**Official Study Title**: **Effect of Chronic Exenatide Therapy on Beta Cell Function and Insulin Sensitivity in T2DM**

**NCT number**: NCT02981069

**IRB Approval Date**: 04-08-2020

**Unique Protocol ID**: HSC20160597H

**Study A.**

***Subjects*:** 80 T2DM subjects (age = 18-70 years; BMI = 21-45 kg/m$^2$; male or female) according to the ADA criteria will participate in the study. Subjects must be drug naïve and/or on a stable dose (more than 3 months) of metformin and/or sulfonylurea and have HbA1c >7.0% and <10.5%. Subjects taking drugs known to affect glucose metabolism (other than metformin and sulfonylurea) will be excluded. Other than diabetes, subjects must be in good general health as determined by physical exam, medical history, blood chemistries, CBC, TSH,, EKG and urinalysis. Only subjects whose body weight has been stable (± 3 lbs) over the preceding three months and who do not participate in an excessively heavy exercise program will be included. Individuals with evidence of proliferative diabetic retinopathy, plasma creatinine >1.4 females or >1.5 males will be excluded. Diabetic subjects will be recruited from the South Texas Veterans Health Care System and Texas Diabetes Institute (TDI) in San Antonio (Deputy Director = Ralph A. DeFronzo, MD). TDI is the largest institute in the United States that provides comprehensive care for ~ 10,000 unduplicated T2DM patients. Therefore, we do not anticipate any problem in recruiting the required number of patients for this study.

***Study design*:** After screening, eligible subjects will receive a measurement of endogenous glucose production (EGP) with a prime-continuous infusion of 3-$^3$H-glucose. The EGP measurement will be performed in the morning after a 10-12 hour overnight fast and will last 8.5 hours (from 6 AM to 2:30 PM). After a 3.5-hour tracer equilibration period, subjects (20 per group) will receive one of the following medications: (i) placebo; (ii) exenatide 5 ug subcutaneously; (iii) dapagliflozin (10 mg); and (iv) dapagliflozin 10 mg plus exenatide 5 ug (see flow diagram on page 11). Following the test medication at 9:30 AM, blood samples will be drawn every 10-20 minutes for an additional 5 hours and plasma glucose, insulin, C-peptide, glucagon concentrations and glucose specific activity will be measured. One-two weeks after the EGP measurement, participants will come back for the Double Tracer Oral Glucose Tolerance Test (DT-OGTT).

**Visit 1: Screening**. Medical history will be obtained and physical exam will be performed. Blood will be drawn for FPG, routine blood chemistries, CBC, lipid profile, HbA1c, and thyroid function. Urinalysis, EKG, albumin/creatinine ratio and pregnancy test will be performed.

**Visit 2: Endogenous Glucose Production Measurement** (EGP)**:** The rate of endogenous glucose production will be measured with 3-$^3$H-glucose infusion. [3-$^3$H]-glucose infusion will be started at 6 AM and continued until 2:30 PM (5 hours after drug administration). At 6 AM a catheter will be placed into an anticubital vein and a prime (40 uCi x FPG/100)- continuous (0.4 uCi) infusion of [3-$^3$H]- glucose will be started and continued until 2:30 PM. Participant's hand will be placed in a box heated to 50-60°C (122-140°F). Baseline blood samples will be obtained at-210, -60, -50, -45, -40, -35, -30, -20, -10, and 0. After 3.5 hours of tracer equilibration blood samples will be obtained every 10-20 minutes from 9:30 AM to 2:30 PM. Plasma glucose, insulin, C-peptide, glucagon, concentrations, and [3-$^3$H]-glucose specific activity will be measured. Urine will be collected from 6 to 9:30 AM and from 9:30 AM to 2:30 PM. Urinary volume and glucose concentration will be measured and urinary glucose excretion rate calculated. The study will end at 2:30 PM.

