COVER PAGE FOR PROTOCOL AND STATISTICAL ANALYSIS PLAN

Official Study Title: Effect of Cycloset on Glycemic Control In Type 2 Diabetic Patients Inadequately Controlled on GLP-1 Analogue Therapy

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VeroScience
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CLINICAL STUDY PROTOCOL

Effect of Cycloset on Glycemic Control In Type 2 Diabetic Patients Inadequately Controlled on GLP-1 Analogue Therapy

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Single center study
US sites only

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PROTOCOL OUTLINE

Study number **HSC20130330H**

Title

Effect of Cycloset on Glycemic Control In Type 2 Diabetic Patients Inadequately Controlled on GLP-1 Analogue Therapy

Investigator(s), Study Site(s)

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Sponsor-Funded, Single Center, Investigator Initiated Trial

Study Duration and Dates	The duration of this study is expected to be approximately 18 months (10-month subject recruitment, up to 3 week screening phase, and 5-month treatment), with subject recruitment to start in May 2014 and the last subject to finish in October 2015.	**Phase**	IV (Open label Cycloset added to usual diabetes treatment)

Objectives

Primary Objective:

To examine the effect of the addition of Cycloset upon glucose metabolism (glycemic control including post prandial glucose metabolism) in individuals with inadequately controlled (HbA1c 7.5-10.0) type 2 diabetes (T2DM) who are already on Bydureon (exenatide once weekly) or Victoza (liraglutide once daily) as part of their standard care.

Secondary Objectives:

Since Cycloset has been shown to reduce cardiovascular events in those over the age of 18 with T2DM, we will also perform mechanistic studies evaluating for potential mechanisms for this cardiovascular benefit including non-invasive tests for the assessment of the effects of Cycloset therapy on endothelial function, aortic compliance, body weight composition, and inflammatory and oxidative stress markers.

Study Design

This is a single-site, prospective, cohort study that will assess the effect of Cycloset as add-on therapy in adult subjects with T2DM that is inadequately controlled (HbA1c 7.5% to 10.0%) on GLP-1 analog therapy with either exenatide (Bydureon) once weekly or liraglutide (Victoza) once

daily.

Entry criteria will be checked at the screening visit. All qualified subjects will undergo baseline studies including non-invasive hemodynamic testing for assessment of aortic stiffness and pulse wave velocity, assessment of body weight composition by dual-energy X-ray absorptiometry (DXA), assessment of endothelial function using the Endo-PAT device, measurement of cytokines and inflammatory biomarkers in the peripheral blood and urine, assessment of oxidative stress and inflammatory markers in white blood cells isolated from a peripheral whole blood sample, a 5-hour mixed meal tolerance test (MMT) for assessment of postprandial glucose metabolism and 24-hour ambulatory BP monitoring.

Following completion of all the baseline studies as above, subjects will be started on Cycloset, 0.8 mg/day in addition to their stable dose of Bydureon (exenatide) (2mg/week) or Victoza (liraglutide) (1.2-1.8 mg/day), and the dose will be increased by 0.8 mg/day every week to a maximum of 3.2 mg/day, or as tolerated to a minimum of 2.4 mg/day.

Subjects will return at months 1, 2, 3, and 4 for interim medical history, body weight, HbA1c, and FPG. Postural blood pressure measurements will be obtained with the subject lying down and then after standing for 5 minutes at each of the visits. At month 4, all of the baseline studies detailed above will be repeated.
All tests will be performed in the Clinical Research Center at the Texas Diabetes Institute/University of Texas Health Science Center, San Antonio.

Number Of Subjects

Planned enrollment = 15

Primary Subject Characteristics at Enrollment

T2DM male or female subjects between the ages of 30 and 70 years with HbA1c between 7.5-10% on a diabetes therapeutic regimen consisting of stable doses of either exenatide (2 mg/week) or liraglutide (1.2-1.8 mg/day) for at least 90 days prior to enrollment with or without metformin and/or pioglitazone and no other glucose lowering agents.

Study Treatments

Cycloset, 0.8 mg/day, with the dose increased by 0.8 mg/day every week to a maximum of 3.2 mg/day, or as tolerated to a minimum dose of 2.4 mg/day, added on to usual diabetes therapy consisting of a stable dose for at least 90 days of exenatide (2mg/week) or liraglutide (1.2-1.8 mg/day). Subjects must be on either exenatide or liraglutide as part of their standard care to be eligible for study participation.

Study Endpoints

The primary endpoint is the effect of Cycloset on glycemic control and postprandial glucose metabolism.

Secondary endpoints include the effects of Cycloset on endothelial function, aortic compliance,, body weight composition, blood pressure and markers of inflammation and oxidative stress.

Statistical Procedures

Sample Size Calculation: Assuming that Cycloset will cause a 0.6% reduction in HbA1c, we computed that 15 subjects provide 90% power to detect a 0.6% decrease from a baseline HbA1c of 8.0 ±0.5% at an alpha of 0.05.

A statistical analysis plan (SAP), providing details of the analyses and presentation structure of the results, will be developed and finalized before the database is locked.

STUDY SCHEDULE

Data collected and/or action	Screening Period	Baseline Period			Treatment Period (16 weeks)							
	Visit 0*	**Visit 1***	**Visit 2**	**Visit 3**	**Phone call 1**	**Phone call 2**	**Phone call 3**	**Visit 4**	**Visit 5**	**Visit 6**	**End of Study Visit 7[α]**	**End of Study Visit 8 [α]**
	Week -3 to -1	**Week 0 (baseline)**	**Visit 1 +7-10 days**	**Visit 2 +3-5 days**	**Day 7**	**Day 14**	**Day 21**	**1 Month**	**2 Months**	**3 Months**	**4 Months**	**Visit 7 +3-5 days**
Informed Consent	X											
Entry Criteria	X		X									
Medical History	X							X	X	X	X	
Physical Exam	X											
Body Weight	X		X					X	X	X	X	
ECG	X											
Hematology and chemistry	X										X	
Lipids	X										X	X
HbA1c	X							X	X	X	X	X
Fasting plasma glucose	X							X	X	X	X	X
Postural Blood Pressure								X	X	X	X*	
Aortic compliance testing		X										X*
DXA for body composition measurements				X							X	
Assessment of endothelial function using Endo-PAT			X[1]								X[1]	
Blood sample for measurement of inflammatory biomarkers and isolation of WBCs				X								X
Mixed Meal Tolerance test			X								X	
Ambulatory BP monitoring device set up			X	Return ABPM device							X	Return ABPM device
24-hour urine collection instruction			X	Return 24 hour urine							X	Return 24 hour urine
Cycloset Titration				X (first dose same day as visit 3)	X	X	X					Discontinue Cycloset
Concomitant meds	To be assessed throughout the study											
Adverse Events	To be assessed throughout the study											
Hypoglycemia	To be assessed throughout the study											
Serious Adverse Events	To be assessed throughout the study **Report serious adverse events to sponsor within 24 hours**											
Mandatory Contact	Weekly titration phone contacts as described in the protocol											

[1] Endo-PAT conducted upon arrival to study site and at 90 minutes into the Mixed Meal Tolerance test

* These tests (DXA and Aortic compliance testing) may be done on either Visit 7 or Visit 8

