The University of Texas Southwestern Medical Center at Dallas

Institutional Review Board

Protocol Title:	**QR-Bromocriptine as an Adjunct to Insulin and Metformin in the Treatment of Type 2 Diabetes**

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1. Purpose:

Cycloset is a quick-release formulation of bromocriptine (QR-bromocriptine), and was approved by the FDA in May 2009. Clinical adoption has been slow despite its ability to lower HbA1c by ~0.5% when used as monotherapy. There is, however, a paucity of efficacy data available when the drug is used in conjunction with other available anti-diabetic agents, including insulin. Because the drug functions as an insulin sensitizer, it may serve to prolong residual ®–cell function, delaying or reducing the need for injectable insulin therapy for glycemic control.

This study is designed to characterize the effects of QR-bromocriptine on glycemic control, body composition and β-cell function in patients with Type 2 diabetes when used in conjunction with existing standard-of-care therapies, insulin and metformin. We hypothesize that the addition of QR-bromocriptine to existing standard-of-care treatment for patients with advanced type 2 diabetes necessitating exogenous insulin therapy will result in improved glycemic control, reduced need for exogenous insulin, increased lean:fat mass and preserved β-cell function. The primary endpoint to measure QR-bromocriptine's effectiveness will be HbA1c reduction. Secondary endpoints will include change in total daily dose of exogenous insulin required, change in fasting plasma glucose, percentage of patients meeting target HbA1c goal of <7.0% as established by the American Diabetes Association (ADA); change in body weight, BMI, waist circumference, and body composition as measured by dual-energy x-ray absorptiometry; and change in glucose excursion, free fatty acids and C-peptide levels on mixed-meal tolerance testing.

The data from this study will be placed in context with existing efficacy studies of QR-bromocriptine to guide clinical decision-making in determining those patients who would most benefit from the addition of QR-bromocriptine to their existing anti-diabetic treatment regimen.

2. Background:

Type 2 diabetes afflicts 37.4 million people or approximately 10% of the adult population (age 20-79 years) in North America according to the International Diabetes Foundation, accounting for the leading cause of mortality and 11% of health care costs in the US. It represents one of the most common non-communicable diseases globally and ranks fourth or fifth as a leading cause of death in high-income countries. Estimated global health expenditures to treat and prevent diabetes and its complications are expected to total at least $376 billion dollars in 2010, which is expected to escalate to $490 billion by 2030 [1]. Although once considered a disease of overnutrition, substantial evidence suggests that diabetes is achieving epidemic proportions in many economically-developing and newly industrialized nations. In fact, the burden of diabetes is growing most rapidly in low and middle-income countries, highlighting the need for cost-effective medications that do not require special temperature-controlled storage, sterile conditions and supplies for subcutaneous injections, as is the case for insulin.

Representing only the second novel class of oral agents to treat type 2 diabetes approved by the FDA in the past decade, QR-bromocriptine acts as a dopamine receptor-2 agonist to lower circulating prolactin, which improves peripheral insulin sensitivity. First detected in migratory birds, the ability to coordinate a state of glucose-intolerance/insulin resistance to

meet periods of intense metabolic activity can confer a survival advantage. Seasonal prolactin elevations allow for body weight accrual to enable hibernation or migration when relative food availability is reduced. Likewise in humans, hyperprolactinemia increases sympathetic and noradrenergic tone to raise circulating cortisol and glucagon levels and drive hepatic glucose output. Both hormones also upregulate adipocyte lipolysis to release free fatty acids (FFA) into circulation which subsequently impairs pancreatic β-cell insulin secretion and reduces glucose uptake in muscle. Elevated plasma glucose and FFA levels stimulate inflammatory cytokine production, prompting further resistance to insulin and leptin. This cascade generates an inflammatory milieu which overtime may result in the development and progression of cardiovascular disease.

The effect of hyperprolactinemia in driving insulin resistance can be overcome in humans through the administration of QR-bromocriptine. Early morning pulse-dose administration of QR-bromocriptine increases postprandial insulin secretion and lowers glucose excursion throughout the day despite its relatively short half-life in the bloodstream. This persistent effect indicates that the hypothalamus fuel-sensing mechanism is altered in a more durable manner outside the drug's immediate pharmacokinetic action.