Visit 3: Double Tracer Oral Glucose Tolerance Test (DT-OGTT): Within one to two weeks after the measurement of EGP, all subjects will have a 5-hour DT-OGTT with measurement of plasma glucose, insulin (I), C-peptide (CP), and glucagon concentrations at -180, -60-, -50-, -45, -40, -35, -30, -20, -10, 0 and every 15-30 minutes thereafter to obtain a measure of overall glucose tolerance, insulin secretion (ΔCP0-120/ΔG0-120), insulin sensitivity (Matsuda index [MI]), beta cell function, (ΔCP0-120/ΔG0-120 x MI), and suppression of plasma glucagon concentration (64). At 7 AM a catheter will be placed into an anticubital vein and a prime (25 uCi x FPG/100)- continuous (0.25 uCi) infusion of [3-$^3$H]- glucose will be started and continued until 3 PM Urine will be collected from 7 to 10 AM and from 10 AM to 3 PM. Urinary volume and glucose concentration will be measured and urinary glucose excretion rate calculated. The study will end at 3 PM.

HbA1c will be measured twice, once on the day of the DTOGTT and once on the day of the EGP measurement.

**Data Analysis and Statistical Methods**: The **primary end point** of the study is the change in EGP during **Study A**. The difference in the rate of EGP during the last hour of the study (i.e. from 240-300 minutes) between drug-treatment and placebo-treatment studies represents the effect of drug treatment on EGP. The difference in EGP will be compared among the 3 drug treatments (exenatide, dapagliflozin, and exenatide plus dapagliflozin) with ANOVA. Post hoc testing will be performed with a Bonferroni correction for multiple

comparisons. The following primary comparison will be performed: (i) the change in EGP above baseline following dapagliflozin alone versus dapagliflozin/exenatide. The following secondary comparisons will be made: (i) the change in EGP above baseline following exenatide alone versus dapagliflozin/exenatide and (ii) the change in EGP above baseline following dapagliflozin alone, exenatide alone, and dapagliflozin/exenatide versus the change in EGP following placebo. Between group comparisons will be made with repeated measures ANOVA with time and treatment group as factors.

**Other secondary end points** will be: (i) the decrement in the fasting plasma glucose conc at the end of the study compared to baseline, (ii) change in plasma glucagon conc at the end of the study compared to baseline; and (iii) change in plasma insulin conc at the end of the study compared to baseline. Secondary end points will be compared using the same statistical methods described for the primary end point.

**Anticipated Results and Data Interpretation**. Consistent with our published data (10), we anticipate that EGP will decrease progressively following placebo administration while, after an initial decline, EGP will increase progressively following dapagliflozin. We anticipate that plasma glucagon conc will increase and plasma insulin concentration will decrease following dapagliflozin administration. We anticipate that a single administration of exenatide will cause an increase in plasma insulin conc and a decrease in plasma glucagon conc compared to placebo. The increase in plasma insulin and decrease in plasma glucagon conc following exenatide administration will result in a greater decline in both EGP and fasting plasma glucose conc compared to placebo. Most importantly, we anticipate that the increase in plasma glucagon conc, the decrease in plasma insulin conc, and rise in EGP following dapagliflozin administration will be prevented, at least in part, if not totally, when exenatide is co-administered with dapagliflozin. Therefore, we anticipate an additive, even synergistic, decrease in plasma glucose conc and EGP following co-administration of dapagliflozin plus exenatide compared to either drug alone.

**Sample Size Calculation:** In our published results (10), the difference in the rate of basal EGP during the last hour of EGP measurement in dapagliflozin-treated and placebo-treated individuals was 0.70±0.34 (mean±SD). To detect a 50% decrease in the difference at alpha = 0.005 (=0.5/10) (split alpha for up to 10 multiple comparisons and a Bonferroni correction) in exenatide plus dapagliflozin versus dapagliflozin alone, we computed that 17 subjects in each group provided 90% power. To ensure 17 completers assuming 15% lost to follow-up, we have set the sample size at 20 (=17/0.85) in each group.