Mixed MEAL TOLERANCE TEST

Time (minutes)	Glucose (0.5 ml)	3-^{3}H-Glu/ (6 ml)	C-pep/Ins (3 ml)	Glucagon (2 ml)	FFA (2 ml)	GLP-1/GIP (3 ml)	(2 ml)
-180	X	X	X	X	X	X	
-180	start 3-3H-glucose						
-30	X	X*					
-20	X	X*	X	X	X	X	
-10	X	X*	X	X	X		X
-5		X*					
0	X	X*	X	X	X	X	X
0	Mixed meal with 1-14C-glucose						
15	X	X	X				
30	X	X	X	X	X		
45	X	X	X				
60	X	X	X	X	X		X
75	X	X	X				
90	X	X	X	X	X		
105	X	X	X				
120	X	X	X	X	X		X
135	X	X					
150	X	X	X	X	X		
165	X	X					
180	X	X	X	X	X		
195	X	X					
210	X	X	X	X	X		
225	X	X					
240	X	X	X	X	X		X
255	X	X	X	X	X		
270	X	X	X	X	X		
285	X	X	X	X	X		
300	X	X	X	X	X		
Number	26	26	21	16	16	3	5
Blood volume (ml)	13	156	63	32	32	9	10

Total blood loss (ml) = 315 ml

* 3-^{3}H-glucose only

ABBREVIATIONS AND DEFINITIONS

ABPM	Ambulatory Blood Pressure Monitoring
AE	Adverse Event
BG	Blood Glucose
BMI	Body Mass Index
CRC	Clinical Research Center
CRF	Case Report Form
DM	Diabetes Mellitus
FPG	Fasting Plasma Glucose
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide
HbA1c	Hemoglobin A1C
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous
MMT	Mixed Meal Tolerance test
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMBG	Self-Monitored Blood Glucose
T2DM	Type 2 diabetes mellitus
VS	Vital Signs

1 INTRODUCTION AND STUDY RATIONALE

A. Summary

Type 2 diabetes mellitus (T2DM) is a common metabolic cardiovascular disorder characterized by multiple pathophysiologic abnormalities (1). Quick release bromocriptine (Cycloset), a D2-dopamine receptor agonist sympatholytic agent, was approved by the U.S. Food and Drug Administration in 2009 for use as monotherapy and in combination with oral antidiabetic agents for the treatment of T2DM (2) in those with T2DM over the age of 18. In humans, Cycloset reduces the postprandial glucose excursion without augmenting insulin secretion or improving insulin sensitivity in muscle (3,4). These results suggest that Cycloset enhances hepatic sensitivity to insulin, perhaps by inhibiting central sympathetic outflow, and are consistent with results obtained in rodents (5).

The glucagon-like peptide (GLP)-1 receptor agonists, liraglutide and exenatide, also reduce postprandial, as well as fasting, hyperglycemia following glucose ingestion (6,7). The reduction in postprandial hyperglycemia results from a delay in gastric emptying and enhanced suppression of hepatic glucose production secondary to increased insulin secretion and decreased glucagon secretion (6,8). To date, no study in man has examined combination therapy with a GLP-1 receptor agonist and Cycloset. Since both agents work by reducing postprandial hyperglycemia and inhibiting post-meal HGP, although by different mechanisms, one might expect them to have an additive or even synergistic effect to reduce postprandial plasma glucose levels. In fact, a synergistic interaction between bromocriptine and exenatide has been demonstrated in the glucose intolerant, insulin resistant Syrian hamster (9).

In the present study we will examine the effect of the addition of Cycloset therapy to inadequately controlled (HbA1c 7.5-10.0) T2DM patients on exenatide (Bydureon) once weekly or liraglutide (Victoza). Since Cycloset has been shown to reduce cardiovascular events in adults with T2DM (10), a beneficial effect that maybe associated with improved endothelial/vascular function, we also will measure endothelial function using the Endo-PAT instrument and assess aortic compliance using non-invasive hemodynamic testing.

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B. Detailed Background

Cycloset is a dopamine receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). Cycloset reduces glucose following each meal without raising plasma insulin levels. As such, Cycloset may be acting as a postprandial insulin sensitizer and/or glucose regulator (Pijl et al 2000) to reduce postprandial hyperglycemia and may be expected to synergize with incretin mimetics that increase postprandial insulin levels.

Available evidence indicates that Cycloset improves glycemic control in patients with type 2 diabetes predominantly by improving postprandial responsiveness to insulin. Once daily morning Cycloset therapy increases insulin-stimulated glucose disposal as assessed by the euglycemic insulin clamp technique and it also reduces post load glucose levels following an oral glucose tolerance test without increasing plasma insulin levels in type 2 diabetes subjects (Pijl et al 2000). The selective effect of timed bromocriptine treatment on postprandial versus post-absorptive glucose metabolism is exemplified by its much more pronounced effect on glucose clearance during a hyperglycemic versus euglycemic insulin clamp (Ezrokhi et al, 2008).

In clinical studies, Cycloset therapy has been shown to reduce postprandial glucose levels across the three standard meals of the day without increasing plasma insulin levels when used alone or in combination with sulfonylurea therapy (Cincotta et al, 1999). Among patients with type 2 diabetes failing sulfonylurea therapy (two identically designed studies with; n= 494; baseline HbA1c of 9,3), the addition of Cycloset as compared to placebo resulted in reductions in post prandial glucose after 24 weeks of treatment (Cincotta 1999).

Post prandial glucose exursions contribute to the excessive morbidity associated with type 2 diabetes (Ceriello, 2008). The mechanism by which timed Cycloset elicits its postprandial glucose metabolism effect is believed to involve its ability to normalize aberrant fuel sensing neurons in the hypothalamus that inappropriately induce insulin resistance respecting regulation of hepatic glucose output, adipose lipolysis, and glucose disposal in liver and muscle. Under normal conditions, in response to a meal, fuel sensing neurons in the hypothalamus act via the neuroendocrine axis to improve insulin sensitivity in liver, adipose, and muscle after a meal to reduce hepatic glucose output and adipose lipolysis, and to increase glucose disposal in liver and muscle. However, in insulin resistant states like T2DM, this fuel sensing mechanism is altered and no longer sends these meal-induced insulin sensitizing signals to the periphery but

rathersends signals that tend to oppose insulin action, and postprandial dysglycemia ensues (Cincotta 2002, Luo et al 2008).

One of the actions of the incretin mimetics such as the GLP-1 analogs is to stimulate postprandial beta cell insulin secretory response to plasma glucose (see drug labeling information; www.fda.gov). Thus the combination of Cycloset that is working as a post prandial insulin senstizier with therapies that increase post prandial insulin would be expected to provide complimentary glucose lowering effects. As described above, Cycloset has been shown to reduce postprandial glucose levels when used in combination with insulin secretagoues. In animal models of insulin resistance, the combination of bromocriptine and a GLP-1 analog was shown to work synergistically to improve glycemic control. The interactive effect of chronic (2 week) bromocriptine treatment on glucose tolerant/insulin resistant animals that were administered a GLP-1 analog just prior to the glucose tolerance test (GTT) was assessed in a 2 week study. Intraperitoneal administered bromocriptine or vehicle was administered daily for 2 weeks at the onset of locomotor activity. A GTT was performed on all animals on day 13. On the day of the GTT, each of the BC and vehicle groups was divided in half and administered either vehicle or Exendin 4 just prior to the initiation of the GTT. The combination of timed bromocriptine plus a GLP-1 analog produced marked improvement in the GTT of severely glucose intolerant hamsters, to an extent much greater than the sum of either therapy (Ezrokhi 2012).

Therefore, both a mechanistic rationale and empirical experimental evidence implicate a beneficial interaction between bromocriptine and the incretin mimetics (GLP-1 analogs) upon postprandial hyperglycemia in insulin resistant states. To date, however, no such studies investigating the interactive effects of a GLP-1 analog and Bromocriptine-QR (Cycloset) have been conducted in humans..

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2 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

The objective of this study is to examine the effect of the addition of Cycloset on glycemic control in inadequately controlled (HbA1c 7.5-10.0) T2DM patients who are already on Bydureon (exenatide once weekly) or Victoza (liraglutide) as part of their standard care.

