction in HbA1c and weight after 2 years of therapy. Dapagliflozin was recently shown to increase EGP, which, in part, may be mediated by increased plasma glucagon (Merovci et al). In contrast, saxagliptin has been demonstrated to reduce glucagon levels, e.g., in response to a meal (Sjöstrand et al 2014) and vildagliptin, also a DPP-4 inhibitor, has been shown to inhibit EGP (Balas et al 2007).

A second-line oral dual add-on therapy with saxagliptin co-administered with dapagliflozin could be a new option, as part of a triple therapy combination that includes drugs with complementary mechanisms of action, opposing effects on plasma glucagon concentration, and possibly EGP, low risk of hypoglycemia, and the potential for moderate weight loss, providing a more effective and patient-friendly approach to the treatment of T2DM.

Study design, dose selection, and control groups

The current study is designed to demonstrate the efficacy and safety of saxagliptin 5 mg plus dapagliflozin 10 mg versus dapagliflozin in patients with inadequate glycemic control on metformin monotherapy or metformin/sulfonylurea combination therapy.

Control group

This is a double-blind, active-controlled study. The comparison of the combination of saxagliptin plus dapagliflozin with dapagliflozin 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 United States (US) and the EU because of its glycemic efficacy, weight neutrality, low risk of hypoglycemia, good tolerability, and low cost (Inzucchi et al 2012). Sulfonylureas have, as their major mechanism of action, the ability to stimulate insulin secretion. In the US and EU because of their glycemic efficacy, good tolerability, and low cost (Inzucchi et al, 2012), sulfonylureas are recommended as second line therapy as add on to metformin when additional therapy is required.

Saxagliptin

Saxagliptin (Onglyza™) is approved by the US FDA as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. The 5 mg dose will be used for this study as it is the dose that is routinely used in the clinic. In addition, this dose is used in the pivotal studies in the saxagliptin/dapagliflozin clinical program.

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 because it has been extensively studied in Phase 3 trials and has demonstrated a favorable benefit-risk profile. In addition, this dose is the most commonly used dose in most countries.

Choice of outcome variables

The primary endpoint is change in EGP, which may contribute to increased circulating glucose.

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

Weight and body mass index (BMI): 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).

FPG and postprandial glucose (PPG) after an oral glucose load: These are well established measures of short-term glycemic efficacy (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 T2DM has been associated with decreased insulin resistance, improved measures of glycemia and lipemia, and reduced blood pressure (BP) (Klein et al 2004).

Glucagon: Glucagon regulates EGP and is a counter-regulatory hormone to insulin. Studies have shown its increase by SGLT2 inhibitors and decrease by DPP-4 inhibitors (Balas et al 2007).

Insulin and insulin secretion: Insulin is secreted by beta cells and its level and rate of secretion are increased in response to hyperglycemia. In patients with T2DM, beta cell function declines and insulin level decreases over time. Decreased blood glucose levels and EGP will subsequently affect insulin levels and insulin secretion.

Beta cell function: Beta cells secrete insulin. In patients with T2DM, beta cell function declines over time, leading to subsequent insulin level decreases and an imbalance of insulin and glucose, which leads to hyperglycemia.

Insulin sensitivity: Insulin sensitivity is lowered in patients with T2DM, therefore more insulin is required to regulate glucose levels in the blood.

Choice of study population

Age

The prevalence of T2DM increases with age; it is therefore important to assess antidiabetic agents in adult patients. In this study, because metformin is used as a background therapy, and the age range will be 18-70 years.

Sex/Ethnicity

Males and females and all ethnic groups are eligible for participation.

HbA1c

The HbA1c inclusion criterion at randomization (i.e., ≥7.5% to ≤11.0%, inclusive) was selected to include patients with poor glycemic control, a population that would potentially achieve the greatest benefit from simultaneous addition of 2 antidiabetic agents, and yet with low probability for potential rescue medication.

Pregnancy or breastfeeding

Neither dapagliflozin nor saxagliptin 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 (e.g., corticosteroid-induced T2DM or hemoglobinopathies that would interfere with the HbA1c analyses) or to exclude patients whose safety could be compromised by participation in the study.

1.3 Benefit/risk and ethical assessment

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

The study will provide efficacy and safety information for saxagliptin plus dapagliflozin, compared with dapagliflozin in patients with T2DM who are on metformin therapy or metformin/sulfonylurea. Patients in the dapagliflozin plus placebo group will receive saxagliptin-matching placebo; and patients in the placebo group will receive both placebos. All patients will be monitored throughout the study to ensure adequate glycemic control.

1.3.1 Ethical safety considerations

Clinical studies with the combination of saxagliptin and dapagliflozin are ongoing. Three 6-month studies with saxagliptin co-administered with dapagliflozin have demonstrated a superior HbA1c lowering effect compared with saxagliptin and dapagliflozin as monotherapy in T2DM patients on stable doses of metformin. In these 3 studies, there has been a consistent positive benefit-risk balance.

Participation in this study will cause a minimal and acceptable risk to the individual patients. The frequent follow-up visits and dietary consultation may result in improved glycemic control, compared with not participating in the trial. The level of radioactivity used in the study is low and unlikely to cause harm to the study patients (Ferrannini et al 1985).

1.3.2 Saxagliptin

Prior to approval, saxagliptin was evaluated in 6 pivotal Phase 3, randomized, double-blind, controlled studies. Compared with the control, treatment with saxagliptin at doses of 2.5 to 10 mg resulted in clinically relevant and statistically significant improvements in HbA1c, FPG, and 2-hour PPG. Reductions in HbA1c were seen across subgroups, categorized by age, gender, race, and baseline BMI.

Overall, saxagliptin has been well tolerated in clinical studies. The majority of adverse events (AEs) reported in clinical studies have been of mild intensity and few have required treatment discontinuation. When added to the standard of care in patients with T2DM with high CV risk, saxagliptin neither reduced nor increased the risk of the primary composite endpoint of CV death, myocardial infarction (MI), or ischemic stroke (Scirica et al 2013).

1.3.3 Dapagliflozin

Dapagliflozin is approved in approximately 52 countries, including the US and countries within the EU. Prior to approval, dapagliflozin was evaluated in 5 core Phase 2b studies, 16 core Phase 3 studies, and 3 regional Phase 3 studies. These studies established that dapagliflozin is effective in reducing HbA1c in a broad range of patients, regardless of disease progression/duration or concomitant use of antidiabetic therapies. Dapagliflozin consistently demonstrated statistically and clinically significant mean reductions in HbA1c versus placebo among the 3 doses typically studied (2.5, 5, and 10 mg). Overall, the dose of 10 mg provided better efficacy than the 2 lower doses. Effects on secondary glycemic efficacy parameters, including FPG and PPG, support the primary HbA1c efficacy findings. Dapagliflozin also resulted in a modest reduction in total body weight relative to placebo or comparator, largely attributable to a decrease in body fat mass, as well as reductions in systolic BP. Placebo-controlled data for up to 2 years indicate that the beneficial effects on glycemic and non-glycemic parameters were maintained.

Overall, dapagliflozin has been well tolerated in clinical studies. For detailed information surrounding the risks associated with saxagliptin and dapagliflozin, please refer to the respective IB. Recently, the US FDA has received information on postmarketing cases (n=20) of ketoacidosis in diabetic (both T2DM and T1DM) patients treated with dapagliflozin. Dapagliflozin is not approved for use in T1DM individuals and the present study includes only T2DM patients. Participants will be warned about the symptoms of ketoacidosis (rapid breathing, weakness, general bad feeling, frequent urination) and asked to call us if any of these symptoms are experienced. Urine ketones will be checked on each follow up visit. If the urine ketones are positive, plasma electrolytes will be measured to check the bicarbonate level and to calculate the anion gap.

Considering the comprehensive previous clinical experience with saxagliptin and dapagliflozin, the study's design features (including the inclusion, exclusion, and discontinuation criteria) and the planned safety procedures, participation in this study presents a minimal and thus acceptable risk to the individual patients who will be included.

1.3.4 Potential benefits to patients

Based on prior clinical trials experience and postmarketing information, both saxagliptin and dapagliflozin have a favorable benefit-risk ratio as monotherapy and add-on combination therapy. Integrated analyses of the safety data from three Phase 3 clinical studies demonstrated that the combined use of saxagliptin and dapagliflozin administered as either a dual or a sequential add-on to metformin was well tolerated in subjects who were inadequately controlled on metformin alone or metformin/sulfonylurea therapy. The combined use of saxagliptin and dapagliflozin was associated with a low risk of hypoglycemia. Overall, the safety profile of administering the 2 agents together was consistent with prior clinical trials, which evaluated the safety of these agents as monotherapy or as add-on therapy. In these 3 prior Phase 3 clinical studies, treatment with saxagliptin and dapagliflozin showed clinically relevant decreases in HbA1c, leading to a large proportion of patients achieving the therapeutic goal of HbA1c <7%, and modest reduction in body weight in patients with T2DM. In the present study, the doses of saxagliptin (5 mg) and dapagliflozin (10 mg) are the most widely used clinical doses. In addition, saxagliptin is expected to be weight neutral and dapagliflozin to reduce weight moderately, while both have shown a low risk for hypoglycemia in combination with metformin. Patients are also expected to receive some benefit in the form of increased medical care/attention when participating in study procedures, which includes multiple clinic visits and physical examinations over the duration of the study. Patients will also receive counseling on dietary and life-style modifications.

1.4 Study design

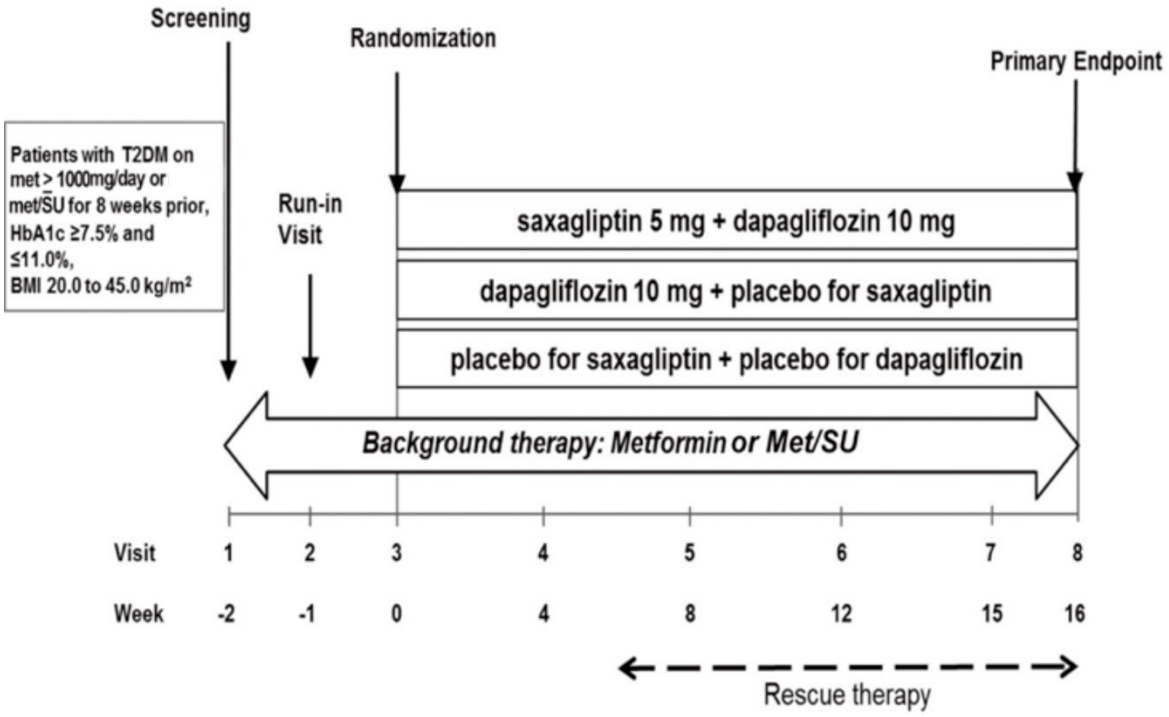
Figure 1 presents the overall design of the study.