**Study B (see flow sheet below)**

Following the measurement of endogenous glucose production [EGP] in Study A, and after the double tracer OGTT visit, subjects who receive Byetta will be started on Byetta, 5 ug sc bid, and they will return for a follow up visit in 7 days (visit 4) at which time the Byetta will be increased to 10 ug sc bid, if tolerated. Subjects will return at days 14, 21, and 28 (visits 5, 6, and 7). If the Byetta dose cannot be increased to 10 ug bid because of side effects on the day 7 visit, the dose will be advanced on the subsequent visit (i.e., day 14 or 21 or 28), side effects permitting. On the day 28 visit the Double Tracer OGTT will be repeated with Byetta dosing at time zero of study (Visit 7).

Subjects who received dapagliflozin will continue on dapagliflozin, 10 mg/day, and will return for follow up visits at days 7, 14, and 21. At the day 28 visit the the DT-OGTT will be repeated. On the day of DT-OGTT, dapagliflozin will be given in the morning prior to the study. Note that this group will not receive Byetta and, thus, will allow us to determine how long the effect of dapagliflozin to increase EGP persists.

Subjects who received dapagliflozin plus Byetta will continue on dapagliflozin and Byetta, and will return for follow up visits at days 7, 14, and 21. At the day 28 visit the DT-OGTT will be repeated. On the day of the DT-OGTT, dapagliflozin will be given in this group will allow us to determine whether the ability of Byetta to inhibit the paradoxical rise in EGP observed with dapagliflozin can be blocked on a chronic basis.

Subjects who received the placebo will not be continued forward. However, these subjects will be allowed to be randomized to the Byetta alone, dapagliflozin alone, or Byetta/dapagliflozin groups.

**Visits 4, 5 and 6: Brief Follow Up Visits** for interim medical history and compliance with the treatment regimen a BMP will be done to check on your kidney function.

**Visit 7: Double Tracer OGTT** will be performed as per **Visit 3**.

**Study C (see flow sheet below).**

Following completion of the OGTT (Visit 7), subjects will be started on Bydureon, 2 mg sc per week. Subjects will return of interim follow up visits at weeks 6, 8, 10, 13-14, (visits 8, 9,10, 11. During the weeks 16-18 (visit 12),subjects will have a repeat Double Tracer OGTT (visit 12) will be performed..

**Visits 8, 9, 10, and 11. Brief Follow Up Visits** for interim medical history and compliance with the Bydureon regimen.

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**Visit 12: Double Tracer OGTT** will be performed as per **Visit 3**.

The treatment period could be extended based upon the circumstances (based upon the situation of COVID-19 pandemic) until the repeat studies are completed.

**Data Analysis**: In **Study B,** we anticipate that dapagliflozin and Byetta will produce similar reductions in HbA1c and that the combination of dapagliflozin plus Byetta will produce an additive/near-additive reduction in A1c. We anticipate that both dapagliflozin and Byetta monotherapy will produce significant weight loss and that the combination will produce an additive, even synergistic, effect on weight loss.

We anticipate that that the dapagliflozin-induced rise in EGP will persist after 1 month in T2DM patients receiving dapagliflozin monotherapy even though both beta cell function and peripheral insulin sensitivity improve. We expect that Byetta-treated T2DM patients will experience a reduction in both fasting and postprandial plasma glucose levels during the DT-OGTT, markedly enhanced beta cell function, improved peripheral tissue insulin sensitivity, and reduced fasting and postprandial plasma glucagon concentrations during the DT-OGTT. In T2DM patients receiving combined Byetta/dapagliflozin therapy, we hypothesize that exenatide will block the dapagliflozin-induced rise in glucagon secretion and overcome the dapagliflozin-induced decrease insulin secretion, resulting in a greater suppression of EGP. Because we anticipate that Byetta will offset the negative effects of dapagliflozin on EGP and on insulin and glucagon secretion, we expect that the decline in fasting and postprandial glucose concentrations during the DT-OGTT will be enhanced in T2DM subjects receiving combination Byetta/dapagliflozin therapy.