An additional co-primary objective of the study is to examine the effect of Cycloset on postprandial glucose metabolism.

2.2 SECONDARY OBJECTIVES

Secondary Efficacy

To assess the potential beneficial effect of Cycloset on endothelial function, arterial stiffness, body weight composition, blood pressure, inflammation and oxidative stress.

Safety

The safety objectives of this study are to investigate the relative differences from baseline to end of study in:

- Occurrence of hypoglycemia
- Adverse events
- Laboratory values: standard blood chemistry and hematology
- Clinical values: physical examination, vital signs and weight.

3 STUDY DESIGN, DURATION AND DATES

3.1 STUDY DESIGN

This is a single center prospective cohort study that will assess the effect of Cycloset in in T2DM subjects who are inadequately controlled (HbA1c 7.5% to 10.0%) on GLP-1 analog therapy with either Bydureon (exenatide once weekly) or Victoza (liraglutide).

Subjects who meet the entry criteria will first undergo non-invasive hemodynamic testing for a baseline assessment of aortic compliance (Visit 1). Subjects will then come to the Clinical Research Center (CRC) at the Texas Diabetes Institute on the morning of Visit 2 following a 10-12 hour overnight fast and restriction from use of caffeine, tobacco, vitamins or medications that might affect vascular tone. Subjects will take their normal dose of exenatide or liraglutide in the

morning prior to this visit. At this visit, subjects will a non-invasive assessment of endothelial function using the Endo-PAT 2000 device Subjects will then receive a 5-hour MMT test. At approximately 90 minutes into the completion of the MMT test, a second Endo-PAT recording will be conducted. Upon completion of the second Endo-PAT test, subjects will be placed on a continuous ambulatory BP monitor and asked to collect a 24 hour urine sample, which they will start the following morning. After completion of the 24-hour urine collection, subjects will return to the CRC for Visit 3. At this visit, the ambulatory BP data will be downloaded and the 24-hr urine sample will be stored. Subjects will also have a DXA scan performed for assessment of body weight composition and have blood samples drawn for the measurement of serum cytokines and inflammatory biomarkers and isolation of white blood cells at this visit.

At Visit 3 subjects will be started on Cycloset, 0.8 mg/day in addition to their stable dose of Bydureon (exenatide) (2mg/week) or Victoza (liraglutide) (1.2-1.8 mg/day). Subjects will receive their first dose of Cycloset in the CRC and will be monitored for one hour after the dose before being sent home. The Cycloset dose will then be increased by 0.8 mg/day every week to a maximum of 3.2 mg/day, or as tolerated to a minimum of 2.4 mg/day. During the Cycloset titration phase subjects will be monitored by phone with weekly phone visits. Subjects who cannot tolerate at least 2.4 mg/day of Cycloset will be replaced.

Subjects will return at months 1, 2, 3, (Visits 4, 5 and 6) for interim medical history, body weight, HbA1c, and FPG. At month 4 (End of Study Visits 7 and 8), all of the tests performed at Baseline Visits 1-3, including non-invasive hemodynamic testing for assessment of aortic compliance, DXA for assessment of body weight composition, Endo-PAT tests for assessment of endothelial function, MMT test, collection of blood samples for measurement of inflammatory/ oxidative stress markers and isolation of white blood cells, 24-hour ambulatory BP recording and collection of a 24-hour urine sample will be repeated as described above. Cycloset administration will be discontinued at the completion of Visit 8.

Two weeks after Cycloset administration is discontinued subjects will return for Visit 10 and complete a final assessment of aortic compliance. There will be no additional follow up after Visit 10.

STUDY PROCEDURES

Endo-PAT

The Endo-PAT 2000 is a device that is used to assess endothelial vasodilator function in a rapid and non-invasive fashion. The device consist of two plethysmographic probes that are placed on the index finger of each hand and record endothelium-mediated changes in the digital pulse waveform known as the PAT (Peripheral Arterial Tone) signal. Blood pressure cuff is then inflated to induce downstream peripheral hyperemia by occluding blood flow through the brachial artery for 5 minutes. The contra-lateral arm is used as a control. Endothelium-mediated changes in the PAT signal are elicited by creating a downstream hyperemic response.

Briefly, the Endo-PAT measurements will be taken in a fasting state and be conducted in a quiet, dimly lit, temperature-controlled exam room to reduce fluctuations in vascular tone. The patient will remain supine and comfortable for 15 minutes so as to attain a cardiovascular steady-state with two arm-supporters along each of the patient's sides to support the patient’s arm. The index

finger will be used to place Endo-PAT probe for the study; however, if this finger is unsuitable, a different digit (except the thumb) may be used, as long as the same finger is used on both hands. Blood pressure will be measured using the control arm (the arm that is not occluded during the Endo-PAT study. A second blood pressure cuff will be placed on the arm to be occluded during the Endo-PAT study. The Endo-PAT device will be employed and the blood pressure cuff will be inflated at that time. During the procedure the patient will be asked to refrain from moving the fingers, as this will create mechanical artifacts. It is important for the patient to be relaxed throughout the study. During the test and while the arm cuff is inflated, subjects may feel some discomfort, numbness, or tingling. In case of incomplete occlusion the cuff may be inflated to a maximum of 300 mmHg. The measurement will be taken for 5 minutes. During that time, the blood pressure cuff will be rapidly inflated to a supra-systolic pressure of 60 mmHg above the patient's systolic pressure or 200 mmHg, whichever is higher. The complete cessation of blood flow to the hand is verified by the absence of a PAT signal from the occluded arm. After 5 minutes occlusion, the cuff will be released as quickly as possible and a five-minute post occlusion measurements will be recorded.

The Endo-PAT system calculates the response to reactive hyperemia and a PAT ratio is created using the post and pre occlusion values. These values are normalized to measurements from the contra-lateral arm, which serves as control for non-endothelial dependent systemic effects. The technique provides values for the calculation of a Reactive Hyperemia Index (RHI), which gives an indication of the endothelial vasodilator function. The RHI, in turn, correlates with the measurement of endothelial vasodilator function in the coronary arteries and thus predicts the potential unfavorable cardiovascular conditions and outcomes.

Noninvasive Hemodynamic Assessment of Aortic Compliance

Subjects will be rested in the supine position for 15 minutes. Measurements for the assessment of aortic pulse wave velocity (PWV) will then be taken immediately after measurement of brachial blood pressure. PWV is determined by simultaneous measurement of arterial pressure waves at the carotid and femoral arteries with sensitive pressure transducers place on the skin overlying the carotid and femoral arteries. This is a completely noninvasive procedure using previously described and published techniques (Circulation 2006; 113: 1213-1225). The surface distance from suprasternal notch to the distal (femoral) recording site is measured, and the pressure wave transit time is calculated using a foot-of-the-wave to foot- of-the-wave method. PWV is calculated by dividing the distance to the distal site by the pressure wave transit time. Data are collected by a single trained observer, and the mean of at least 2 PWV measurements is taken for each subject.

Meal Tolerance Test (MMT)

Following a 10-12 hour overnight fast, catheters will be placed in the antecubital vein or hand vein, one for infusion of tritiated glucose and one for blood withdrawal. At -180 minutes baseline blood samples (see attached flow sheet) will be obtained and a prime (40 uCi x FPG/100) – continuous (0.40 uCi/min) will be started. Blood samples for determination of plasma, glucose, insulin, C-peptide, glucagon, FFA, glucagon-like peptide-1, and glucose-dependent insulinotropic polypeptide and tritiated glucose and 14C-glucose radioactivity will be obtained at -180, -30, -20, -10, and 0 minutes. At time zero subjects will ingest a mixed meal (75 grams of glucose, 25 grams of fat, 20 grams of protein, 600 kcal) over 15-20 minutes. The glucose will be labeled with

100 uCi of 1-14C-glucose. Plasma samples for substrates, hormones, and radioactivity will be obtained every 15 minutes for 5 hours. Plasma samples for catecholamines (CA) will be collected at – 10, 0, 60, 120, and 240 minutes.