The study is a 16-week, single center, randomized, double-blind, active-controlled, parallel-group, Phase 3b efficacy and safety study of simultaneous administration of saxagliptin 5 mg plus dapagliflozin 10 mg once daily (QD) compared with dapagliflozin in patients with T2DM who have inadequate glycemic control on metformin or metformin plus sulfonylurea.

All potentially eligible patients will provide informed consent, 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 (≥1000 mg/day) or metformin (≥ 1000 mg/day) plus sulfonylurea (glipizide, ≥ 5 mg/day; glyburide, ≥ 5 mg/day; glimepiride, ≥ 4 mg/day) for at least 8 weeks prior to Screening. Subjects will remain on the same type and dose of metformin or metformin/sulfonylurea therapy for the duration of the study as the background therapy for all treatment arms. Eligible patients will be randomized at Visit 3 (Week 0) to receive saxagliptin 5 mg plus dapagliflozin 10 mg, dapagliflozin 10 mg plus placebo for saxagliptin, or placebo for

saxagliptin plus placebo for dapagliflozin during the 16-week treatment period. Patients will attend study Visits 4 to 8 at Weeks 4, 8, 12, 15, and 16 during the treatment period.

Figure 1 Study Design



Abbreviations: BMI body mass index, HbA1c hemoglobin A1c, T2DM Type 2 diabetes mellitus.

2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	Outcome Measure:
To compare the post-IP minus pre-IP endogenous glucose production (EGP) during the glucose turnover study in saxagliptin 5 mg plus dapagliflozin 10 mg vs dapagliflozin at Week 15.	• Post-IP minus pre-IP EGP (mg/kg/min) during the glucose turnover study at Week 15.

2.2 Secondary objectives

Secondary Objectives:	Outcome Measures:
To compare the post-IP minus pre-IP EGP during the glucose turnover study in saxagliptin plus dapagliflozin vs dapagliflozin at Week 0.	• Post-IP minus pre-IP EGP (mg/kg/min) during the glucose turnover study at Week 0.
To compare the change from Week 0 to Week 15 in post-IP minus pre-IP EGP during the glucose turnover study in saxagliptin plus dapagliflozin vs dapagliflozin.	• Change from Week 0 to Week 15 in post-IP minus pre-IP EGP (mg/kg/min) during the glucose turnover study.
To compare pre-IP EGP during the glucose turnover study in saxagliptin plus dapagliflozin vs dapagliflozin at Week 15.	• Pre-IP EGP (mg/kg/min) during the glucose turnover study at Week 15.
To compare the change from Week 0 to Week 15 in pre-IP EGP during the glucose turnover study in saxagliptin plus dapagliflozin vs dapagliflozin.	• Change from Week 0 to Week 15 in pre-IP EGP (mg/kg/min) during the glucose turnover study.
To compare pre-glucose load EGP during the OGTT at Week 16 in saxagliptin plus dapagliflozin vs dapagliflozin.	• Pre-glucose load EGP (mg/kg/min) during the OGTT at Week 16.
To compare post-glucose load EGP during the OGTT at Week 16 in saxagliptin plus dapagliflozin vs dapagliflozin.	• Post-glucose load EGP (mg/kg/min) during the OGTT at Week 16
To compare the change from Week -1 to Week 16 in pre-glucose load EGP during the OGTT in saxagliptin plus dapagliflozin vs dapagliflozin.	• Change from Week -1 to Week 16 in pre-glucose load EGP (mg/kg/min) during the OGTT.
To compare the change from Week -1 to Week 16 in post-glucose load EGP during the OGTT in saxagliptin plus dapagliflozin vs dapagliflozin.	• Change from Week -1 to Week 16 in post-glucose load EGP during OGTT.

Secondary Objectives:	**Outcome Measures:**
To compare the change from Week -1 to Week 16 in the rate of glucose disposal (Rd) and the absolute rate of glucose appearance (Ra) during OGTT in saxagliptin plus dapagliflozin vs dapagliflozin.	• Change from Week -1 to Week 16 in Rd and Ra during OGTT.
To compare the mean change from Week 0 to Week 16 in hemoglobin A1c (HbA1c) in saxagliptin plus dapagliflozin vs dapagliflozin.	• Change from Week 0 to Week 16 in HbA1c (% and mmol/mol).
To compare the mean change from Week 0 to Week 15 in pre-IP fasting plasma glucose (FPG) during glucose turnover study in saxagliptin plus dapagliflozin vs dapagliflozin.	• Change from Week 0 to Week 15 in pre-IP plasma glucose (mmol/L) during glucose turnover study.
To compare the mean change from Week -1 to Week 16 in pre-glucose load FPG and post-glucose load postprandial glucose (PPG) during OGTT in saxagliptin plus dapagliflozin vs dapagliflozin.	• Change from Week -1 to Week 16 in pre-glucose load FPG and post-glucose load PPG (mean and area under the curve [AUC] [mg/mL·time]).
To compare the mean change from Week -1/0 to Week 15/16 in fasting (pre-IP during glucose turnover study/pre-glucose load during OGTT) plasma glucagon, plasma C-peptide, and plasma insulin in saxagliptin plus dapagliflozin vs dapagliflozin.	• Change from Week -1/0 to Week 15/16 in fasting plasma glucagon (pg/mL) during the glucose turnover study and OGTT.. • Change from Week -1/0 to Week 15/16 in fasting plasma C-peptide (ng/mL) during the glucose turnover study and OGTT.. • Change from Week -1/0 to Week 15/16 in fasting plasma insulin (µU/mL) during the glucose turnover study and OGTT..
To compare the mean change from Week -1/0 to Week 15/16 in post-IP (during glucose turnover study) and post-glucose load (during OGTT) plasma glucagon, plasma C-peptide, and plasma insulin in saxagliptin plus dapagliflozin vs dapagliflozin.	• Change from Week -1/0 to Week 15/16 in plasma glucagon (mean [pg/mL] and AUC [pg/mL·time]) during the glucose turnover study and OGTT. • Change from Week -1/0 to Week 15/16 in plasma C-peptide (mean [ng/mL] and AUC [µU/m·time]) during the glucose turnover study and OGTT. • Change from Week -1/0 to Week 15/16 in plasma insulin (mean [µU/mL] and AUC [µU/m·time]) during the glucose turnover study and OGTT.
To compare the mean change from Week 0 to Week 15 in post-IP minus pre-IP plasma glucagon, plasma C-peptide, and plasma insulin during glucose turnover study and post-glucose load (during OGTT) in saxagliptin plus dapagliflozin vs dapagliflozin.	• Change from Week 0 to Week 15 in post-IP minus pre-IP plasma glucagon (pg/mL), C-peptide (ng/mL), and insulin (µU/mL) during the glucose turnover study.

Secondary Objectives:	**Outcome Measures:**
To compare the mean change from Week -1 to Week 16 in insulin secretion, beta cell function, and insulin sensitivity during the OGTT in saxagliptin plus dapagliflozin vs dapagliflozin.	• Change from Week -1 to Week 16 in insulin secretion (change in C-peptide or insulin and change in C-peptide or insulin/change in glucose, as mean and AUC). • Change from Week -1 to Week 16 in beta cell function (as change in C-peptide [ng/mL] or insulin/change in glucose [mg/dL] ÷ insulin resistance). • Change from Week -1 to Week 16 in insulin sensitivity (mg/kg·min per μU/mL).
To compare the mean change from Week 0 to Week 15 in pre-IP, post-IP, and post-IP minus pre-IP counterregulatory hormones during glucose turnover study achieved with saxagliptin plus dapagliflozin vs dapagliflozin.	• Change from Week 0 to Week 15 in pre-IP cortisol (ng/mL). • Change from Week 0 to Week 15 in post-IP cortisol (ng/mL). • Change from Week 0 to Week 15 in post-IP minus pre-IP cortisol (ng/mL). • Change from Week 0 to Week 15 in pre-IP epinephrine, norepinephrine, and growth hormone (pg/mL). • Change from Week 0 to Week 15 in post-IP epinephrine, norepinephrine, and growth hormone (pg/mL). • Change from Week 0 to Week 15 in post-IP minus pre-IP epinephrine, norepinephrine, and growth hormone (pg/mL).
To compare the mean change from Week -2 to Week 16 in body weight, body mass index (BMI), percent body fat, and fat distribution in saxagliptin plus dapagliflozin vs dapagliflozin.	• Change from Week -2 to Week 16 in body weight (kg). • Change from Week -2 to Week 16 in BMI. • Change from Week -2 to Week 16 in percent body fat and fat distribution (per Dual Energy X-ray Absorption [DEXA] scan).
To compare the mean change (Weeks 15/16 minus Weeks - 1/0 in plasma ketone concentration, glucose oxidation, and lipid oxidation post-IP minus pre-IP during glucose turnover study (baseline) and during OGTT (baseline and post-glucose load)	• Change from Weeks 15/16 minus weeks – 1/0 in plasma ketone concentration • Change from Weeks 15/16 minus weeks – 1/0 in lipid oxidation • Change from Weeks 15/16 minus weeks – 1/0 in glucose oxidation

2.3 Safety objectives

Safety Objective:	Outcome Measures:
To evaluate the safety and tolerability of saxagliptin plus dapagliflozin vs dapagliflozin, and vs placebo at Week 16.	• AEs/Serious AEs (SAEs) • Vital signs • Clinical laboratory tests • Electrocardiogram (ECG; including date and time, and normal/abnormal) • Physical examinations

2.4 Exploratory objectives

Exploratory Objectives:	Outcome Measures:
To compare post-IP minus pre-IP EGP during the glucose turnover study at Week 15 in: - saxagliptin plus dapagliflozin vs placebo - dapagliflozin vs placebo.	• Post-IP minus pre-IP EGP (mg/kg) during glucose turnover study at Week 15.
For each secondary outcome measure, the comparisons between the following groups will be explored as exploratory objectives: - saxagliptin plus dapagliflozin vs placebo - dapagliflozin vs placebo	(as indicated in secondary measures)
To explore the mean change from Week -1 to Week 16 in plasma glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), and free fatty acids (FFA) during OGTT in: - saxagliptin plus dapagliflozin vs dapagliflozin - saxagliptin plus dapagliflozin vs placebo - dapagliflozin vs placebo	• Change from Week -1 to Week 16 in plasma GLP-1 (pM/mL and AUC [pg/ml.time]), GIP (pg/mL and AUC [pg/mL·time]), and FFA (mmol/L and AUC [mmol/L.time]) during OGTT.
To explore the mean change from Week -2 to Week 16 in FFA in: - saxagliptin plus dapagliflozin vs dapagliflozin - saxagliptin plus dapagliflozin vs placebo - dapagliflozin vs placebo.	• Change from Week -2 to Week 16 in FFA (mmol/L and AUC).
To explore the mean change from Week 0 to Week 16 in waist to hip ratio, blood pressure (BP), and lipids within each treatment group and between: - saxagliptin plus dapagliflozin vs dapagliflozin - saxagliptin plus dapagliflozin vs placebo - dapagliflozin vs placebo	• Change from Week 0 to Week 16 in waist to hip ratio (cm), BP (mmHg), and lipids.