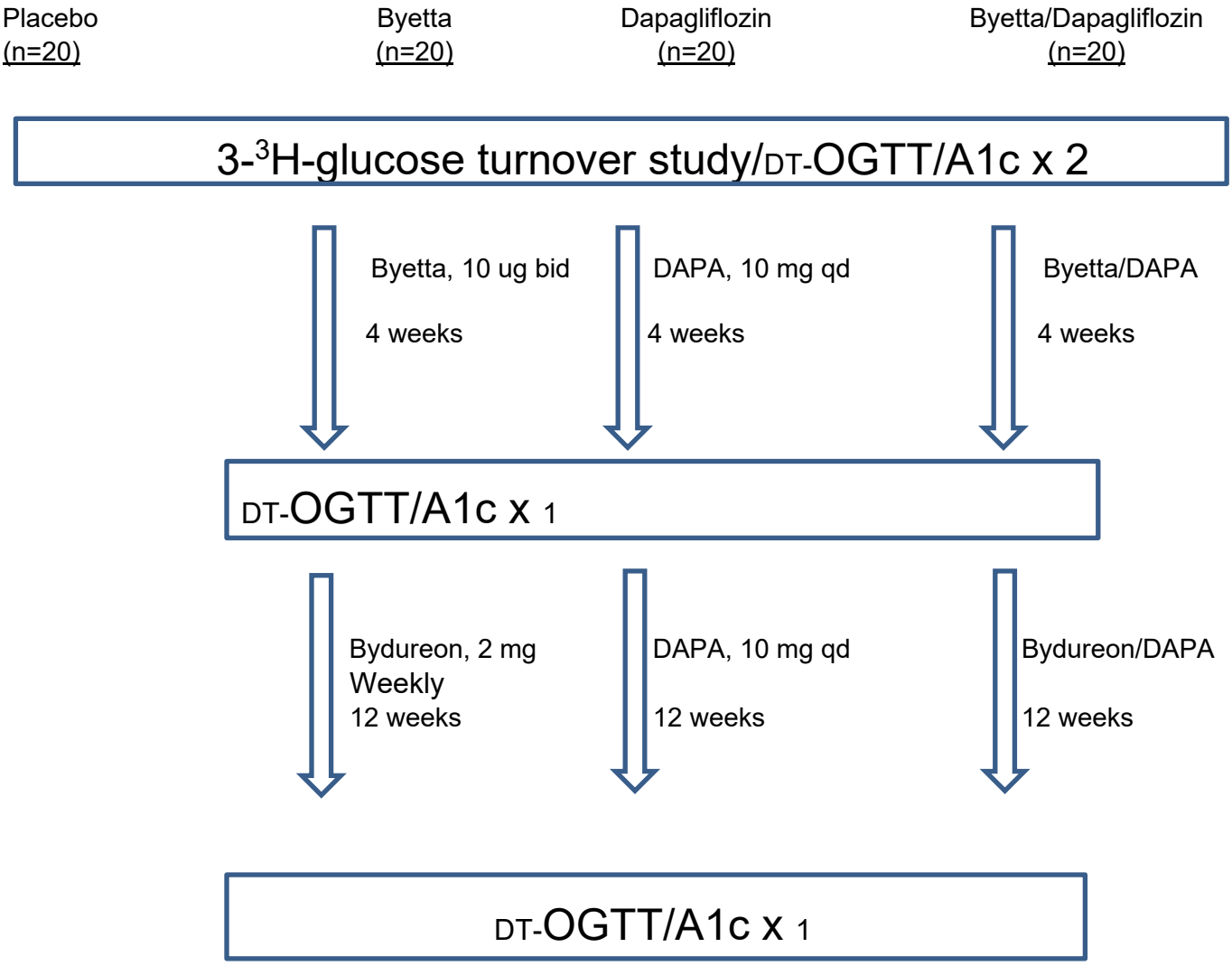
**Sample Size Calculation**: In our published results (10), the difference in the rate of basal EGP during the last hour of EGP measurement in dapagliflozin-treated and placebo-treated individuals was 0.70±0.34 (mean ±SD). To detect a 50% decrease in the difference at alpha = 0.167 (=0.5/3) (split for 3 comparisons and a Bonferroni correction) in Byetta plus dapagliflozin versus dapagliflozin alone, we computed that 13 subjects in each group will provide 90% power.