Meal tolerance will be determined by calculating the glucose AUC (trapezoidal rule) during the MTT. Insulin secretion will be calculated as I0-300/G0-300, CP0-300/G0-300, and ISR0-300/G0-300, where ISR = insulin secretary rate (deconvolution of the plasma C-peptide curve). Beta cell function (11) will be calculated as the insulin secretion/insulin resistance (disposition) index: ISR0-300/G0-300 x Matsuda Index of insulin sensitivity (12). The same measures will be examined for the following time intervals: -10, 0, 0-60, 0-120, 0-180, and 0-240.
During the fasting postabsorptive state, the rate of HGP equals the rate of glucose uptake by all tissues in the body and is calculated as the tritiated glucose infusion rate (DPM/min) divided by the plasma tritiated glucose specific activity (DPM/mg). Following meal ingestion, non-steady state conditions prevail and the rates of total (RaT) and oral (RaO) glucose appearance in the systemic circulation are calculated using Steele's equation from the 14C-glucose and 3H-glucose specific activities, respectively, as previously described (13). The difference between RaT and RaO yields the rate of endogenous HGP. Subtraction of RaO from 75 grams (ingested glucose load) gives the splanchnic (primarily reflects) glucose uptake.

Dual-Energy X-ray Absorptiometry (DXA)

After an overnight fast, a DXA scan for body composition scan will be performed using a Hologic DXA scanner. Subjects will be resting comfortably in supine position in a quiet room and the entire body will be scanned. The acquired images will be integrated and analyzed by a software IBM computer program and total amount of fat and fat-free mass and total body water will be estimated. Total and regional fat and fat-free mass will be measured by a licensed radiology technician using a Discovery 010-1596 instrument from Hologic that is housed on the CRC at the Texas Diabetes Institute.

3.2 STUDY DURATION AND DATES

The duration of this study is expected to be 18 months, with subject recruitment proposed to start in May 2014 and end in October 2015. The actual overall study duration or subject recruitment period may vary.

4 SELECTION OF SUBJECTS

4.1 NUMBER OF SUBJECTS

15 subjects

4.2 INCLUSION CRITERIA

1. Type 2 diabetes male or female subjects between the ages of 30 and 70 years of age, inclusive, at Screening

2. BMI = 24-40 kg/m2

3. HbA1c = 7.5-10.0%

4. Stable body weight (±3-4lbs) over the preceding 3 months

5. Subjects currently receiving a stable dose of exenatide (2mg/week) or liraglutide (1.2-1.8 mg/day) for at least 90 days prior to determination of baseline A1C and eligibility for enrollment in the study protocol.

6. Subjects with a daytime feeding/night time sleeping schedule

7. Subjects with no evidence of major organ system disease as determined by physical exam, history, and screening laboratory data

8. Women must be of non-childbearing potential as defined by one of the following:
    a. Women >45 and < 60 years of age at Screening, who have been amenorrheic for at least 2 years
    b. Women who have had a documented hysterectomy and/or bilateral oophorectomy
    c. Women > 60 years of age

9. Females of childbearing potential with a negative pregnancy test at Screening and using one of the following forms of contraception for the duration of participation in the study (i.e., until Follow-up 7-14 days post last dose):
    a. Oral contraceptive
    b. Injectable progesterone
    c. Subdermal implant
    d. Spermicidal foam/gel/film/cream/suppository
    e. Diaphragm with spermicide
    f. Copper or hormonal containing IUD
    g. Sterile male partner vasectomized > 6 month pre-dosing.

10. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study

11. Subjects must be willing and able to comply with scheduled visits, treatment, laboratory tests and study procedures.

4.3 EXCLUSION CRITERIA

1. Recent (i.e., within three (3) months prior to Screening) evidence or medical history of unstable concurrent disease such as: documented evidence or history of clinically significant hematological, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, immunological, or clinically significant neurological disease.

2. No history of T2DM

3. BMI of less 24 and greater 40 kg/m2

4. Unstable body weight (change of greater than ±3-4lbs over the preceding 3 months

5. Subjects not currently receiving exenatide or liraglutide

6. Subjects participating in an excessively heavy exercise program

7. Subject with a feeding/sleeping schedule different from a daytime feeding/night time sleeping schedule

8. Subjects taking medications known to alter glucose metabolism (with the exception of any combination of metformin,pioglitazone, sulfonylureas, and insulin) or which affect brain neurosynaptic function are excluded.

9. Subjects with evidence of major organ system disease as determined by physical exam, history, and screening laboratory data

10. Pregnant subjects or subjects unwilling to use birth control during their study enrollment

11. Blood donation of approximately 1 pint (500 mL) within 8 weeks prior to Screening 12. Subjects that are allergic to bromocriptine or any of the other ingredients in Cycloset, or take ergot medicines, breastfeeding or have history of syncope or Type 1 diabetes mellitus0
12. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results that, in the judgment of the investigator, would make the subject inappropriate for entry into this study subjects of reproductive potential

Female subjects must not become pregnant during the study. Absence of pregnancy must be checked by serum pregnancy testing at the screening visit (Visit 0).

Female subjects of childbearing potential must use a medically accepted contraceptive regimen. If a female subject becomes pregnant during the trial, she must be withdrawn and followed up until the outcome of the pregnancy is known. If pregnancy occurs, the investigator must contact the sponsor immediately for further instruction. Both the detection and the outcome of the pregnancy must be reported to the sponsor on special forms (“Drug Exposure Via Parent – Data Collection Form”), which will be provided to the investigator as needed.

5 STUDY TREATMENTS

5.1 DETAILS OF STUDY TREATMENTS

All subjects will receive Cycloset, 0.8 mg/day, with the dose increased by 0.8 mg/day every week to a maximum of 3.2 mg/day, or as tolerated to a minimum dose of 2.4 mg/day, added on to usual diabetes therapy consisting of a stable dose for at least 90 days of exenatide (2mg/week) or liraglutide (1.2-1.8 mg/day). Subjects must be on either exenatide or liraglutide as part of their standard care to be eligible for study participation. Subjects will maintain their maximum tolerated dose of Cycloset for the duration of the study.

5.2 SUPPLIES AND ACCOUNTABILITY

Cycloset tablets will be provided by the Sponsor. Accountability will be performed at the study site at the end of each subject's treatment period.

5.3 COMPLIANCE

Subjects will be instructed to bring their current, used and unused (vials) of study drug to every visit.

5.4 RUN-IN MEDICATION

There is no run-in period prior to enrollment. Subjects will remain on their current regimen of either exenatide or liraglutide. No medications known to alter glucose metabolism (with the exception of metformin and/or pioglitazone),or which effect brain neurosynaptic function are allowed.

6 PRIOR AND CONCOMITANT ILLNESSES AND TREATMENTS

6.1 PRIOR AND CONCOMITANT ILLNESSES

Additional illnesses present at the time informed consent is given are regarded as concomitant illnesses and must be documented in the case report form. Relevant past illnesses must also be documented in the case report form.

Illnesses first occurring or detected during the study, and worsening of a concomitant illness during the study, are to be regarded as adverse events and must be documented as such in the case report form.

6.2 PRIOR AND CONCOMITANT TREATMENTS

All treatments being taken by the subjects on entry to the study or at any time during the study in addition to the study drug are regarded as concomitant treatments and must be documented on the appropriate pages of the case report form.