BECAUSE THE PRECISE TIME AT WHICH EGP INCREASES FOLLOWING DAPAGLIFLOZIN VARIES FROM ONE DIABETIC INDIVIDUAL TO ANOTHER (MEROVCI, 2014), WE ALSO WILL COMPARE THE MAXIMUM CHANGES IN EGP AND PLASMA INSULIN/GLUCAGON/C-PEPTIDE/EPINEPHRINE/NOREPINEPHRINE/ CORTISOL/GH/FFA DURING THE GLUCOSE TURNOVER STUDY, AS WELL AS CHANGES IN THESE VARIABLES AT SPECIFIC TIME POINTS IN SAXAGLIPTIN PLUS DAPAGLIFLOZIN VS DAPAGLIFLOZIN

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 legislation), communicate with the Investigator, and understand and comply with protocol requirements, including the use of diary and glucose meter measurements.
3. Age = 18-70 years.
4. Has a diagnosis of T2DM.
5. Has HbA1c ≥7.5% and ≤11.0% obtained at Screening.
6. Treated with a stable dose of metformin ≥1000 mg/day or stable dose of metformin (≥1000 mg/day) plus sulfonylurea (glipizide, ≥ 5 mg/day; glyburide, ≥ 5 mg/day; glimepiride, ≥ 4 mg/day) for at least 8 weeks prior to Screening.
7. Has a BMI of 20 to 45 kg/m^2 (inclusive) at Screening.
8. Is male, or is female, and meets all the following criteria:
   -Not pregnant or breastfeeding.

   -Negative pregnancy test result at Visit 1 (Screening).

   -Women of childbearing potential (WOCBP; [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 that results in a low failure rate, i.e., 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.

3.2 Exclusion criteria

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

Target Disease Exceptions

1. Clinically diagnosed with Type I diabetes .

2. History of diabetic ketoacidosis, hyperosmolar nonketotic coma, or corticosteroid-induced Type 2 diabetes.

Medical History and Concurrent Diseases

3. History of bariatric surgery or lap-band surgery, or either procedure is planned during the time period of the study.

4. History of any unstable endocrine, psychiatric, rapidly progressing, or unstable renal disease, or rheumatic disorder, as judged by the Investigator.

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

6. Has evidence of current abuse of drugs or alcohol or a history of abuse within the past 52 weeks that, in the Investigator's opinion, would cause the individual to be noncompliant.

Cardiovascular Conditions

7. Cardiovascular disease within 3 months of Screening (i.e., MI, cardiac surgery, revascularization, unstable angina, stroke, transient ischemic attack, or arrhythmia).

8. Presence or history of severe congestive heart failure (New York Heart Association Class III and IV [CCNYHA 1994]), unstable or acute congestive heart failure, and/or known left ventricular ejection fraction of ≤40%.

Note: Eligible patients with congestive heart failure, especially those who are on diuretic therapy, should have careful monitoring of their volume status throughout the study.

Kidney Conditions

9. Estimated (eGFR) <60±5 mL/min/1.73 m^2 or a measured serum creatinine of >1.4 mg/dL for female patients and >1.5 mg/dL for male patients. If the serum creatinine is ≤ 1.4 (female) or ≤ 1.5 (male) and the eGFR is ≥ 60±5 ml/min/1.73m^2, the subject is eligible to participate in the study.

10. Congenital renal glucosuria.

Hepatic Conditions

11. Significant hepatic disease, including, but not limited to, severe hepatic insufficiency and/or significant abnormal liver function defined as aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) of >3x upper limit of normal (ULN).

12. Serum total bilirubin (TB) >2 mg/dL.

13. History of, or currently have, acute or chronic pancreatitis or have triglyceride concentrations ≥500 mg/dL at Visit 1 (Screening).

14. Suspicion that the patient is infected with an infectious substance according to World Health Organization risk categories A and B (see Appendix C).

15. Known severe hepatic disease, including chronic active hepatitis.

16. Positive serologic evidence of current infectious liver disease, including patients positive for hepatitis B viral antibody IgM, hepatitis B surface antigen, and hepatitis C virus antibody.

Hematological/Oncological Conditions

17. Malignancy within 5 years of Visit 1 (Screening), with the exception of treated in situ basal cell or squamous cell carcinoma of the skin.

18. Hematocrit of <34% for both males and females.

Prohibited Medications

19. Administration of any antihyperglycemic therapy, other than metformin or metformin/sulfonylurea, for more than 14 days (consecutive or not) during the 12 weeks prior to Visit 1 (Screening) and during the study unless per protocol for rescue.

20. Current treatment with potent cytochrome P450 3A4/5 inhibitors (e.g., atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin).

21. Administration of any other investigational drug or participation in any interventional clinical studies 30 days prior to Visit 1 (Screening).

22. Treatment with systemic corticosteroids for the last 3 months prior to Visit 1 (Screening).

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

Other

24. Patients with abnormal thyroid stimulating hormone (TSH) or free thyroxine (T4) values at Visit 1 (Screening) will be excluded.

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

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

27. Has known contraindications, allergies, or hypersensitivities to any study medication or excipient as outlined in the IBs or local package inserts for saxagliptin and dapagliflozin.

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

29. Is currently pregnant (confirmed with positive pregnancy test) or breast feeding.

30. Is on a commercial weight loss program with ongoing weight loss more than 5% over the last 3 months prior to Visit 1 (Screening), or is on an intensive exercise program.

31. Involvement in the planning and/or conduct of the study (applies to both the study sponsor staff and/or staff at the study site).

32. Patient with any condition that, in the judgment of the Investigator, may render the patient unable to complete the study or which may pose a significant risk to the patient or patient suspected or with confirmed poor protocol or medication compliance.

33. Previous randomization in the present study.

3.3 Subject enrollment and randomization

Investigator(s) 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.

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

4. Assign an eligible patient unique randomization code.

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 randomized to 1 of 3 treatment groups (while continuing on metformin therapy) at Visit 3 (Randomization):

- saxagliptin 5 mg + dapagliflozin 10 mg;
- dapagliflozin 10 mg + placebo for saxagliptin;
- placebo for dapagliflozin + placebo for saxagliptin.

Stratification will be conducted according to baseline HbA1c level (≤8.5% or >8.5%) and baseline therapy (metformin or metformin/sulfonylurea). Randomization codes will be assigned strictly sequentially within each stratum as patients become eligible for randomization. The HbA1c level collected at Visit 1 (Screening) will be used as the baseline HbA1c level for randomization purposes.

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 be replaced to ensure adequate patient number as described in the sample size calculation.

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. 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 enrolled, 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 will decide whether to continue or discontinue the patient from treatment.

Methods for assigning treatment groups

After written informed consent has been obtained, the patient will be assigned an enrollment code that is patient specific. The code will be used to identify the patient throughout study participation. Patient eligibility will be established before treatment randomization. Patients will be randomized strictly sequentially within each baseline (Visit 1) HbA1c stratum and baseline treatment (metformin and metformin/sulfonylurea) status at Visit 3 (Week 0), as patients are eligible for randomization. Assignment to treatment groups will be determined by a computer-generated random sequence.

The number and size of tablets will be identical for the investigational products (IPs) for the 3 treatment arms. Clinical supplies will be identified by randomization kit numbers, where each kit number is specific to a treatment arm. If a patient discontinues from the study, the patient code and randomization number will not be reused, and the patient will not be allowed to re-enter the study.

The site will randomize patients by allocating the lowest available randomization code in sequential order within the stratum (baseline HbA1c ≤8.5% or >8.5%) and baseline treatment (metformin or metformin/sulfonylurea) status. Randomization will be balanced in blocks within each baseline HbA1c stratum and baseline treatment status and each center.

Methods for ensuring blinding

Blinding is ensured by using a double-blind, single-dummy technique. Patients, the Investigator, and study site personnel involved with data review and analysis will be blinded throughout the study until database lock. The active tablets and the respective placebo tablets will be identical in size, color, smell, and taste. The bottles with IPs will be labelled with unique identification numbers.

No member at the study site handling data will have access to the randomization scheme during the conduct of the study, with the exception of the individual generating the randomization scheme.

In order to allow emergency unblinding, code envelopes with randomization codes only will be provided to the sites along with the drug supplies.

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 at the study site.

The treatment codes, as sealed paper code envelopes, should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomization.

The Principal Investigator retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IP 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.

3.8 Restrictions

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

- Fast overnight for at least 10 hours prior to each study site visit, i.e., no food or beverage except water. Allowed medications can be taken with water only.
- Continue metformin or metformin/sulfonylurea therapy at current dosage and at approximately the same time each day, except that any morning dose of metformin or metformin/sulfonylurea should be delayed on the morning of study site visits.
- Delay administering the IPs (as applicable) and metformin or metformin/sulfonylurea on the morning of the clinic visit and bring study medication and metformin or metformin/sulfonylurea to each site visit.
- Refrain from alcohol intake and intense exercise 24 hours prior to each visit and recommend to not use tobacco/nicotine within 12 hours prior to each visit.
- Do not donate blood for the duration of the study and for 3 months following the last study visit.
- Comply with prescribed dosing regimen to preserve study integrity and ensure patient safety.
- Discuss any new prescriptions and over-the-counter or herbal/nutritional therapies with the Investigator, as concomitant use could result in alterations to their glycemic control and may place them at risk for significant hypoglycemic episodes.
- Make every attempt to adhere to the diet and exercise counselling and to the protocol visit schedule.
- Women must immediately contact the Investigator if they suspect they might be pregnant and if they have changed or plan to change their birth control method.

If a patient comes to a visit without having followed the above instructions then the patient should be re-scheduled for the entire visit (if possible within the allowed time-window).

3.9 Discontinuation of investigational product

Patients may be discontinued from IPs 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 or SAE 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 an SAE or a clinically significant abnormal laboratory value, appropriate measures will be taken.
- Severe noncompliance with the study protocol.
- Creatinine clearance <60 (±5) mL/min/1.73 m^2 for sustained period of time, according to the Investigator's judgment.
- Initial and repeat laboratory tests meet any of the following criteria (see Appendix C):
  - ALT and/or AST are >3 x ULN and TB >2 x ULN
  - ALT and/or AST are >5 x ULN for ≥14 consecutive days, at any time after initial confirmatory results
  - ALT and/or AST are >8 x ULN
- Hypoglycemic episodes.

3.9.1 Discontinuation guidelines for protocol-defined major hypoglycemia episodes or recurrent non-major hypoglycemia episodes

Patients should not be discontinued from any treatment phase based on single episodes of hypoglycemia or symptoms of hypoglycemia unless clinically indicated. The assessment of a single finger stick or laboratory glucose value should not be the sole assessment used to determine patient discontinuation for hypoglycemia.