Existing efficacy data on QR-bromocriptine in obese, type 2 diabetic patients treated with or without sulfonylurea showed that HbA1c levels decline from 8.7 to 8.1 ($p = 0.009$) in the intervention group while the placebo-treated group experienced an increase (8.5 to 9.1%, NS) for a combined intergroup difference of 1.2% ($p=0.01$) [2]. Improvements observed in mean plasma glucose concentration during oral glucose tolerance test (OGTT) and in glucose disposal during insulin clamp studies show that QR-bromocriptine improves both fasting and postprandial glucose levels to enhance overall glycemic control in patients with type 2 diabetes.

Phase III studies submitted as the basis for FDA approval found that add-on QR-bromocriptine with sulfonylurea (SU) resulted in an HbA1c decline of 6mmol/mol (treatment effect: -0.5%) [3] compared with a HbA1c decline of 5mmol/mol (treatment effect: -0.4%) in patients on QR-bromocriptine monotherapy [4]. Combined QR-bromocriptine + SU lowered FPG, postprandial (PP) glucose, and insulin concentrations. Improvements in glycemic control were greater in individuals with shorter duration of diabetes and greater residual β-cell function [5]. Reductions in fasting PP triglycerides were also observed, and while a small increase in total cholesterol was measurable, this did not translate to changes in LDL or HDL cholesterol. Combination QR-bromocriptine + SU was associated with weight gain compared to placebo, although underwater weighing suggests that this was due primarily to gain in lean body weight.

Consensus guidelines from the ADA currently call for the initiation of metformin at the time of diagnosis of Type 2 Diabetes [6]. With declining glycemic control on metformin, the second step involves the addition of a sulfonylurea or insulin (1-4 injections daily). Less well validated second-tier agents include thiazolidinediones and GLP-1 agonists, followed by α-glucosidase inhibitors, pramlintide or DPP-4 inhibitors--each agent independently produces an approximate 0.5-1.0% decline in HbA1c. The American Association for Clinical Endocrinologists (AACE) similarly advises a ladder approach with the addition of anti-diabetic agents based on increasing HbA1c values. QR-bromocriptine does not appear in either set of guidelines because their publication preceded the drug's approval by the FDA; yet the few studies available reflect that QR-bromocriptine produces similar HbA1c declines of approximately 0.5% when combined with other agents. Therefore, the proposed study will

contribute to the body of available evidence to inform future design of clinical practice guidelines for the management of Type 2 diabetes and aid point-of-care decision-making between patients and their providers.

Several advantages of QR-bromocriptine exist over currently available second-tier agents. With oral administration, approximately 65-95% of QR-bromocriptine is absorbed, leaving a small, unabsorbed portion to interact in the gastrointestinal tract. The drug undergoes extensive hepatic extraction, and first-pass metabolism, allowing only 7% to enter systemic circulation. Because only 6% of the drug is cleared through the kidney, no dose adjustment is necessary for patients with renal insufficiency. The drug also does not require routine laboratory monitoring and is weight neutral.

As a consequence of the recent regulatory review of QR-bromocriptine and the heightened scrutiny surrounding the cardiovascular risk profile of other similar insulin-sensitizing antidiabetic agents, an FDA-mandated cardiovascular safety study was carried out in over 4000 patients. On a baseline regimen consisting of diet, exercise and two anti-diabetic agents, one of which could be insulin, patients randomized to receive QR-bromocriptine reported fewer serious adverse events than those taking placebo [3]. Patients treated with metformin + SU + QR-bromocriptine also demonstrated a similar improvement in HbA1c. At the conclusion of the 52-week trial, 25% of patients enrolling with a baseline HbA1c >7.5% who received QR-bromocriptine attained a target HbA1c < 7.0%, while only 9% of the placebo-treated group attained this goal over the same time period.

VeroScience and its founders, who originated much of the original drug research and development, have sought to study QR-bromocriptine with metformin previously (ClinicalTrials.gov ID: NCT00441363), but enrollment was discontinued due to resource constraints for this start-up pharmaceutical company. Questions of the drug's efficacy, particularly with concomitant use of other anti-diabetic agents, remain central to driving its clinical adoption. Because insulin-sensitizers have demonstrated ability to reduce the dose of exogenous insulin required, QR-bromocriptine likely has similar benefits which have yet to be quantified and this data has potential to change standard-of-care treatment for type 2 diabetes. Given UT Southwestern's experience in defining metformin as an adjunct to insulin, this clinical setting offers a broad referral base, research infrastructure and experienced clinicians and research staff necessary to successfully answer this question.