**Data Analysis**: In Study C, we anticipate that dapagliflozin and Bydureon will produce similar reductions in HbA1c and that the combination of dapagliflozin plus Bydureon will produce an additive/near-additive reduction in A1c. We anticipate that both dapagliflozin and Bydureon monotherapy will produce significant weight loss and that the combination will produce an additive, even synergistic, effect on weight loss.

We anticipate that that the dapagliflozin-induced rise in EGP will persist after 4 months in T2DM patients receiving dapagliflozin monotherapy even though both beta cell function and peripheral insulin sensitivity improve. We expect that Bydureon-treated T2DM patients will experience a reduction in both fasting and postprandial plasma glucose levels during the OGTT, markedly enhanced beta cell function, improved peripheral tissue insulin sensitivity, and reduced fasting and postprandial plasma glucagon concentrations during the DT-OGTT. In T2DM patients receiving combined Bydureon-dapagliflozin therapy, we hypothesize that exenatide will block the dapagliflozin-induced rise in glucagon secretion and overcome the dapagliflozin-induced decrease insulin secretion, resulting in suppression of EGP. Because we anticipate that Bydureon will offset the negative effects of dapagliflozin on EGP and on insulin and glucagon secretion, we expect that the decline in fasting and postprandial glucose concentrations during the DT-OGTT will be enhanced in T2DM subjects receiving combination Bydureon/dapagliflozin therapy.

**Sample Size Calculation:** In our published results (10), the difference in the rate of basal EGP during the last hour of EGP measurement in dapagliflozin-treated and placebo-treated individuals was 0.70±0.34 (mean ±SD). To detect a 50% decrease in the difference at alpha = 0.167 (=0.5/3) (split for 3 comparisons and a Bonferroni correction) in Bydureon plus dapagliflozin versus dapagliflozin alone, we computed that 13 subjects in each group will provide 90% power.

**STUDY DESIGN**




COMPARISONS during initial 3-$^{3}$H-glucose turnover study

Byetta/Dapa vs Dapa
vs Byetta
vs Placebo

Dapa vs Byetta
vs Placebo

Byetta vs Placebo

## 3-$^{3}$H-GLUCOSE TURNOVER STUDY

| Time (min) | Glucose (0.5 ml) | Insulin (1.5 ml) | C-peptide (1.5 ml) | Glucagon (1.5 ml) | 3-$^{3}$H-glucose (2 ml) |
|---|---|---|---|---|---|
| -210 | X | | | | |
| Start 3-$^{3}$H-glucose AT -210 | | | | | |
| -60 | X | X | X | X | X |
| -50 | X | X | X | X | X |
| -45 | X | | | | X |
| -40 | X | X | X | X | X |
| -35 | X | X | | | X |
| -30 | X | X | X | X | X |
| Ingest dapagliflozin at -30 minutes | | | | | |
| -20 | X | X | X | X | X |
| -10 | X | X | X | X | X |
| 0 | X | X | X | X | X |
| Inject Byetta at time zero | | | | | |
| 15 | X | X | X | X | X |
| 30 | X | X | X | X | X |
| 45 | X | X | X | X | X |
| 60 | X | X | X | X | X |
| 75 | X | | | | X |
| 90 | X | X | X | X | X |
| 105 | X | | | | X |
| 120 | X | X | X | X | X |
| 135 | X | | | | X |
| 150 | X | X | X | X | X |
| 165 | X | | | | X |
| 180 | X | X | X | X | X |
| 200 | X | | | | X |
| 220 | X | X | X | X | X |
| 240 | X | | | | X |
| 260 | X | X | X | X | X |
| 280 | X | X | X | X | X |