Clinical indications for discontinuation because of hypoglycemia may include the following:

- Multiple occasions of episodes outlined below that, in the opinion of the Investigator, indicate that continued treatment with study therapy is not in the best interest of the patient. This includes, but is not limited to:
  - Symptoms suggestive of hypoglycemia (e.g., sweating, shakiness, increased heart rate, confusion, dizziness, light-headedness, or hunger) in the absence of environmental factors known to contribute to hypoglycemia (i.e., excess physical activity, concurrent illness, or missed or delayed meal) **and/or**
  - Documented finger stick glucose values <54 mg/dL (<3.0 mmol/L).
- A patient may also be discontinued from the study because of severe hypoglycemia, as determined by the Investigator.

If finger stick glucose values are discordant from glycemic control assessed by the laboratory or with clinical symptoms, the patient's glucose meter should be tested and the instructions for use reviewed with the patient.

- A patient may be discontinued from the study because of the development of ketoacidosis.

3.9.2 Procedures for discontinuation of a subject from investigational product

At any time, patients are free to discontinue IP or withdraw from the study (i.e., IP and assessments – see Section 3.10), without prejudice to further treatment. A patient who decides to discontinue IP will always be asked about the reason(s) and the presence of any AEs. If

possible, the patient will be seen and assessed by an Investigator(s). Any AEs will be followed up; patient diaries and all study drugs should be returned by the patient.

Patients who discontinue from the study medication will have an Early Termination Visit equivalent to the Week 16 assessments plus a glucose turnover study at the time of study medication discontinuation. The following data will be collected and entered onto the clinical database:

- Concomitant medication
- AEs

In the case of a decision to discontinue treatment, the Investigator will follow the patient until the event has resolved or stabilized, at least until Week 16.

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.

2. Withdrawal by Patient.
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. 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. The documentation must include the reason for the withdrawal and details of any sequelae (followed until symptoms resolve or improve, as appropriate).

If a patient is withdrawn from the study, will be encouraged to complete the procedures outlined in Visits 15 and 16.

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" (i.e., patient does not meet the

required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not randomized patients).

If a patient was classified as a screen failure, dependent upon the reason for failure (e.g., low hematocrit, low T4, etc.), the patient may be rescreened one time only 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.

3.10.2 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (IP 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.

3.11 Discontinuation of the study

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

- meet individual stopping criteria or are otherwise considered significant
- are assessed as causally related to IP
- 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 patient's source records. All reasons for discontinuation of treatment must be documented.

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

4. STUDY PLAN AND TIMING OF PROCEDURES

Table 1 presents the schedule of assessments for this study.

Table 1 Study Plan

Evaluation	Screening	Run-in	Treatment Period					End of treatment/Early Termination or Rescue[a]
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Week	**-2**	**-1**	**0**	**4**	**8**	**12**	**15**	**16**
Relative to Randomization (days)	**-14**	**-9**	**R**	**28**	**56**	**84**	**103**	**112**
Visit Window (±days)	**(+7)**	**(±4[b])**	**0**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±4 [b])**
Obtain Informed Consent	X							
Review Medical and Surgical History	X							
Review Eligibility Criteria (Inclusion/Exclusion Criteria)	X							
Review Randomization Criteria			X					
Verify Patient Fasted 10 Hours	X	X	X	X	X	X	X	X
Complete Physical Examination	X							X
Brief Physical Assessment (at the Investigator's discretion)				X	X	X	X	
Body Weight	X		X	X	X	X	X	X
Height	X							
Body Mass Index	X							X
Vital signs (reclining/standing BP and HR)	X		X	X	X	X	X	X
Waist and Hip Circumference	X		X	X	X	X		X
12-lead ECG	X							X
Review Concomitant Medications[c]	X	X	X	X	X	X	X	X
Provide Diet and Exercise Counseling	X		X		X			
Verify IP Compliance				X	X	X	X	X
Dispense Study Medication			X	X	X	X		
Provide Glucose Meter and Supplies/Instructions for 7-point SMBG		X						
Perform 7-point SMBG Prior to Site Visit			X[d]	X	X	X	X[d]	X

Evaluation	Screening	Run-in	Treatment Period					End of treatment/Early Termination or Rescue[a]
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Week	**-2**	**-1**	**0**	**4**	**8**	**12**	**15**	**16**
Relative to Randomization (days)	**-14**	**-9**	**R**	**28**	**56**	**84**	**103**	**112**
Visit Window (±days)	**(+7)**	**(±4[b])**	**0**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±4 [b])**
Review 7-point SMBG and hypoglycemia episodes			X	X	X	X	X	X
Collect Glucose Meter/Unused Supplies								X
Collect unused study medication								X
Dispense Rescue Medication (if needed)					X	X	X	
Assess AEs		X	X	X	X	X	X	X
Pregnancy Test (urine and serum if urine test positive) WOCBP only	X	X	X	X	X	X	X	X
Clinical Chemistry, Hematology[e]	X				X			X
eGFR and Serum Creatinine	X	x	x	x	X	x	x	X
HbA1C	X	X		X	X	X	X	X
FPG/ketones	X	X	X	X	X	X	X	X
Fasting Serum Lipids[f]	X	X			X		X	X
Thyroid function (TSH and T4)	X							
FFA	X							X
Urinalysis[e]	X							X
Double Tracer OGTT[h] with IC		X						X
Glucose Turnover Study[i]			X				(X)[j]	
DEXA	X							X

Abbreviations: AE adverse event, β-hCG beta subunit of human chorionic gonadotropin, BP blood pressure, CrCl creatinine clearance, DEXA Dual Energy X-ray Absorption, ECG electrocardiogram, FFA free fatty acids, FPG fasting plasma glucose, GIP glucose-dependent insulinotropic polypeptide, GLP-1 glucagon-like peptide-1, HbA1c hemoglobin A1c, HDL high-density lipoprotein, HR heart rate, IgM immunoglobulin M, IP investigational product, LDL low-density lipoprotein, OGTT oral glucose tolerance test, R randomization, SMBG self-monitored blood glucose profile, T4 thyroxine, TSH thyroid stimulating hormone, WOCBP women of childbearing potential, IC = indirect calorimetry.

[a] Early Termination procedures are to be completed for all patients who terminate the study or are rescued before Visit 8 (Week 16) of the Treatment Period. Discontinued patients should return to the study site and complete a glucose turnover study and all assessments required for Visit 8 (Week 16) 3 to 5 days later.

[b] The glucose turnover study at Visit 3 should take place 5 to 14 days after OGTT at Visit 2. The Visit 7 glucose turnover study should take place approximately 10 days prior to OGTT at Visit 8.

[c] Review of concomitant medications includes over the counter drugs and herbal/nutritional therapies.

[d] 7-point SMBG should not be performed the day immediately before clinic visit 3 and 7.

[e] Details for safety laboratory variables are shown in Table 5.

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

[g] Hepatitis panel includes hepatitis B viral antibody IgM, hepatitis B surface antigen, and hepatitis C virus antibody.

[h] The double tracer OGTT will include blood draws for plasma glucose, plasma insulin, plasma C-peptide, plasma glucagon, plasma GLP-1, plasma GIP, plasma ^{3}H-glucose, ^{14}C-glucose specific activities (until Time 300 minutes) and urine will be collected.

[i] The glucose turnover test will include blood draws for glucose, insulin, C-peptide, glucagon, cortisol, growth hormone, adrenaline, and noradrenaline; and ^{3}H-glucose specific activities (until Time 300 minutes); and urine will be collected. Glucose turnover tests will include administration of IP at Time 0.

[j] Patients who are receiving rescue therapy or are early terminating: glucose turnover study will be performed 5 to 14 days prior to OGTT and Visit 8 assessments will also be completed prior to rescue. Glucose turnover study and Visit 8 procedures will be performed again at end of treatment for rescued patients.

4.1 Enrollment/Screening Period

Procedures will be performed according to the Study Plan (Table 1). Patients will be instructed to arrive in the morning for each scheduled visit. Prior to each study visit, including the Screening Visit, patients are to have fasted overnight for at least 10 hours (no food or beverage, except water). Patients are to refrain from alcohol intake and intense exercise 24 hours prior to each visit and recommend not to use tobacco/nicotine within 12 hours prior to each visit. Patients should delay administering their morning dose of metformin or metformin/sulfonylurea on the morning of the Run-in visit (Visit 2) and metformin or metformin/sulfonylurea and study medication on the morning of the study site visits during Treatment Period.

4.1.1 Screening Visit (Visit 1, Week -2)

At Screening, informed consent will be obtained prior to performing any protocol-required procedures. Patients will be assessed to ensure that they meet eligibility criteria. Patients who do not meet these criteria must not be enrolled in the study.

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:

- The patient's complete medical and surgical history will be recorded.
- Inclusion and exclusion criteria will be verified.
- A complete physical exam will be conducted.
- Body weight and height will be measured.
- BMI will be calculated.
- Vital signs (reclining and standing systolic and diastolic BP and heart rate [HR]) will be measured.
- Waist and hip circumference will be measured.
- 12-lead ECG will be performed.
- All prior medications (prescription medications within 3 months) and concomitant medications (including over the counter and herbal/nutritional supplements) will be reviewed.
- Diet and exercise counselling will be provided.
- Urinary pregnancy test for all female patients (WOCBP only) will be performed.
- Blood samples will be collected for the following assessments:
    - Chemistry and hematology
    - Serum creatinine (estimated GFR)
    - HbA1c
    - Fasting plasma glucose (FPG) and ketones

- Fasting serum lipid concentrations (total cholesterol, low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol, non-HDL cholesterol, and triglycerides
- Thyroid function (TSH and T4)
- FFA
- Serum pregnancy test for all female patients (WOCBP only) if urine pregnancy test result is positive
- Urine will be collected for urinalysis.
- DEXA scan will be performed.

Individuals will be screen failed if results of any laboratory test are abnormal and clinically significant as judged by the Investigator or medical monitor. Individuals may qualify for study run-in following an acceptable repeated lab result for an initially abnormal result as judged by the Investigator).

4.1.1.1 Rescreening

If a patient was classified as a screen failure, dependent upon the reason for failure (i.e., low hematocrit, low T4, etc.), the patient may be rescreened for study inclusion as long as rescreening takes place at least 2 weeks 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 per patient is permitted. If the patient does not meet all study requirements at the rescreening visit, the patient should be considered a screen failure.

4.1.2 Run-in Visit (Visit 2, Week -1)

Visit 2 should take place 3 to 5 days prior to Visit 3. Prior to this visit, patients are to have fasted overnight (at least 10 hours). Patients are to refrain from alcohol intake and intense exercise 24 hours prior to each visit and recommend not to use tobacco/nicotine within 12 hours prior to each visit. Patients should delay administering their morning dose of metformin or metformin/sulfonylurea on the morning of the study site visit. The following will be performed during this visit:

- Concomitant medications (including over the counter and herbal/nutritional supplements) will be reviewed.
- Urinary pregnancy test for all female patients (WOCBP only) will be performed.

Double tracer OGTT will be performed.