3. Concise Summary of Project:

Patients with advanced type 2 diabetes to warrant treatment with exogenous insulin and metformin (dose 1-2gm daily) will be recruited through physician referral or posted flyers from their existing primary care physician or endocrinology offices affiliated with or adjacent to UT Southwestern. Following screening and informed consent, patients will be randomized in an open-label study to receive QR-bromocriptine versus non-treatment while continuing on metformin, insulin and routine diabetic care. An overview of study activities is provided in Figure 1.

Following Visit 1, patient will begin a dose escalation period taking one tablet daily within one hour of waking starting on the following Sunday; each week an one additional tablet will added to the daily dose such that the patient will eventually reach six tablets daily and continue this dose for the remainder of the 18-week treatment period. In prior studies, this dose escalation pattern has been shown to ease side effects. VeroScience and its marketing

affiliate Santarus provide two patient education brochures which explain this titration program.

During the dose escalation period, patients will be contacted weekly by phone to monitor for adverse effects and if present, to offer pre-emptive counseling and instructions prior to the next office visit. Nausea from QR-bromocriptine most often occurs with a daily dose of 2-3 tablets (1.6-2.4mg daily) and can be mitigated by returning to the lower maximum tolerated dose for the duration of the 6-week dose escalation period and the 18-week trial period to complete a total of 24 weeks. Given the large numbers of patients treated with metformin and insulin, at UT Southwestern and affiliated hospitals, we estimate the total enrollment and study duration to last 12 months.

The study is powered to assess the change in HbA1c as its primary endpoint. Secondary endpoints will include the change in fasting glucose, lipid profile and C-peptide values; change in total daily dose (TDD) of insulin; and change in percentage of patients meeting ADA target HbA1c goal of 7.0%. Other secondary endpoints include determining a change in body weight, waist circumference, BMI, and body weight composition as measured by lean:fat mass ratio using dual-energy x-ray absorptiometry (DXA). Lastly, β–cell function will be measured using a 4-hour mixed meal tolerance test (MMTT) protocol to measure basal and stimulated levels of glucose and C-peptide from which an area under the curve (AUC) calculation will be taken.

4. Study Procedures:

Screening and Randomization

Inclusion and Exclusion criteria will be reviewed using the last known HbA1c and serum creatinine levels provided by the referring provider or medical record. Informed consent will be obtained. Activities during the Enrollment visit/Visit 1 include:

- Complete history and physical exam including hip and weight circumference
- Urine pregnancy, if female
- Fasting laboratory testing consisting of a plasma glucose, C-peptide, insulin and lipid profile
- Review of a seven-point glucose profile with calculation of the average daily dose of insulin in the preceding seven days leading up to the visit
- Whole-body DXA for body composition performed through UT Southwestern
- 4hr-MMTT with measurement of glucose, free fatty acid, and C-peptide levels at baseline (fasting), 15 min., 30 min., 45 min., 60 min., 90 min., 120 min., 150 min., 180 min., and 240 min

A total time for this initial visit will be five hours. The physician investigator will adjust the patient's insulin dose to maintain blood sugars within 80-150 mg/dL according to outpatient management of hyperglycemia as defined by the ADA. At the conclusion of Visit 1, the patient will be randomized through a minimization technique to receive the study drug or placebo. The patient will continue on a home regimen of insulin and metformin and began the study drug on Sunday following the initial visit.

The study participants will follow a dose escalation protocol as described previously, increasing the daily dose by one tablet each Sunday to achieve a maximum of six tablets daily on week six. The investigator will contact the patient by phone 2-3 days after the last

dose increase to assess for symptoms of nausea and/or adverse events including hypoglycemia. If the patient is unable to tolerate a dose increase after 3 to 4 days investigator will instruct the patient to decrease to the last tolerated dose and continue this dose for the remainder of the study. No dose adjustments for metformin will be made after enrollment.