Concomitant medications should be kept to a minimum during the study and adhere to the inclusion/exclusion criteria described above. However, if these are considered necessary for the subject's welfare and are unlikely to interfere with the investigational products, they may be given at the discretion of the investigator and recorded in the case report form.

Subjects on systemic corticosteroids will be excluded.

7 OVERVIEW OF DATA COLLECTION AND STUDY PROCEDURES

7.1 STUDY PROCEDURES AND SCHEDULES

The study will consist of a screening visit, followed by visits at week 0, months 1,2, 3, and 4 and a final visit two weeks after discontinuation of Cycloset.

7.2 DESCRIPTION OF STUDY DAYS

7.2.1 Screening - Visit 0

Screening of subjects will occur at Visit 0.

- Consent form will be signed
- Each subject will be assigned a study subject number
- Assessment of inclusion/exclusion criteria will be performed
- Medical history, including demographic and background assessments will be documented in the CRF
- Routine physical examination will be performed
- ECG test will be performed
- Blood will be taken for the determination of HbA1c, FPG, lipids, clinical chemistry variables (and serum pregnancy test for women of child-bearing potential); and hematology (see study schedule). Total amount of blood drawn at this visit will be approximately 20 ml.

7.2.2 Study Days – Treatment Period

7.2.2.1 Baseline – Visit 1 (Week 0) ± *3 days*

- Baseline assessment of aortic compliance

7.2.2.2 Baseline – Visit 2 (Visit 1 + 7-10 days)

- Subjects will arrive in the morning after an overnight fast (defined as no caloric intake for 10-12 hours)
- Study entry criteria will be reviewed
- All adverse events (including serious adverse events), hypoglycemia and concomitant medications since the last visit will be documented
- Subject will be weighed.
- Postural blood pressure measurements will be obtained first with the subject lying down and then repeated after 5 minutes of standing.
- Endo-PAT will be performed t0 and t90 of meal tolerance test
- 5-hour Mixed Meal Tolerance test (MMT) will be conducted.
- Blood samples will be drawn at various time points as detailed in the Study Design section and Study Schedule table above. Total amount of blood drawn at this visit will be approximately 350 ml.
- Ambulatory Blood Pressure Monitoring (ABPM) device will be set up
- 24 hour urine collection instructions will be given

7.2.2.3 Baseline – Visit 3 (Visit 2 + 3-5 days)

- ABPM device will be returned and data downloaded.
- 24 hour urine collection will be returned
- DXA for body composition will be conducted
- Bloods for inflammatory markers and white blood cell isolation. Total amount of blood drawn at this visit will be approximately 20 ml.
- First dose of Cycloset will be administered in the CRC with a one hour post dose observation period
- Instructions for titration of Cycloset will be reviewed.

7.2.2.4 Call 1 (day 7)

- Study site will contact the subject by telephone to remind them to increase the dose of Cycloset to 2 tablets and assess tolerance. Subjects will be instructed to contact the study site if they experience intolerable nausea or vomiting.

- Assessment for any AE/SAE will be completed

7.2.2.5 Call 2 (day 14)

- Study site will contact the subject by telephone to remind them to increase the dose of Cycloset to 3 tablets and assess tolerance. Subjects will be instructed to contact the study site if they experience intolerable nausea or vomiting.

- Assessment for any AE/SAE will be completed

7.2.2.6 Call 3 (day 21)

- Study site will contact the subject by telephone to remind them to increase the dose of Cycloset to 4 tablets and assess tolerance. Subjects will be instructed to contact the study site if they experience intolerable nausea or vomiting.

- If at any time a subject is not able tolerate the next higher dose of Cycloset, they may stay at the current dose, providing it is at least 3 tablets per day.

- Assessment for any AE/SAE will be completed

- Subjects will schedule an appointment for the 1 month follow up visit on day 28 ± 3 days

7.2.2.7 Visit 4 (Month 1) ± 3 days

- Assessment for any AE/SAE will be completed

- Medical history and weight will be taken

- Postural blood pressure measurements will be obtained first with the subject lying down and then repeated after 5 minutes of standing.

- Blood will be drawn for FPG and A1c. Total amount of blood drawn at this visit will approximately 10 ml.

- Subject will be reminded to increase the dose of Cycloset to 4 tablets if appropriate

7.2.2.8 Visit 5 (Month 2) ± 3 days

- Assessment for any AE/SAE will be completed

- Medical history and weight will be taken

- Postural blood pressure measurements will be obtained first with the subject lying down and then repeated after 5 minutes of standing.

- Blood will be drawn for FPG and A1c. Total amount of blood drawn at this visit will be

approximately 10 ml.

-

7.2.2.9 Visit 6 (Month 3) ± 3 days

- Assessment for any AE/SAE will be completed
- Medical history and weight will be taken
- Postural blood pressure measurements will be obtained first with the subject lying down and then repeated after 5 minutes of standing.
- Blood will be drawn for FPG and A1c. Total amount of blood drawn at this visit will be approximately 10 ml.

7.2.3 End of Study (Visits 7 and 8): Endpoint

NOTE: Aortic compliance testing and DXA scan may be done on either Visit 7 or Visit 8).

7.2.3.1 Visit 7 (Month 4) ± 3 days

- Subjects will arrive in the morning after an overnight fast (defined as no caloric intake for 10-12 hours)
- Assessment for any AE/SAE will be completed
- Medical history and weight will be taken
- Postural blood pressure measurements will be obtained first with the subject lying down and then repeated after 5 minutes of standing
- Assessment of aortic compliance may be conducted at this visit or on a separate day
- DXA for body composition will be conducted
- 5-hour Mixed Meal Tolerance test (MMT) will be conducted.
- Endo-PAT will be performed t0 and t90 of meal tolerance test
- Blood samples will be drawn for lipids, HbA1c and fasting glucose
- lood samples will also be drawn at various time points as part of the MMT test as detailed in the Study Design section and Study Schedule table above. Total amount of blood drawn at this visit will be approximately 350 ml.

- Ambulatory Blood Pressure Monitoring (ABPM) device will be set up

7.2.3.2 24 hour urine collection instructions will be given Visit 8 (Visit 7+ 3-5 days)

- Subjects will arrive in the morning after an overnight fast (defined as no caloric intake for 10-12 hours)
- Assessment for any AE/SAE will be completed
- Assessment of aortic compliance will be conducted if not done at Visit 7
- Blood samples will be drawn for lipids, HbA1c and fasting glucose.
- ABPM device will be returned and data downloaded.
- 24 hour urine collection will be returned
- DXA for body composition will be conducted if not done at Visit 7.
- Bloods for inflammatory markers and white blood cell isolation. Total amount of blood drawn at this visit will be approximately 20 ml.
- Cycloset will be discontinued

7.2.4 Follow-up

The study site will phone the subject on the day after visit 8 to follow-up on hypoglycemia and adverse events that occurred in the 24 hours after the last dose of study medication in this study.

7.3 METHODS

Data will be collected relating to primary and secondary efficacy variables and safety.

A local laboratory will be utilized for collection and analysis of the laboratory tests associated with efficacy, and safety. Standardized guidelines for preparation, collection, and centralized analysis of blood and urine specimens will provide uniformity of the data and will avoid potential inter – laboratory variability due to inconsistent methodology.

7.3.1 **Primary efficacy data will be:** Change from baseline in HbA1c and change from baseline in postprandial glucose metabolism.

7.3.2 **Secondary efficacy data:** Change from baseline in endothelial function, aortic compliance, body weight composition, blood pressure and oxidative stress/inflammatory markers.

7.3.3 Safety Data

Safety will be assessed on the basis of an analysis of hypoglycemia events, adverse events, clinical chemistry, clinical hematology and clinical values; physical examination weight, and vital signs.