- Blood samples will be collected for the following assessment:
    - HbA1c
    - FPG and ketones
    - Fasting serum lipid concentrations (total cholesterol LDL cholesterol, HDL cholesterol, non-HDL cholesterol, and triglycerides)
    - Serum pregnancy test for all female patients (WOCBP only) if urine pregnancy test result is positive
    - Serum creatinine (estimated GFR)

- AEs will be reviewed.
- Patient instructions will be provided.
- Glucose meter and supplies will be provided.
- 7-point self-monitored blood glucose (SMBG) instructions will be provided.

Study site personnel will instruct patients to take metformin or metformin/sulfonylurea (with food) after the study visit is complete.

4.1.3 Randomization and Baseline Visit (Visit 3, Week 0)

Visit 3 should take place 3 to 5 days after Visit 2. Prior to this visit, patients are to have fasted overnight (at least 10 hours). Patients are to refrain from alcohol intake and intense exercise 24 hours prior to each visit and recommend not to use tobacco/nicotine within 12 hours prior to each visit. 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:

- Randomization criteria will be verified.
- Body weight will be measured.
- Vital signs (sitting systolic and diastolic BP and HR) will be assessed.
- Waist and hip circumference will be measured.
- Concomitant medications (including over-the-counter and herbal/nutritional supplements) will be reviewed.
- Urinary pregnancy test for all female patients (WOCBP only) will be performed.
- Patients will perform 7-point SMBG prior to the visit.

- AEs will be reviewed.
- Blood samples will be collected **prior to glucose turnover study and administration of study medication** for the following assessments:
  - FPG and ketones
  - Serum pregnancy test for all female patients (WOCBP only) if urine pregnancy test result is positive
- Glucose turnover study will be initiated.

- During the baseline infusion period of the glucose turnover study, prior to Time 0 collection, the following will be performed:
- Diet and exercise counselling will be provided.
- 7-point SMBG will be reviewed and recorded.
- Patients will be randomly assigned to 1 of 3 treatment groups (while continuing on metformin therapy):
  - saxagliptin 5 mg + dapagliflozin 10 mg;
  - dapagliflozin 10 mg + placebo for saxagliptin;
  - placebo for dapagliflozin + placebo for saxagliptin.
- Study medication will be dispensed during Time 0 of glucose turnover study. Study site personnel will monitor administration of study medication. Glucose turnover study will be completed.

4.2 Treatment Period

After the Randomization visit (Visit 3), patients will complete study visits at 1- to 4-week intervals according to the Study Plan (Table 1) until the end of the randomized treatment period (Visit 8, Week 16). During Weeks 6 to 16 of the double-blind treatment period of the trial, patients may be eligible for the addition of open-label rescue medication to their blinded treatment regimen in order to treat ongoing hyperglycemia, based upon established laboratory FPG values and repeat, confirmatory FPG criteria (Table 2).

Table 2 Criteria for Initiation of Rescue Therapy During the Randomized Treatment Period

Visit Period	Central Laboratory FPG
Week 6	FPG >270 mg/dL (15.0 mmol/L)
After Week 6 to Week 12 (excluding Week 12)	FPG >240 mg/dL (13.3 mmol/L)
After Week 12 to Week 16 (excluding Week 16)	FPG >200 mg/dL (11.1 mmol/L)

Abbreviation: FPG fasting plasma glucose.

Patients with a 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 laboratory FPG value and review the patient's glucose meter readings. If the repeat laboratory FPG value still meets the criterion, the patient must be rescued. Patients should continue receiving study medication while receiving rescue therapy. Patients who meet rescue criteria in the double-blind treatment period must first complete an OGTT and the Visit 8/End of Treatment procedures, including a glucose turnover study and DEXA scan, before receiving open-label rescue medication, to ensure that important trial endpoint measurements are collected. Rescued patients will be given open-label antidiabetic rescue medication in accordance with the approved product label in the applicable country at the discretion of the Investigator, in addition to their double-blinded study medication. Rescued patients will then continue in the double-blind treatment period according to their original visit schedule.

Following initiation of open-label rescue medication, rescued patients should have their glycemic response to the rescue medication evaluated by the Investigator. At the end of the study or at early termination, rescued patients should undergo a double tracer OGTT, glucose turnover study, and DEXA scan.

4.2.1 Treatment Period visits (Visits 4 to 7, Weeks 4, 8, 12, and 15)

Prior to these visits, patients are to have fasted overnight (at least 10 hours). Patients are to refrain from alcohol intake and intense exercise 24 hours prior to each visit and recommend not to use tobacco/nicotine within 12 hours prior to each visit. Patients should delay administering their morning dose of metformin or metformin/sulfonylurea and study medication on the morning of the study site visits. Patients should bring their metformin or metformin/sulfonylurea and study medication with them to the study site and will self-administer study medication as directed by study site personnel.

The following will be performed during these visits:

- A brief physical assessment may be conducted at the Investigator's discretion.
- Body weight will be measured.
- Vital signs (reclining and standing systolic and diastolic BP and HR) will be assessed.
- Waist and hip circumference will be measured (Visits 4, 5, and 6).
- Concomitant medications (including over-the-counter and herbal/nutritional supplements) will be reviewed.
- Diet and exercise counselling will be provided (Visit 5 only).
- Study medication compliance will be reviewed.
- Patients will perform 7-point SMBG prior to visits.
- 7-point SMBG will be reviewed and recorded.
- Rescue medication will be dispensed (if needed, see Table 2).
- AEs will be reviewed.

- Urinary pregnancy test for all female patients (WOCBP only) will be performed.
- Blood samples will be collected **prior to administration of study medication** for the following assessments:
    - Chemistry and hematology (Visit 5 only)
    - Serum creatinine (calculated creatinine clearance; Cockcroft-Gault formula; Visit 5 only)
    - HbA1c
    - FPG and ketones
    - Fasting serum lipid concentrations (Visits 5 and 7 only)
    - Serum pregnancy test for all female patients (WOCBP only) if urine pregnancy test result is positive
    - Serum creatinine (estimated GFR)
    -
- Glucose turnover study will be performed. **Study medication will be ingested at the end of the 3-hour tracer equilibration period**.

Study site personnel will instruct patients to take IP and metformin (with food) after the study visit is complete.

4.2.2 End of Treatment Period Visit/Early Termination during Treatment Period or Rescue (Visit 8, Week 16)

Prior to this visit, patients are to have fasted overnight (at least 10 hours). Patients are to refrain from alcohol intake and intense exercise 24 hours prior to each visit and recommend not to use tobacco/nicotine within 12 hours prior to each visit. Patients should delay administering the morning dose of metformin and study medication on the morning of the visit and bring metformin and study medication to the study site visit.

The following procedures will be conducted:

- A complete physical examination will be conducted.
- Body weight will be measured.
- BMI will be calculated.
- Vital signs (sitting systolic and diastolic BP and HR) will be assessed.
- Waist and hip circumference will be measured.
- 12-lead ECG will be performed.
- Concomitant medications (including over-the-counter and herbal/nutritional supplements) will be reviewed.

- Study medication compliance will be reviewed.
- Patient will perform 7-point SMBG prior to Visit 8.
- 7-point SMBG will be reviewed and recorded.
- Glucose meter and supplies will be collected.
- Unused study medication will be collected.
- AEs will be assessed.
- Urinary pregnancy test for all female patients (WOCBP only) will be performed.
- Blood samples will be collected **prior to administration of study medication** for the following assessments:
    - Chemistry and hematology
    - Serum creatinine (calculated creatinine clearance; Cockcroft-Gault formula)
    - HbA1c
    - FPG and ketones
    - Fasting serum lipid concentrations
    - FFA
    - Serum pregnancy test for all female patients (WOCBP only) if urine pregnancy test result is positive
    - Serum creatinine (estimated GFR)
    -
- Urine will be collected for urinalysis.
- Double tracer OGTT will be performed (approximately 10 days after glucose turnover study.
- DEXA scan will be performed or can be performed on a separate day.

If a patient is early discontinued or rescued, see visits 15 and 16 in Table for procedures.

4.3 Follow-up period (Not applicable)

5. STUDY ASSESSMENTS

The Investigator will ensure that data are recorded in an appropriately designed excel data sheet and will ensure the accuracy, completeness, and timeliness of the data collection.

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). The instructions for collection, processing, packaging, and shipping of the samples will be detailed in the laboratory manual.

5.1.2 Fasting plasma glucose

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

5.1.3 Body weight

Body weight will be measured according to the schedule presented in the Study Plan (Table 1). The study site staff should record the weight in kilograms or pounds to the first decimal point (e.g., 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.

5.1.4 Body height

Body height will be measured according to the schedule presented in the Study Plan (Table 1). The study site staff should record the height in centimeters. The patient should remove their footwear and head gear and stand with feet together, heels against the back board, and knees straight.

5.1.5 Waist and hip circumference

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

- The patient stands and the examiner places a Gulick II measuring tape in a horizontal plane around the abdomen at the level of the umbilicus for waist circumference and at the maximum circumference of the buttocks for hip circumference.
- 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 and hip circumference will be measured according to the schedules presented in the Study Plan (Table 1).

5.1.6 7-point self-monitored blood glucose profiles

Patients will be instructed to perform 7-point SMBG profiles at home on the same day of the week (±2 days), the week before Visits 3, 4, 5, 6, 7, and 8 (Table 1). A 7-point SMBG profile consists of blood glucose measurements obtained prior to and 2 hours after the morning, midday, and evening meals, and before bedtime.

The 7-point SMBG should not be performed the day immediately before Visits 3 and 7.

5.1.7 Dual Energy X-ray Absorption (DEXA) scan

Patients will be assessed for percent body fat with a DEXA scanner at Visits 1 and 8 (Table 1). A complete DEXA scan report will be kept as source documentation.

5.1.8 Glucose turnover study

A glucose turnover study will be performed according to schedule presented in Table 1. A glucose turnover study will be performed at Visit 3, which should be 5 to 14 days after the OGTT (Visit 2). An end of treatment glucose turnover study will be performed at Visit 7 and should be done approximately 10 days prior to the OGTT.

Patients will report to the study site after a 10-hour overnight fast and should be asked to void before beginning the glucose turnover study. At approximately 0600 (Time -180 minutes), a catheter will be placed into an anticubital vein and a primed (25 micro Curie [μCi] x FPG/100 up to a maximum of 50 μCi) – continuous infusion of [3-^{3}H-glucose will be started]. The continuous infusion (0.25 μCi/min) of [3-^{3}H]-glucose will be started and will be maintained throughout the study duration. A second catheter will be placed retrogradely into a vein on the dorsum of the hand, which will be placed in a heated box (50-60°C) for arterialized blood withdrawal. Prior to oral administration of study medication (saxagliptin, dapagliflozin, placebo), blood samples will be taken at the timepoints indicated in Table 3 for measurement of plasma glucose, insulin, C-peptide, glucagon, counter-regulatory hormones (i.e., plasma cortisol, growth hormone, adrenaline, and noradrenaline), and [3-^{3}H]-glucose specific activity. During the glucose turnover study, patients will receive assigned study medication 3 hours after the start of [3-^{3}H]-glucose infusion (Time 0). Blood samples will be obtained according to the timepoints indicated in Table 3 until the end of the study (Time 300 minutes/5 hours after drug is received). Metformin or metformin/sulfonylurea will **NOT** be taken until after the glucose turnover study has been completed.

Urine will be collected from the start of the study (Time -180 minutes) until Time 0 and again from Time 0 to 300 to measure urinary volume and urinary glucose concentration (to quantitate urinary glucose excretion). The glucose turnover study will end 5 hours after receiving study medication (Time 300 minutes) and patients will be given a meal and metformin or metformin/sulfonylurea and allowed to return home.