| | | | | | |
|---|---|---|---|---|---|
| 285 | X | | | | X |
| 290 | X | | | | X |
| 295 | X | | | | X |
| 300 | X | X | X | X | X |
| Number | 30 | 20 | 20 | 19 | 30 |
| Volume (ml) | 15 | 30 | 30 | 29 | 60 |

Total Volume = 164 ml

## DOUBLE TRACER ORAL GLUCOSE TOLERANCE TEST (DT-OGTT)

| **Time (min)** | **Glucose (0.5 ml)** | **Insulin (1.5 ml)** | **C-peptide (1.5 ml)** | **Glucagon (1.5 ml)** | **3-$^{3}$H-glucose (2 ml)** | **1-$^{14}$C-glucose (4 ml)** |
|---|---|---|---|---|---|---|
| -180 | x | | | | | |
| Start tritiated glucose at -180 minutes | | | | | | |
| -60 | X | X | X | X | X | |
| -50 | X | | | | X | |
| -45 | X | X | X | X | X | |
| -40 | X | | | | X | |
| -35 | X | | | | X | |
| -30 | X | X | X | X | X | |
| Ingest dapagliflozin at -30 minutes | | | | | | |
| -20 | X | X | X | X | X | |
| -10 | X | X | X | X | X | |
| 0 | X | X | X | X | X | X |
| Inject Byetta at time zero; ingest 75 gm glucose with $^{14}$C-glucose at time zero | | | | | | |
| 15 | X | X | X | X | X | X |
| 30 | X | X | X | X | X | X |
| 45 | X | X | X | X | X | X |
| 60 | X | X | X | X | X | X |
| 75 | X | X | X | | X | X |
| 90 | X | X | X | X | X | X |
| 105 | X | X | X | | X | X |
| 120 | X | X | X | X | X | X |

| | | | | | | |
|---|---|---|---|---|---|---|
| 150 | X | X | X | X | X | X |
| 180 | X | X | X | X | X | X |
| 210 | X | X | X | X | X | X |
| 240 | X | X | X | X | X | X |
| 270 | X | X | X | X | X | X |
| 280 | X | X | X | X | X | X |
| 290 | X | X | X | X | X | X |
| 300 | X | X | X | X | X | X |
| Number | 24 | 22 | 22 | 20 | 25 | 17 |
| Volume (ml) | 12 | 33 | 33 | 30 | 50 | 68 |

Total blood volume = 226 ml

Exclusion Criteria

1. Presence of significant systemic disease, heart problems including congestive heart failure, unstable angina or acute myocardial infarction, current infectious liver disease, acute stroke or transient ischemic attacks, history of pancreatitis, urosepsis and pyelonephritis, genital mycotic infections, or Type 1 diabetes mellitus
2. Any hepatic diseases in the past (infectious liver disease, viral hepatitis, toxic hepatic damage, jaundice of unknown etiology) or severe hepatic insufficiency and/or significant abnormal liver function tests defined as aspartate aminotransferase (AST) >3x upper limit of normal (ULN) and/or alanine aminotransferase (ALT) >3x ULN
3. Renal impairment (e.g., serum creatinine levels ≥1.4 mg/dL for women or ≥1.5 mg/dl for men, or eGFR <60 mL/min/1.73 m2) or history of unstable or rapidly progressing renal disease or end stage renal disease.
4. Uncontrolled thyroid disease , Cushing's syndrome, congenital adrenal hyperplasia or hyperprolactinemia
5. Significantly elevated triglyceride levels (fasting triglyceride > 400 mg/dl), uncontrolled increased LDL-C
6. Untreated or poorly controlled hypertension (sitting blood pressure > 160/95 mm Hg)
7. Use of anti-obesity drugs or weight loss medications (prescription or OTC) and medications known to exacerbate glucose tolerance (such as isotretinoin, , GnRH agonists, glucocorticoids, anabolic steroids, C-19 progestins) stopped for at least 8 weeks. Use of anti-androgens that act peripherally to reduce hirsutism such as 5-alpha reductase inhibitors (finesteride, spironolactone, flutamide) stopped for at least 4 weeks