Occurrence of hypoglycemia

The general symptoms of hypoglycemia most subjects experience include one or more of the following: headache, dizziness, general feeling of weakness, drowsiness, confusion, paleness, irritability, trembling, sweating, rapid heartbeat and a cold, clammy feeling. In severe cases seizure, loss of consciousness and even lapse into coma can occur.

Definitions of hypoglycemia events that must be recorded on the CRF hypoglycemia page:

- **Severe hypoglycemia -** in which the assistance of another party is required (not merely requested), and either:
    - a recorded self monitored blood glucose of <36 mg/dL, or
    .
    - there was treatment with oral carbohydrates, intravenous glucose or glucagons and there was prompt response to that therapy.

    For further clarification, the definition for severe hypoglycemia included all episodes in which neurological impairment was severe enough to prevent self-treatment and which were thus thought to place subjects at risk for injury to themselves or others. Requires assistance means that the subject could not help her/himself. Someone being kind that assists the subject when not necessary does not qualify as " assistance required".

- **Mild to moderate documented hypoglycemia** – events not considered severe (by the above definition) but with SMBG < 70 mg/dl.

- **Hypoglycemia symptoms with or without SMBG values that according to the Investigator represent true hypoglycemia**

    Symptoms consistent with an adrenergic surge, such as those observed during hypoglycemia (headache, dizziness, general feeling of weakness, drowsiness, confusion, paleness, irritability, trembling, sweating, rapid heartbeat and/or a cold clammy feeling), but with a documented SMBG >70 mg/dL or no recorded SMBG value, are to be recorded on the hypoglycemia event page, if, in the opinion of the investigator/study coordinator, they represent true hypoglycemia.

The following hypoglycemia events are considered serious adverse event (SAEs):

A hypoglycemia event associated with:

- Coma/loss of consciousness ("hypoglycemia coma") or

- Hypoglycemia seizure/convulsion ("hypoglycemia seizure").

These serious hypoglycemia events need to be reported on an SAE form, as well as in the CRF hypoglycemia event and adverse event pages.

Subjects will be instructed to record the following variables for events suspected of being hypoglycemia: date and time started, whether the event occurred after the subject went to bed and prior to waking, whether the event was associated with symptoms, whether assistance was required, and if so, whether there was prompt recovery after oral CHO, glucagon, or intravenous (IV) glucose was used, SMBG value with associated date and time, any special circumstances (e.g. exercise), date and time of last meal, and date and time of last dose of long-acting and/or rapid-acting insulin. The study coordinator will review the diaries with the subject at every visit.

Adverse Events

AE monitoring will be conducted at all study visits, as well as, all titration contacts. *(Please refer to Section 8 for additional information regarding AEs.)*

8 ADVERSE EVENTS

8.1 DEFINITIONS

8.1.1 Adverse Event

The term **adverse event** covers any unfavorable and unintended sign, symptom, syndrome, or illness that develops or worsens during the period of observation in the clinical study. Clinically relevant abnormal results of diagnostic procedures including abnormal laboratory findings (e.g., requiring unscheduled diagnostic procedures or treatment measures, or resulting in withdrawal from the study) are considered to be adverse events.

Worsening of a sign or symptom of the condition under treatment will normally be measured by efficacy parameters. However, if the outcome fulfills the definition of “serious adverse event”, it must be recorded as such (see *Section 8.1.2*).

The adverse event may be:

- A new illness
- Worsening of a concomitant illness
- An effect of the study medication, including comparator
- A combination of two or more of these factors

No causal relationship with the study medication or with the clinical study itself is implied by the use of the term “adverse event”.

Adverse events fall into the categories “non-serious” and “serious” (see *Section 8.1.2*).

Surgical procedures themselves are not adverse events; they are therapeutic measures for

conditions that require surgery. The condition for which the surgery is required is an adverse event, if it occurs or is detected during the study period. Planned surgical measures permitted by the clinical study protocol and the condition(s) leading to these measures are not adverse events, if the condition(s) was (were) known before the start of study treatment. In the latter case the condition should be reported as medical history.

Hypoglycemia events will be captured on a specific hypoglycemia CRF page and should not be considered an adverse event unless classified as a serious AE (see Section 7.3.3). Therefore, hypoglycemic events not classified, as serious adverse events do not need to be entered on the adverse event CRF page.

8.1.2 Serious Adverse Event

A serious adverse event is one that at any dose (including overdose):

- Results in death
- Is life-threatening[1]
- Requires in subject hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity[2]
- Is a congenital anomaly or birth defect
- Is an important medical event[3]

[1]"Life-threatening" means that the subject was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.

[2]"Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.

[3]Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-subject hospitalization, or the development of drug dependency or drug abuse. A diagnosis of cancer during the course of a treatment should be considered as medically important. The List of Critical Terms (1998 adaptation of WHO Adverse Reaction Terminology Critical Terms List, provided in the "Instructions for completing the 'Serious Adverse Event/Expedited Report from a Clinical Trial' form") should be used as guidance for adverse events that may be considered serious because they are medically important.

Clarification of the difference in meaning between "severe" and "serious"
The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild,

moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious", which is based on the outcome or action criteria usually associated with events that pose a threat to life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

8.1.3 Alert Terms and Other Reasons for Expedited Reporting to Pharmacovigilance

No special events are subject to reporting as alert terms in this study.

However, cases in which a "significant overdose" of the investigational product was taken and a non-serious adverse event or no adverse event occurred are to be reported to the sponsor in an expedited manner on a "Serious Adverse Event/Expedited Report from a Clinical Trial" form.

In a context of this protocol, an overdose of study insulin should be reported only if the subject administered a significant larger than prescribed dose of insulin. The definition of a "significant overdose" of study insulin will be based on clinical judgment and will be at the discretion of the investigator.

In addition, any pregnancy diagnosed in a female subject or in the female partner of a male subject during treatment with the investigational product must be reported to the sponsor immediately. Information related to the pregnancy must be given on a "Drug Exposure Via Parent – Data Collection" form that will be provided by the sponsor.

8.2 PERIOD OF OBSERVATION

For the purposes of this study, the period of observation for collection of adverse events extends from the time the subject gives informed consent until 24 hours after the last dose of study medication was given.

If the investigator detects a serious adverse event in a study subject after the end of the period of observation, and considers the event possibly related to prior study treatment, he or she should contact the sponsor to determine how the adverse event should be documented and reported.

8.3 DOCUMENTATION AND REPORTING OF ADVERSE EVENTS BY INVESTIGATOR

All adverse events that occur during the observation period set in this protocol (see *Section 8.2*) must be documented on the pages provided in the case report form in accordance with the instructions for the completion of adverse event reports in clinical studies. These instructions are provided in the investigator's study file and in the case report form itself.

The following approach will be taken for documentation:

- **All adverse events** (whether serious or non-serious, or considered as an alert term) must be documented on the "Adverse Event" page of the case report form.
- If the adverse event is serious (see *Section 8.1.2*), the investigator must complete, in addition to the "Adverse Event" page in the case report form, a "Serious Adverse Event/Expedited Report from a Clinical Trial" form at the time the serious adverse event is detected.

- **This form must be completed and faxed to the sponsor's Pharmacovigilance department within 24 hours.**
- If the adverse event is listed as an alert term (see Section 8.1.3) even if the "alert term" is non-serious, the investigator must complete, in addition to the "Adverse Event" page in the case report form, a "Serious Adverse Event/Expedited Report from a Clinical Trial" form at the time the adverse event is detected.
- **This form must be completed and faxed to the sponsor's Pharmacovigilance department within 24 hours.**
- When a "significant overdose" of the investigational product occurs without an adverse event or in other situations where the sponsor requires an expedited report without an adverse event (see *Section 8.1.3*), the investigator should only complete a "Serious Adverse Event/Expedited Report from a Clinical Trial" form. Instructions on where to send this form will be provided by the sponsor. In this case, there is no need to complete the "Adverse Event" page in the case report form.