Table 3 Glucose Turnover Study

Timepoint (clock time)[a]	Glucose	3-^{3}H-glucose	Insulin/ C-peptide	Glucagon	CR hormones[b]
-180 (0600)	X	X			
-30	X	X	X	X	X
-20	X	X			
-10	X	X	X	X	X
-5	X	X			
0 (0900)[c]	X	X	X	X	X
15	X	X	X	X	
30	X	X	X	X	X
45	X	X	X	X	
60 (1000)	X	X	X	X	X
75	X	X	X	X	
90	X	X	X	X	
105	X	X	X	X	
120 (1100)	X	X	X	X	X
135	X	X	X	X	
150	X	X	X	X	
165	X	X	X	X	
180 (1200)	X	X	X	X	X
195	X	X			
210	X	X	X	X	
225	X	X			
240 (1300)	X	X	X	X	X
255	X	X			
270	X	X	X	X	
285	X	X			
300 (1400)	X	X	X	X	X
Number of samples	*26*	*26*	*19*	*19*	*9*

[a] Study start time is approximate (between 0600 and 0700), but collection of samples relative to time of study medication ingestion is critical (i.e., -180, -30, -20 minutes, etc.).

[b] CR counter-regulatory hormones include: plasma or serum cortisol, growth hormone, adrenaline, and noradrenaline.

c During Visit 3 glucose turnover study, patient will perform some Visit 3 assessments during the 3 hour priming period and be randomized prior to Time 0 then receive assigned study medication at Time 0.

5.1.9 Double tracer oral glucose tolerance test

An OGTT will be performed according to the schedule presented in Table 1, which will occur 5 to 14 days prior to a glucose turnover study.

Patients will report to the clinic after a 10-hour overnight fast and should be asked to void before beginning the double tracer OGTT study. At approximately 0600 hours, a catheter will be inserted into an antecubital vein, and primed (25 µCi x FPG/100 up to maximum of 50 µCi) – continuous infusion of 3-^{3}H-glucose will be started. The continuous (0.25 µCi/min) infusion of [3-^{3}H]-glucose will be started 3 hours (Time -180 minutes) prior to administering glucose challenge and will be maintained for the entire study duration (7 hours). A second catheter will be placed retrogradely into a vein on the dorsum of the hand, which will be placed in a heated box (50-60°C) for arterialized blood withdrawal. Prior to glucose challenge, blood samples will be taken at time points indicated in Table 4 for measurement of FPG, insulin, C-peptide, glucagon, FFA, GLP-1, and GIP concentrations and plasma ^{3}H-glucose and ^{14}C-glucose specific activities. Three hours after the start of [3-^{3}H]-glucose infusion (Time 0), patients will receive 75 grams of glucose containing 100 µCi 1-^{14}C-glucose orally. Blood samples will be collected at the time points indicated in Table 4 until the end of the study (Time 240 minutes/4 hours after glucose challenge).

Urine will be collected from the start of the study (Time -180 minutes) until Time 0 and again from Time 0 to 240 to measure glucose and creatinine to account for urinary glucose loss following glucose ingestion. Rates of EGP, oral glucose appearance, and whole body glucose disposal will be calculated from ^{3}H-glucose and ^{14}C-glucose specific activities, as previously described (Ferrannini et al 1985). We have previously shown that 4 hours is sufficient for complete absorption of the ingested glucose load. Therefore, splanchnic (primarily reflects hepatic) glucose uptake will be determined as the ingested glucose load (75 grams) minus the amount of ^{14}C-glucose (integrated area from 0 to 240 minutes) that appears in the systemic circulation.

Table 4 Double Tracer Oral Glucose Tolerance Test

Timepoint (clock time)[a]	Glucose	Insulin	C-peptide	Glucagon	FFA	GIP/ GLP-1	3-^{3}H-Glucose	1-^{14}C-Glucose
-180 (0600)	X	**Start 3-^{3}H-glucose infusion**						X
-30	X						X	X
-20	X	X	X	X	X	X	X	X
-10	X	X	X	X	X	X	X	X
-5	X						X	X
0 (0900)	X	X	X	X	X	X	X	X
Ingest glucose (75 grams) containing 100 µCi 1-^{14}C-glucose								

Timepoint (clock time)[a]	Glucose	Insulin	C-peptide	Glucagon	FFA	GIP/ GLP-1	3-^{3}H-Glucose	1-^{14}C-Glucose
15	X	X	X				X	X
30	X	X	X	X	X	X	X	X
45	X	X	X				X	X
60 (1000)	X	X	X	X	X	X	X	X
75	X	X	X				X	X
90	X	X	X	X	X	X	X	X
105	X	X	X				X	X
120 (1100)	X	X	X	X	X	X	X	X
135	X						X	X
150	X	X	X	X	X	X	X	X
165	X						X	X
180 (1200)	X	X	X	X	X	X	X	X
195	X						X	X
210	X	X	X	X	X	X	X	X
225	X						X	X
240 (1300)	X	X	X	X	X	X	X	X
Number of samples	*22*	*15*	*15*	*11*	*11*	*11*	*21*	*22*

Abbreviations: FFA free fatty acids, GIP glucose-dependent insulinotropic polypeptide, GLP-1 glucagon-like peptide-1.

[a] Study start times are approximate (between 0600 and 0700), but timepoints relative to study start time are critical.

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.

Samples will be collected according to the schedules presented in the Study Plan (Table 1).

5.2.1 Laboratory safety assessments

Laboratory safety assessments will be performed as presented in the Study Plan (Table 1). Sample tubes and sample sizes may vary depending on laboratory method used and routine

practice at the site. Additional safety samples may be collected if clinically indicated at the discretion of the Investigator.

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.

5.2.1.1 Hematology

Hematology assessments (see Table 5) will include the following: red blood cell count, hemoglobin (Hb), hematocrit, white blood cell count, platelets, and differential counts.

5.2.1.2 Chemistry

Chemistry assessments (see Table 5) will include the following: creatinine, total bilirubin, alkaline phosphatase, AST, ALT, albumin, potassium, calcium, sodium, creatine kinase, chloride, bicarbonate, urea nitrogen, uric acid, magnesium, and phosphorus.

Table 5 Laboratory Variables

Hematology/Hemostasis (whole blood)	Clinical Chemistry (serum or plasma)
B-Hemoglobin (Hb)	S/P-Creatinine
B-Hematocrit	S/P-Bilirubin, total (TB)
B-Leukocyte count	S/P-Alkaline phosphatase
B-Leukocyte differential count (absolute count)	S/P-Aspartate transaminase (AST)
B-Platelet count	S/P-Alanine transaminase (ALT)
Urinalysis (dipstick)	S/P-Albumin
U-Hb/Erythrocytes/Blood	S/P-Potassium
U-Protein/Albumin/Creatinine	S/P-Calcium, total
	S/P-Sodium
	S/P-Creatine kinase
	S/P-Chloride
	S/P-Bicarbonate
	S-Urea nitrogen
	S/P-Phosphate
	S/P-Magnesium
	S/P-Uric acid

Abbreviations: AST aspartate transaminase, ALT alanine transaminase, B blood, U urine, Hb hemoglobin, P plasma, S serum, TB total bilirubin.

5.2.1.3 Urinalysis

Urinalysis assessments will be performed according to the Study Plan (Table 1) and will include the following: hemoglobin, erythrocytes, blood, protein, albumin, and creatinine.

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 according to the Study Plan (Table 1).

Thyroid hormones

Blood samples will be collected for the measurement of TSH and T4 at Visit 1 (Screening), as presented in the Study Plan (Table 1). Patients with abnormal TSH or free T4 values will be excluded.

Pregnancy testing

All female patients, regardless of childbearing status (unless patient has had a hysterectomy), will provide urine or blood samples for pregnancy tests according to the schedule presented in the Study Plan (Table 1). 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.

5.2.2 Physical examination

A complete physical examination will be performed according to the schedule presented in the Study Plan (Table 1). The complete physical examination includes an assessment of the following: general appearance including skin inspection (including injection site), respiratory, cardiovascular, lymph nodes, thyroid, musculoskeletal/extremities, lungs, abdomen, and reflexes. Baseline physical examination data are collected at Week 0 and new findings at the following physical examinations are recorded as change from baseline.

A physical examination, either complete or a brief assessment, could be performed at any of the other visits at the Investigator's discretion.

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.

5.2.3 ECG

A 12-lead ECG will be performed at Visit 1 (Screening) and Visit 8, according to the schedule presented in the Study Plan (Table 1).

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. The ECGs will be interpreted by a qualified physician (the Investigator or qualified designee) at the clinical study site.

5.2.4 Vital signs

Vital sign measurements in this study will include reclining (for 5 minutes) and standing (for 2 minutes) systolic and diastolic BP and HR. Vital signs should be measured at every visit after the patient reclines for approximately 5 minutes and after standing for 2 minutes.

Blood pressure measurement will be performed with the Dynamap. An appropriate-sized cuff (cuff bladder encircling at least 80% of the arm) should be used to ensure accuracy. At least 2 measurements should be made at least 30 seconds apart and the average recorded. The same arm should be used for all BP measurements during the study.

5.2.5 Other safety assessments

5.2.5.1 Cardiovascular events

Deaths (including cause of death [CV related vs. non-CV]) and CV events (including MI, 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.

Adjudication for heart failure will be performed according to the respective charter.

5.2.5.2 Liver function test abnormalities

Please see Appendix C, "Algorithm on Management of Sustained Elevated Liver Safety Abnormalities," for further guidance.

5.3 Other assessments

5.3.1 Hypoglycemia

Subjects will be informed about the signs and symptoms of hypoglycemia when a glucometer is dispensed. Subjects will be asked to check their blood glucose when:

- The subject experiences signs or symptoms of hypoglycemia.
- At additional time points at the Investigator's discretion, which may include change of dose of standard of care medications or any other relevant signs or symptoms.

Subjects will be instructed to contact the study team anytime they experience a hypoglycemic event. Subjects will also be instructed to document any hypoglycemia events that have occurred since their last visit in a diary anytime they experience either of the following:

- Signs and symptoms of hypoglycemia (regardless of blood glucose value by finger stick)
- Blood glucose value by finger stick ≤70 mg/dL (3.9 mmol/L) (regardless of symptoms)

For these hypoglycemic events, subjects must record the following information in the diary:

- Date and time of hypoglycemic event
- Symptoms
- Blood glucose value by finger stick and time of finger stick
- Whether the subject experienced incoherence, unconsciousness, or required assistance of another person to recover
- Treatments administered

Subjects should be instructed to document exact date and time of last dose of study medication prior to each event. The diary will be returned by the subject and reviewed by site personnel at every subsequent visit. Hypoglycemic events will be added to the subject's source record, and data will be entered in the appropriate record. Subjects will also be requested to document any AEs and any concomitant medications they have taken since the last visit, and

to contact the site with any questions about AEs and/or concomitant medications. The Investigator should ensure these are transcribed onto the source documents during AE review.

The incidence of hypoglycemia will be tabulated in accordance with the FDA/ADA guidance.