8. Prior history of a malignant disease requiring chemotherapy, prior history of bladder cancer regardless treatment
9. Patients at risk for volume depletion due to co-existing conditions or concomitant medications, such as loop diuretics should have careful monitoring of their volume status
10. History of unexplained microscopic or gross hematuria, or microscopic hematuria at visit 1, confirmed by a follow-up sample at next scheduled visit.
11. Presence of hypersensitivity to dapagliflozin or other SGLT2 inhibitors (e.g. anaphylaxis, angioedema, exfoliative skin conditions
12. Known hypersensitivity or contraindications to use GLP1 receptor agonists (exenatide, liraglutide)
13. Use of , thiazolidinediones, GLP-1 receptor agonists, DPP-4 inhibitors, SGLT2 inhibitors stopped for at least 8 weeks.
14. Eating disorders (anorexia, bulimia) or gastrointestinal disorders
15. Suspected pregnancy (documented negative serum β-hCG test), desiring pregnancy in next 6 months, breastfeeding, or known pregnancy in last 2 months
16. Active history of illicit substance abuse or significant intake of alcohol
17. Having a history of bariatric surgery
18. Patient not willing to use two barrier method contraception during study period (unless sterilized or have an IUD)
19. Debilitating uncontrolled psychiatric disorder such as psychosis or neurological condition that might confound outcome variables
20. Inability or refusal to comply with protocol
21. Current participation or participation in an experimental drug study in previous three months

***Safety***

**Definition of adverse events**

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

**Definitions of serious adverse event**

A serious adverse event (SAE) is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfils 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 subject or may require medical intervention to prevent one of the outcomes listed above

The causality of SAEs (their relationship to all study treatment) will be assessed by the investigator(s) and communicated to AstraZeneca (AZ).

**Recording of adverse events**

Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last AE assessment at the end of the study are followed up by the investigator for as long as medically indicated, but without further recording in the CRF. AstraZeneca retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

The following variables will be collected for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no)
- Action taken with regard to investigational product*:* (AE caused subject's withdrawal from study *(*yes or no*)*
- Outcome

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study drug(s)
- Causality assessment in relation to Other medication
- Causality assessment in relation to Additional Study Drugs
- Description of AE.

Causality assessment:

- The Investigator will assess causal relationship between Investigational Product and each Adverse Event, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'
- For SAEs, a causal relationship will also be assessed for other concomitant medications, study procedures, and comparator study drugs. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

**Reporting of serious adverse events**

Investigators and other site personnel will 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 AZ. A copy of the MedWatch/AdEERs report will be faxed to AZ 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 AZ at the same time.

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

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

Investigative site will also indicate, either in the SAE report or in 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 (PI).

The SAE report and accompanying cover page will be sent by way of fax to AZ's designated fax line: 1-302-886-4114 or via email: AEMailboxClinicalTrialTCS@astrazeneca.com.

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

In the case of blinded trials, AZ 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 will be reported to AZ, whether or not considered causally related to the investigational product. All SAEs will be documented. The investigator will be responsible for informing the WCMC-Institutional Review Board (IRB) of the SAE.

**Safety assessments**

Safety assessments will consist of monitoring and recording all TEAEs, SAEs, AEs leading to discontinuation/withdrawal from study, laboratory evaluation for hematology, blood chemistry, and urine values; pregnancy testing; measurement of vital signs and ECGs; and performance of physical examinations.