Every attempt should be made to describe the adverse event in terms of a diagnosis. If a clear diagnosis has been made, individual signs and symptoms will not be recorded unless they represent atypical or extreme manifestations of the diagnosis, in which case they should be reported as separate events. If a clear diagnosis cannot be established, each sign and symptom must be recorded individually.

All subjects who have adverse events, whether considered associated with the use of the investigational products or not, must be monitored to determine the outcome. The clinical course of the adverse event will be followed up according to accepted standards of medical practice, even after the end of the period of observation, until a satisfactory explanation is found or the investigator considers it medically justifiable to terminate follow-up. Should the adverse event result in death, a full pathologist's report should be supplied, if possible.

All questions on the completion and supply of adverse event report forms and any further forms issued to the investigator at a later date to clarify unresolved issues should be addressed to the sponsor.

8.4 IMMEDIATE REPORTING BY INVESTIGATOR TO SPONSOR

Serious adverse events and adverse events that fulfill a reason for expedited reporting to Pharmacovigilance (alert term and/or "significant overdose", as defined in *Section 8.1.3*) must be documented on a **"**Serious Adverse Event/Expedited Report from a Clinical Trial" form in accordance with the "Instructions for completing the 'Serious Adverse Event/Expedited Report from a Clinical Trial' form**".**

- **This form must be completed and faxed to the sponsor's Pharmacovigilance department within 24 hours.**

The **"**Serious Adverse Event/Expedited Report from a Clinical Trial" form and the instructions are provided in the investigator's study file. The sponsor will ensure that all legal reporting requirements are met.

The initial report must be as complete as possible, including details of the current illness and (serious) adverse event, and an assessment of the causal relationship between the event and the investigational product(s).

Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up **"**Serious Adverse Event/Expedited Report from a Clinical Trial" form.

The "Instructions for completing the 'Serious Adverse Event/Expedited Report from a Clinical Trial' form" give more detailed guidance on the reporting of serious adverse events, adverse events that comply with alert terms, and adverse events initially reported as non-serious that become serious. In the latter situation, when a non-serious event becomes serious, details must be forwarded immediately to the sponsor on a "Serious Adverse Event/Expedited Report from a Clinical Trial" form.

9 WITHDRAWALS

9.1 WITHDRAWAL OF SUBJECTS

Subjects may be withdrawn from the study (i.e. from any further study medication or study procedure) for the following reasons:

- At their own request or at the request of their legally authorized representative*
- If, in the investigator's opinion, continuation in the study would be detrimental to the subject's well-being
- At the specific request of the sponsor

* “Legally authorized representative” means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject’s participation in the procedure(s) involved in the research.

Subjects must be withdrawn from the investigational product under the following circumstances:

- Women who become pregnant
- Women of childbearing potential who discontinue contraception with the intention of becoming pregnant.

In all cases, the reason for and date of withdrawal must be recorded in the case report form and in the subject's medical records. The subject must be followed up to establish whether the reason was an adverse event, and, if so, this must be reported in accordance with the procedures in *Section 8*.

The investigator must make every effort to contact subjects lost to follow-up. Attempts to contact such subjects must be documented in the subject’s records (e.g., times and dates of attempted telephone contact, receipt for sending a registered letter).

Subject withdrawal due to deterioration of glycemic control

Subjects with 2 consecutive fasting blood glucose values >275 mg/dl after completion of the study drug titration phase will be evaluated for withdrawal and initiation of rescue therapy at the discretion of the study investigators. Subjects that are withdrawn will be referred to their primary care physician or endocrinologist for further diabetes medication adjustments as needed.

Replacement of subjects

Subjects that are withdrawn within <2 months following completion of study drug titration will be replaced. As far as possible, for subjects who complete at least 2 months on a stable dose of the study drug following the study drug titration phase, all examinations scheduled for the final study day will be performed prior to withdrawal. Subjects who complete at least 2 months on a stable dose of the study drug following the study drug titration phase but are unable to complete the final study day procedures will also be replaced.

9.2 EMERGENCY SPONSOR CONTACT

In emergency situations, the investigator should contact the sponsor by telephone at the number given on the title page of the protocol.

9.3 EMERGENCY IDENTIFICATION OF INVESTIGATIONAL PRODUCTS

This section is not applicable as this is an open-label study.

9.4 EMERGENCY TREATMENT

During and after a subject's participation in the trial, the investigator and/or institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator and/or institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

10 STATISTICAL PROCEDURES

10.1 ANALYSIS VARIABLES

A statistical analysis plan (SAP), providing details of the analyses and presentation structure of the results, will be developed and finalized before the database is locked.

10.2 ANALYSIS POPULATIONS

Samples from all patients who complete the clinical study period will be assayed.

Dropouts will be replaced as described in section 9.1.

10.3 SAMPLE SIZE

Assuming that Cycloset will cause a 0.6% reduction in HbA1c, 15 subjects would provide 90% power to detect a 0.6% decrease from a baseline HbA1c of 8.0 ±0.5% at an alpha of 0.05.

11 REGULATORY REQUIREMENTS

11.1 GOOD CLINICAL PRACTICE

This study is to be conducted according to globally accepted standards of good clinical practice (as defined in the ICH E6 Guideline for Good Clinical Practice, 1 May 1996), in agreement with the Declaration of Helsinki and in keeping with local regulations.

11.2 DELEGATION OF INVESTIGATOR DUTIES

The investigator will ensure that all persons assisting with the trial are adequately qualified, informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions.

The investigator will maintain a list of sub investigators and other appropriately qualified persons to whom he or she has delegated significant trial-related duties.

11.3 SUBJECT INFORMATION AND INFORMED CONSENT

Before being enrolled in the clinical study, subjects must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to them.

An informed consent document that includes information about the study will be prepared and given to the subject. This document will contain all the elements required by the ICH E6 Guideline for Good Clinical Practice and any additional elements required by local regulations. The document must be in a language understandable to the subject and must specify who informed the subject. Where required by local law, the person who informs the subject must be a physician.

After reading the informed consent document, the subject must give consent in writing. The subject's consent must be confirmed at the time of consent by the personally dated signature of the subject and by the personally dated signature of the person conducting the informed consent discussions.

If the subject is unable to read, oral presentation and explanation of the written informed consent form and information to be supplied to subjects must take place in the presence of an impartial witness. Consent must be confirmed at the time of consent orally and by the personally dated signature of the subject or by a local legally recognized alternative (e.g., the subject's thumbprint or mark). The witness and the person conducting the informed consent discussions must also sign and personally date the consent document.

A copy of the signed consent document must be given to the subject. The original signed consent document will be retained by the investigator.

"Legally authorized representative" means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

The investigator will not undertake any measures specifically required only for the clinical study until valid consent has been obtained.

It is recommended that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

11.4 CONFIDENTIALITY

Subject names will not be supplied to the sponsor. Only the subject number and subject initials will be recorded in the case report form, and if the subject name appears on any other document (e.g., laboratory report), it must be obliterated on the copy of the document to be supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed that representatives of the sponsor, independent ethics committee (IEC)/ institutional review board (IRB), or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

The investigator will maintain a personal subject identification list (subject numbers with the corresponding subject names) to enable records to be identified.

11.5 PROTOCOL AMENDMENTS

Neither the investigator nor the sponsor will alter this clinical study protocol without obtaining the written agreement of the other. Once the study has started, amendments should be made only in exceptional cases. The changes then become part of the clinical study protocol.