Hypoglycemia events will be summarized descriptively. Summaries will be provided overall for all events of hypoglycemia as well as the subcategories severe hypoglycemia, documented symptomatic hypoglycemia, asymptomatic hypoglycemia, probable symptomatic hypoglycemia, and relative hypoglycemia consistent with the 2008 FDA guidance for the evaluation of drugs for the treatment and prevention of diabetes.

5.4 Pharmacokinetics (not applicable)

5.5 Pharmacodynamics (not applicable)

5.6 Pharmacogenetics (not applicable)

5.7 Biomarker analysis (not applicable)

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

The Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

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 (e.g., nausea and chest pain), signs (e.g., tachycardia and enlarged liver), or the abnormal results of an investigation (e.g., 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 (i.e., run-in, treatment, washout, or follow-up) that fulfills one 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 one of the outcomes listed above.

For further guidance on the definition of an 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 Screening, Run-in, and Randomization periods, and throughout the treatment periods.

All AEs will be recorded on source documents.

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.

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 SAE
- Date Investigator became aware of SAE
- 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. 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 an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

6.3.4 Causality collection

The Investigator will assess causal relationship between IP and each AE, and provide an 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'.

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 patient's source records. 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.

Adverse events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be recorded in the source document. Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should 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 uses the clinical, rather than the laboratory term (e.g., anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as an AE.

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 (Appendix C)

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥3x ULN together with total bilirubin ≥2x ULN may need to

be reported as SAEs. Specific guidance on the managing of liver abnormalities can be found in Appendix D of the protocol.

6.3.8 Hypoglycemia

Patients will be asked to test their blood glucose if they experience symptoms suggestive of hypoglycemia and to record specific symptoms and glucose values in the patient diary.

Study-site personnel must obtain accurate information for the patient's file and for episodes of hypoglycemia.

Hypoglycemia events will be summarized descriptively. Summaries will be provided overall for all events of hypoglycemia as well as by the following subcategories (Seaquist et al 2013):

Severe hypoglycemia: An event requiring assistance of another person to actively administer carbohydrate, glucagon, or other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

Documented symptomatic hypoglycemia: Typical symptoms of hypoglycemia accompanied by a measured plasma glucose concentration ≤70 mg/dL (3.9 mmol/L).

Asymptomatic hypoglycemia: Measured plasma glucose concentration ≤70 mg/dL (3.9 mmol/L), but not accompanied by typical symptoms of hypoglycemia.

Probable symptomatic hypoglycemia: Symptoms of hypoglycemia that are not accompanied by a plasma glucose determination, but that was presumably caused by a plasma glucose concentration ≤70 mg/dL (3.9 mmol/L).

Pseudo-hypoglycemia: Patient reports typical symptoms of hypoglycemia, with a measured plasma glucose concentration of >70 mg/dL (3.9 mmol/L) but approaching that level.

Additional subcategory: Blood glucose ≤55 mg/dL (3.1 mmol/L) with or without symptoms of hypoglycemia.

6.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the IP, or to the study procedure(s). All SAEs will be recorded in the source document and reported annually to the UTHSCSA IRB during continuing review.

Serious adverse events that do not require expedited reporting to the FDA need to be reported to AstraZeneca at least quarterly preferably using the MedDRA coding language for serious adverse events.

Investigator will review all SAEs and determine whether the reviewed incident, experience, and outcome represents a possible UPIRSO (Unanticipated Problem Involving Risk To

Subjects Or Others). All possible UPIRSOs will be reported to the UTHSCSA IRB using the Prompt Reporting Form.

a) Prompt reporting timeframe - report is made to the IRB within 7 days for UPIRSOs based on internal information (e.g., experienced by subjects enrolled by the investigator(s) at an institution affiliated with the UTHSCSA IRB) or 14 days for UPIRSOs based on external information (e.g., experienced by subjects enrolled by the investigator(s) at an institution not affiliated with the UTHSCSA IRB)

b) Special shortened reporting timeframe: All UPIRSOs based on internal information that are either life threatening or fatal events must be reported within 48 hours.

Investigators and other site personnel must inform the FDA, via a MedWatch/AdEERs form, of any serious or unexpected adverse events that occur in accordance with the reporting obligations of 21 CFR 312.32, and will concurrently forward all such reports to AstraZeneca. A copy of the MedWatch/AdEERs report must be faxed to AstraZeneca at the time the event is reported to the FDA. It is the responsibility of the investigator to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines and to ensure that these reports are also submitted to AstraZeneca at the same time.

When reporting to AstraZeneca, a cover page should accompany the MedWatch/AdEERs form indicating the following:

- Investigator Sponsored Study (ISS)
- The investigator's name and address
- The trial name/title and AstraZeneca ISS reference number

Investigative site must also indicate, either in the SAE report or the cover page, the causality of events in relation to all study medications and if the SAE is related to disease progression, as determined by the principal investigator.

Send SAE report and accompanying cover page by way of fax to AstraZeneca's designated fax line: 1-302-886-4114 or email to AEMailboxClinicalTrialTCS@astrazeneca.com

Serious adverse events that do not require expedited reporting to the FDA need to be reported to AstraZeneca preferably using the MedDRA coding language for serious adverse events.

In the case of blinded trials, AstraZeneca will request that the Sponsor either provide a copy of the randomization code/ code break information or unblind those SAEs which require expedited reporting.

All SAEs have to be reported to AstraZeneca, whether or not considered causally related to the investigational product. All SAEs will be documented. The investigator is responsible for

informing the IRB and/or the regulatory authority (FDA) of the SAE as per local requirements.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. The investigators or other site personnel will inform the UTHSCSA IRB of any follow-up information on a previously reported UPIRSO within 2 calendar days i.e., immediately but **no later than 48 hours** of when he or she becomes aware of it.

6.5 Adverse Events of Special Interest

Event categories of special interest for this study may include, but are not limited to, hypoglycemia, decreased lymphocyte count, decreased thrombocyte count, infections (including opportunistic infections, genital infections, and urinary tract infections), pancreatitis, hepatic, fractures, severe hypersensitivity, severe cutaneous adverse reactions, worsening of renal function, pancreatic cancer, bladder neoplasms, breast neoplasms, volume depletion (including hypotension, dehydration, and hypovolemia), ketoacidosis, and cardiac failure.

For the purposes of regulatory reporting, the following events must be reported in **24 hours** regardless of whether the events are classified as serious or non-serious.

Liver test abnormalities accompanied by jaundice or hyperbilirubinemia

This category of events includes all AEs where hepatocellular damage (with elevation of ALT or AST >3 x ULN) is combined with hepatic dysfunction (with elevation of total bilirubin >2 x ULN) or jaundice. With respect to liver function test abnormalities, both central-lab results and AEs will be monitored.

Opportunistic infections

This category of events includes: infections of interest that are consistent with AIDS-defining diagnoses and are specific for immunosuppression, including unusual infections caused by bacteria, mycobacteria, fungi, viruses, and protozoa. Herpes Zoster is of interest only if the case is multidermatomal, neurological, or systemic.

Severe Hypersensitivity

This category of events includes all cases of severe hypersensitivity including: angioedema, anaphylaxis, and Stevens-Johnson Syndrome.

When one of these events meets the criteria for a SAE, report the event using SAE reporting procedures. When one of these events does not meet the criteria for an SAE, report the event **within 24 hours** as a non-serious event.

For each non-serious event in these categories, the Investigator will notify the UTHSCSA IRB.

6.6 Overdose

Overdose is defined as the accidental or intentional ingestion of any dose of IP that is considered both excessive and medically important. For the purpose of this study, an overdose is defined as a dose of study medication in excess of that specified in the CSP (i.e., more than 1 tablet per day of either study drug).

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 in the source document.
- If the AE associated with the overdose meet any of the criteria for SAE, it should be reported according to the standard reporting timelines.

If an overdose on a study drug occurs in the course of the study then the Investigator or other site personnel will inform the UTHSCSA IRB immediately, or **no later than 24 hours** of when they become aware of it.

For overdoses associated with an SAE, the standard reporting timelines apply. For other overdoses, reporting must occur within 30 days.

In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status. Saxagliptin and its active metabolite are removed by hemodialysis (23% of dose over 4 hours). The removal of dapagliflozin by hemodialysis has not been studied.

6.7 Pregnancy

All pregnancies and outcomes of pregnancy will be reported to the UTHSCSA IRB.

6.7.1 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 will inform the UTHSCSA IRB within 1 day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated study sponsor representative will work with the Investigator to ensure that all relevant information is provided to the safety data entry site within 1 or 5 calendar days for SAEs and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

6.7.2 Paternal exposure

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

6.8 Management of IP related toxicities

Dose reductions are not permitted in this study.

6.9 Study governance and oversight

6.9.1 Hepatic Adjudication

Adjudication for drug-related hepatic injury will be performed by the Investigator to 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; see Appendix D
- AST and/or ALT >10x ULN

6.9.2 Cardiovascular Adjudication Committee

Adjudication for heart failure will be performed by the Investigator.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational products

Investigational product	Dosage form and strength	Manufacturer
Dapagliflozin	10 mg – green, plain, diamond shaped, film-coated tablet (Dimensions: approximately 0.4258''X 0.3100'')	AstraZeneca
Matching placebo for dapagliflozin	Green, plain, diamond shaped, film-coated tablet (Dimensions: approximately 0.4258''X 0.3100'')	AstraZeneca
Saxagliptin	5 mg – plain, yellow, biconvex, round, film-coated tablet	AstraZeneca

Investigational product	Dosage form and strength	Manufacturer
Matching placebo for saxagliptin	Plain, yellow, biconvex, round, film-coated tablet	AstraZeneca

The formulation number and batch number will be recorded in the trial master file.

Dapagliflozin, saxagliptin, and their matching placebo tablets will be packed in bottles and provided as individual patient kits at Visit 3. The tablets may contain lactose, which may cause discomfort in lactose-intolerant individuals. For additional information refer to the prescribing information for saxagliptin and dapagliflozin.

7.2 Dose and treatment regimens

The study consists of a Screening visit (Visit 1), a Run-in visit (Visit 2), a Randomization visit (Visit 3), followed by a 16-week randomized, double-blind treatment period. Double-blind study medication will be dispensed at time 0 (baseline) and monthly thereafter (visits 4, 5, and 6) during the treatment period.

In the event the patient loses her/his study medication, the Investigator will provide replacement.

16-week Treatment period (Visits 3 to 8)

At Visit 3, patients will be randomly assigned to 1 of the 3 treatment arms and randomized study medication will be dispensed as saxagliptin 5 mg tablets, dapagliflozin 10 mg tablets, and matching placebo tablets. The first doses of study medication will be taken at the study site. Patients will subsequently self-administer saxagliptin, dapagliflozin, or matching placebo QD orally for the 16-week treatment period.

On days of scheduled study visits, patients should bring their study medication with them to the study site and will take that daily dose as directed by study site personnel.

If any dose is missed, it should be taken as soon as noticed, 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.

7.3 Labelling

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

The label will include the following information:

1. Pharmaceutical dosage form, route of administration, and quantity of dosage units
2. Code number to identify the contents and packaging operation
3. Study code
4. Enrollment code (to be added on the label when IP is dispensed)
5. Directions for use
6. "For clinical trial use only"
7. Storage conditions
8. Period of use, e.g., expiration date
9. "Keep out of the reach of children"
10. The name of the Investigator, where applicable (to be added on the label when IP is dispensed)
11. Randomization code

7.4 Storage

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

7.5 Compliance

The patient will be asked about compliance at each study visit. Patients judged to be noncompliant (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 patient's source records.