11.6 APPROVAL OF THE CLINICAL STUDY PROTOCOL AND AMENDMENTS

Before the start of the study, the clinical study protocol, informed consent document, and any other appropriate documents will be submitted to the IEC/IRB with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities, in accordance with local legal requirements.

Investigational products can only be supplied to the investigator after documentation on **all** ethical and legal requirements for starting the study has been received by the sponsor. This documentation must also include a list of the members of the IEC/IRB and their occupation and qualifications. If the IEC/IRB will not disclose the names of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. Formal approval by the IEC/IRB should preferably mention the study title, study code, study site (or region or area of jurisdiction, as applicable), amendment number where applicable, and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member.

Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IEC/IRB and, if applicable, the authorities must be informed of all subsequent protocol amendments and administrative changes, in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the informed consent document should also be revised.

The investigator must keep a record of all communication with the IEC/IRB and, if applicable, between a coordinating investigator and the IEC/IRB. This also applies to any communication between the investigator (or coordinating investigator, if applicable) and the authorities.

11.7 ONGOING INFORMATION FOR INDEPENDENT ETHICS COMMITTEE/ INSTITUTIONAL REVIEW BOARD

Unless otherwise instructed by the IEC/IRB, the investigator must submit to the IEC/IRB:

- Information on serious or unexpected adverse events from the investigator's site, as soon as possible
- Expedited safety reports from the sponsor, as soon as possible
- Periodic reports on the progress of the study

11.8 CLOSURE OF THE STUDY

The study must be closed at the site on completion. Furthermore, the sponsor or the investigator has the right to close this study site at any time. As far as possible, premature closure should occur after mutual consultation. Depending on local legislation, it may be necessary to inform IEC/IRB and the regulatory authorities when the study site is closed.

Study materials must be returned, disposed of or retained as directed by the sponsor.

11.9 RECORD RETENTION

The investigator must obtain approval in writing from the sponsor before destruction of any records.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, because of international regulatory requirements, the sponsor may request retention for a longer period.

Essential documents include:

- Signed informed consent documents for all subjects
- Subject identification code list, screening log (if applicable) and enrollment log
- Record of all communications between the investigator and the IEC/IRB
- Composition of the IEC/IRB (or other applicable statement as described in *Section 12.6*)

- Record of all communications between the investigator and sponsor (or CRO)
- List of sub-investigators and other appropriately qualified persons to whom the investigator has delegated significant trial-related duties, together with their roles in the study and their signatures
- Copies of case report forms and of documentation of corrections for all subjects
- Investigational product accountability records
- Record of any body fluids or tissue samples retained
- All other source documents (subject medical records, hospital records, laboratory records, etc.)
- All other documents as listed in section 8 of the ICH E6 Guideline for Good Clinical Practice (Essential Documents for the Conduct of a Clinical Trial)

Normally, these records will be held in the investigator's archives. If the investigator is unable to meet this obligation, he or she must ask the sponsor for permission to make alternative arrangements. Details of these arrangements should be documented.

11.10 LIABILITY AND INSURANCE

Liability and insurance provisions for this study are given in separate agreements.

11.11 FINANCIAL DISCLOSURE

Before the start of the study, the investigator will disclose to the sponsor any proprietary or financial interests he or she might hold in the investigational products or the sponsor company as outlined in the financial disclosure form provided by the sponsor. The investigator agrees to update this information in case of significant changes during the study or within one year of its completion. The investigator also agrees that, where required by law or regulation, the sponsor may submit this financial information to domestic or foreign regulatory authorities in applications for marketing authorizations.

Similar information will be provided by each sub-investigator to whom the investigator delegates significant study related responsibilities.

12 STUDY MONITORING AND AUDITING

Monitoring and auditing procedures will be followed according to study site policy in order to comply with GCP guidelines.

12.1 STUDY MONITORING AND SOURCE DATA VERIFICATION

Monitoring will be done by personal visits from a representative of the sponsor (study monitor) who will check the case report forms for completeness and clarity, and crosscheck them with source documents. In addition to the monitoring visits, frequent communications (letter, telephone, and fax), by the study monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements.

Study close-out will be performed by the study monitor upon closure of the study.

12.2 ON-SITE AUDITS

Domestic and foreign regulatory authorities, the IEC/IRB, and an auditor authorized by the sponsor may request access to all source documents, case report forms, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities. Medical records and other study documents may be copied during audit or inspection provided that subject names are obliterated on the copies to ensure confidentiality.

13 DOCUMENTATION AND USE OF STUDY FINDINGS

13.1 DOCUMENTATION OF STUDY FINDINGS

A case report form will be provided for each subject.

All protocol-required information collected during the study must be entered by the investigator, or designated representative, in the case report form. Details of case report form completion and correction will be explained to the investigator. If the investigator authorizes other persons to make entries in the case report form, the names, positions, signatures, and initials of these persons must be supplied to the sponsor.

The investigator, or designated representative, should complete the case report form pages as soon as possible after information is collected, preferably on the same day that a study subject is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data.

A source data location list will be prepared prior to study start. This list will be filed in both the trial master file and the investigator study file and updated as necessary.

The completed case report form must be reviewed and signed by the investigator named in the clinical study protocol or by a designated sub-investigator.

The sponsor will retain the originals of all case report forms. The investigator will retain a copy of all completed case report form pages.

13.2 USE OF STUDY FINDINGS

All information concerning the product as well as any matter concerning the operation of the sponsor, such as clinical indications for the drug, its formula, methods of manufacture and other scientific data relating to it, that have been provided by the sponsor and are unpublished, are confidential and must remain the sole property of the sponsor. The investigator will agree to use the information only for the purposes of carrying out this study and for no other purpose unless prior written permission from the sponsor is obtained.

The sponsor has full ownership of the original case report forms completed as part of the study.

By signing the clinical study protocol, the investigator agrees that the results of the study may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. The authorities will be notified of the investigator's name, address, qualifications, and extent of involvement.

The sponsor will ensure that a final report on the study is prepared.

The investigator (or coordinating investigator) will be required to sign a statement that he or she

confirms that, to the best of his or her knowledge, it accurately describes the conduct and results of the study.

All materials, documents and information supplied by the sponsor to the investigator, and all materials, documents and information prepared or developed in the course of the study to be performed under this protocol, shall be the sole and exclusive property of the sponsor. Subject to obligations of confidentiality, the investigator reserves the right to publish only the results of the work performed pursuant to this protocol, provided, however, that the investigator provides an authorized representative of the sponsor with a copy of any proposed publication for review and comment at least 45 days in advance of its submission for publication. In addition, if requested, the investigator will withhold publication an additional 90 days to allow for filing a patent application or taking such other measures as sponsor deems appropriate to establish and preserve its proprietary rights.

It is agreed that, consistent with scientific standards, publication of the results of the study shall be made only as part of a publication of the results obtained by the investigator performing the protocol.

14 DECLARATIONS OF SPONSOR AND INVESTIGATOR

14.1 DECLARATION OF SPONSOR

This clinical study protocol was subject to critical review and has been approved by the sponsor. The information it contains is consistent with:

- The current risk-benefit evaluation of the investigational product
- The moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the principles of GCP as described in the US Code of Federal Regulations, part 50, 54, 56, and 312, as well as in the ICH Guidelines, May 9, 1997.
- The investigator will be supplied with details of any significant or new findings, including adverse events, relating to treatment with the investigational product.

Sponsor Representative

Date: _____ Signature: _____

Name (block letters): _____

14.2 DECLARATION OF INVESTIGATOR

I confirm that I have read the above protocol. I understand it, and I will work according to the principles of GCP as described in 21 CFR parts 50, 54, 56, and 312 and according to applicable local requirements.

Investigator

Date: _____ Signature: _____

Name (block letters): _____