7.6 Accountability

The study drug provided for this study will be used as directed in the Study Protocol.

The study personnel will account for all study drugs dispensed 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 used to record all study medication dispensed to or returned from each patient. Upon completion of the study, all unused study medication will be destroyed.

The study site personnel will 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 during the study. Dosages for certain concomitant medications should be maintained constant during the study, unless instructed otherwise by the Investigator. Concomitant herbal or nutritional therapies will be recorded.

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

Restricted Medication/Class of drug:	**Usage**
Cytochrome P450 3A4/5 inhibitors (e.g., atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin)	Prohibited during the study.
Other investigational drugs or participation in any interventional clinical study	Prohibited within 30 days prior to Visit 1 (Screening) and during the study.
Antihyperglycemic therapy	Administration of any antihyperglycemic therapy, other than metformin or sulfonylurea, for more than 14 days (consecutive or not) during the 12 weeks prior to Visit 1 (Screening) and during the study unless per protocol for rescue.
Systemic corticosteroids	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.

7.7.1 Metformin/Sulfonylurea

Up to Visit 8 (Week 16), patients should continue to administer the same type and dose of metformin or metformin/sulfonylurea therapy they were using at study entry.

Neither metformin nor sulfonylurea will not be provided by the Investigator.

7.7.2 Rescue therapy

Patients must first complete a glucose turnover study and all Week 16 visit procedures, including OGTT, before receiving open-label rescue therapy. Patients who require rescue therapy (i.e., FPG rescue criteria met) should receive standard of care treatment; however, Bydureon 2 mg subcutaneously is highly suggested. Patients should continue receiving study medication while receiving rescue therapy. Bydureon will be provided by the Sponsor.

If rescue therapy fails, further therapy will be given at the discretion of the Investigator.

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 source documents.

8. STATISTICAL ANALYSES

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 16-week randomized treatment period.

The primary efficacy measure of EGP will be derived by the Investigator. The remaining statistical analysis of this study will be performed by the Investigator.

Baseline: Unless otherwise specified, baseline refers to the last measurement collected prior to the first dose of study medication at the Randomization Visit. For parameters derived from the glucose turnover study and OGTT, several time points prior to the first dose of study medication may be averaged to calculate baseline.

All collected data will be listed. A comprehensive Statistical Analysis Plan (SAP) is described in the following sections.

8.2 Sample size estimate

This study will randomize patients to the following treatment arms (while continuing on metformin therapy):

- saxagliptin 5 mg + dapagliflozin 10 mg (n=21)
- dapagliflozin 10 mg + placebo for saxagliptin (n=21)
- placebo for dapagliflozin + placebo for saxagliptin (n=11).

The primary endpoint will compare the change in baseline EGP for saxagliptin (5 mg) plus dapagliflozin (10 mg) versus dapagliflozin (10 mg) at Week 16.

With 19 subjects per treatment group, there will be 90% power to detect a difference in mean EGP of 0.39 mg/kg/min between saxagliptin 5 mg plus dapagliflozin 10 mg and dapagliflozin 10 mg groups assuming a standard deviation of 0.32 using a 2 group t-test with a 0.050 2-sided significance level. Assuming that 10% of subjects in the primary comparison arms early terminate, are rescued, or do not have a Week 16 assessment for any other reason, a total of 21 subjects per treatment arm need to be randomized for each of the saxagliptin 5 mg plus dapagliflozin 10 mg and dapagliflozin 10 mg treatment arms. Approximately 11 subjects will be randomized to the placebo treatment arm for exploratory comparisons of saxagliptin 5 mg

plus dapagliflozin 10 mg to placebo (approximately 80% power), for a total of approximately 53 subjects randomized.

Assuming that 70% of screened patients will fail to meet screening criteria, a total of 177 patients will need to be screened.

8.3 Definitions of analysis sets

Classification into Full analysis (FA), Per protocol (PP), and Safety sets will be conducted prior to the database lock.

Primary analyses of efficacy endpoints (primary and secondary) will be performed on the FA set. Supportive analyses will be carried out with the PP analysis set if more than 10% of patients from the FA set are excluded from the PP analysis set for important protocol deviations. All safety analyses will be based on the Safety set.

8.3.1 Efficacy analysis set

Full analysis set

- The FA set will be defined as all randomized patients with a baseline and a post baseline efficacy assessment value. Patients will be analyzed according to the treatment assigned.

Per protocol analysis set

- The PP analysis set will be defined as all FA patients without an important protocol deviation that might affect the primary analyses. The criteria for important protocol deviations will be defined in the SAP. Patients will be analyzed according to the treatment received.

Safety analysis set

- The Safety analysis set will be defined as all randomized patients who received at least 1 dose of study medication. Patients will be analyzed according to the actual treatment received.

8.4 Outcome measures for analyses

The mean values will be compared between the treatment groups for the following measures:

1. Post-IP minus pre-IP EGP during glucose turnover study at Week 15.

2. Post-IP minus pre-IP EGP during glucose turnover study at Week 0 and the change from Week 0 to Week 15.

3. Pre-IP EGP during glucose turnover study at Week 15 and the change from Week 0 to Week 15.

4. Pre-glucose load EGP during the OGTT at Week 16 and the change from Week -1 to Week 16.

5. Change from Week -1 to Week 16 in post-glucose load EGP during the OGTT.

6. Change from Week -1 to Week 16 in Rd and Ra during OGTT.

7. Change from Week 0 to Week 16 in HbA1c.

8. Change from Week 0 to Week 15 in pre-IP plasma glucose during glucose turnover study.

9. Change from Week -1 to Week 16 in pre-glucose load FPG and post-glucose load PPG during the glucose turnover study.

10. Change from Week -1/0 to Week 15/16 in fasting plasma glucagon, C-peptide, and insulin during the glucose turnover study and OGTT.

11. Change from Week -1/0 to Week 15/16 in plasma glucagon, C-peptide, and insulin during the glucose turnover study and OGTT.

12. Change from Week 0 to Week 15 in post-IP minus pre-IP plasma glucagon, C-peptide, and insulin during the glucose turnover study.

13. Change from Week -1 to Week 16 in insulin secretion, beta cell function, and insulin sensitivity during OGTT.

14. Change in glucose oxidation and lipid oxidation during the baseline of the glucose turnover study, during the baseline of the OGTT, and post-glucose load during the OGTT.

15. Change in plasma ketones during the baseline of the glucose turnover study and OGTT.

16. Change from Week 0 to Week 15 in pre-IP, post-IP, and post-IP minus pre-IP in counterregulatory hormones during glucose turnover study.

17. Change from Week -2 to Week 16 in body weight and BMI; and percent body fat and fat distribution calculated from the DEXA scans.

18. Change from Week -1 to Week 16 in plasma GLP-1, GIP, and FFA during OGTT.

19. Change from Week -2 to Week 16 in FFA.

20. Change from Week 0 to Week 16 in waist to hip ratio, BP, and lipids.

8.5 Methods for statistical analyses

Continuous variables will be presented with mean, median, 25th percentile, 75th percentile, standard deviation, minimum, maximum, and (if appropriate) the number of nonmissing observations. Categorical data will be displayed via absolute and relative frequencies for each category, including a category labeled as 'missing' when appropriate. The 'missing' category will not contribute to the denominators of relative frequencies.

All analyses will be done using values prior to rescue/intensification of treatment. Values collected after this time will be excluded from analyses. Sensitivity analyses may be conducted using all available data and including a time varying covariate that indicates rescue status.

The primary endpoint (EGP) will be tested for saxagliptin 5 mg/dapagliflozin 10 mg versus dapagliflozin 10 mg groups at the α=0.05 level (2-sided). Other comparisons (contrasts) will be tested in an exploratory fashion at the α=0.05 (2-sided) level. Therefore, no multiplicity control is required.

8.5.1 Analysis of the primary variable

The primary efficacy analysis will be performed using an analysis of covariance (ANCOVA) method for the change from baseline at Week 16, with terms for treatment group, baseline HbA1c subgroup (≤8.5% versus >8.5%), baseline treatment (metformin versus metformin/sulfonylurea) and baseline value in the model. Point estimates and 95% confidence intervals will be calculated for the adjusted mean changes within each treatment group as well as for the differences in adjusted mean changes between treatment groups. A subject who early terminates, is rescued, or does not have a Week 16 assessment for any other reason will not contribute to the primary analysis.

All inferential procedures of the secondary efficacy endpoints will be done at a 5% level of significance (2-sided).

8.5.2 Analysis of the secondary and exploratory variables

The continuous secondary endpoints will be analyzed using a repeated measures model when the endpoints are collected at visits in addition to Week 16. A longitudinal repeated measures analysis (using a MIXED model) for the change from baseline at Week 16, with terms for treatment group, baseline HbA1c subgroup (≤8.5% versus >8.5%), baseline treatment (metformin versus metformin/sulfonylurea) baseline value, time (each relevant visit), the interaction of treatment and time, and the interaction of baseline value and time in the model. Point estimates and 95% confidence intervals will be calculated for the adjusted mean changes within each treatment group as well as for the differences in adjusted mean changes between treatment groups.

The continuous secondary endpoints will be analyzed using an ANCOVA model like the primary endpoint when the endpoints are collected at baseline visit (Visit 3) and Week 16 only.

8.5.3 Subgroup analysis

The subgroup analysis will be performed according to the baseline HbA1c cutoff: ≤8.5% or >8.5%.

Subgroup analyses will be analyzed in an exploratory fashion with respect to the primary efficacy endpoint as was done for the original analysis with terms for treatment group and baseline value, but for the applicable subset of subjects. Interaction tests will be performed by using the same primary analysis model with terms for treatment group, baseline HbA1c subgroup (≤8.5% or >8.5%), and baseline value but with treatment-by-HbA1c subgroup interaction terms added.

8.5.4 Sensitivity analysis

Sensitivity analyses may be conducted using all available data and including a time varying covariate that indicates rescue status.

8.5.5 Safety analyses

Descriptive statistics of demographic and other baseline characteristics will be calculated. Safety and tolerability will be assessed using standard tabulations of AEs and AEs of special interest (using predefined lists of preferred terms), laboratory values and marked abnormalities, vital signs, physical examinations, and ECGs. The number and percentage of patients with hypoglycemia will be tabulated and presented by treatment group.

8.6 Interim analysis

No interim analysis on the efficacy or safety parameters is planned for this study.

9. STUDY AND DATA MANAGEMENT

9.1 Training of study site personnel

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

Monitoring of the study

A UTHSCSA Compliance Monitor:

- Will review the study progress, protocol deviations, and adverse events every 2-4 weeks.
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded, and that study drug accountability checks are being performed

- Perform source data verification including verification of informed consent of participating patients.
- 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.

9.2.1 Archiving of study documents

All source documents will be stored in a locked room on the third floor Clinical Research Center at the Texas Diabetes Institute.

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 3nd Quarter of 2015. The study is expected to complete 1st Quarter 2017.

9.4 Database lock

Once all patient casebooks are locked, the final data will be analyzed.

10.4 Informed consent

The Investigator 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 Audits and inspections

Authorized representatives of the UTHSCSA or a regulatory authority 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 IRB, and any applicable regulatory requirements.

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