Visit 2 (one month) is expected to require a 30-min office visit and will entail the following activities:

- Measurement of vital signs, body weight, hip and waist circumference, and basic physical exam
- Review of a seven-point glucose profile with calculation of the average daily dose of insulin in the preceding seven days leading up to the visit
- Insulin dose titration as per routine diabetic management
- Assessment of adverse events/side effects via questionnaire and interview

Visit 3 (two month) is expected to require a 45-min office visit and will entail the following activities:

- Basic physical exam with vital signs, body weight and hip and waist circumference
- Measurement of HbA1c
- Review of a seven-point glucose profile with calculation of the average daily dose of insulin in the preceding seven days leading up to the visit
- Insulin dose titration as per routine diabetic management
- Assessment of adverse events/side effects via questionnaire and interview

Visit 4 (four month) is expected to require a 45-min office visit and will entail the following activities:

- Basic physical exam with vital signs, body weight and hip and waist circumference
- Measurement of HbA1c
- Review of a seven-point glucose profile with calculation of the average daily dose of insulin in the preceding seven days leading up to the visit
- Insulin dose titration as per routine diabetic management
- Assessment of adverse events/side effects via questionnaire and interview

Visit 5 (six month) is expected to require five hours and will entail the following activities:

- Basic history and physical exam including hip and waist circumference
- Fasting laboratory testing consisting of a plasma glucose, A1c, C-peptide, and lipid profile
- Review of a seven-point glucose profile with calculation of the average daily dose of insulin in the preceding seven days leading up to the visit
- Assessment of adverse events/side effects via questionnaire and interview
- Whole-body DXA for body composition performed through UT Southwestern
- 4hr-MMTT with measurement of glucose, free fatty acid, and C-peptide levels at baseline (fasting), 15 min., 30 min., 45 min., 60 min., 90 min., 120 min., 150 min., 180 min., and 240 min

The patient will be asked to provide a seven point glucose profile using their home diabetic equipment and self monitored blood glucose (SMBG) checks as would ordinarily be expected through their primary care or endocrinology office care. Patients will be given additional test strips needed to conduct SMBG seven times daily instead of the customary four times daily. A questionnaire of common side effects will be given to study participants during each visit to expedite the interviewing process. Hypoglycemia will be defined a random SMBG <70mg/dL. A summary of the planned evaluations is shown in Table 2.

5. Inclusion Criteria

1) Male and female patients, age 30 to 65 years of age,
2) Clinical diagnosis of type 2 diabetes at least 6 months prior to enrollment,
3) Stable on current treatment consisting of either human or recombinant multi-dose insulin therapy (MDI) with metformin,
4) HbA1c of 7.5-12%, inclusive,
5) Demonstrated willingness to check and record blood glucose readings at seven time points as instructed in the study protocol.
6) Medically controlled hypertension, at least on one anti-hypertensive
7) Medically controlled hypercholesterolemia, on or off cholesterol-lowering therapy
8) BMI >30

6. Exclusion Criteria

1) Pregnancy or Lactating,
2) Type 1 Diabetes,
3) Concomitant use of forbidden medications: prescription sympathomimetics (within seven days of screening), ergot alkaloid derivatives, and anti-migraine medications,
4) Patients with history of drug or alcohol abuse within 3 years of enrollment,
5) Patients at risk for hypotension, including those who have:
a. Recent blood donation within 30 days of enrollment,
b. A history of syncopal migraines, or
c. Significant gastroparesis or orthostatic hypotension which could signify advanced autonomic neuropathy.
6) Uncontrolled mental illness especially with history of psychosis,
7) Any severe, uncontrolled or terminal medical condition which the investigator feels would interfere with the patient's ability to participate and comply with the study protocol,
8) Serum creatinine >1.4mg/dL in females or >1.5mg/dL in males that would preclude the patient from taking metformin,
9) LFTs elevated >3x upper limit of normal,
10) Patients working rotating, varying or night shifts, or
11) Patient with circumstances or abnormalities (e.g. blindness or history of non-compliance) that would interfere with the interpretation of safety or efficacy data or completion of the study.

7. Withdrawal Criteria

Following enrollment, all efforts will be made to ensure full compliance with the study protocol and completion of all study visits. However, his/her treatment may be discontinued if one or more of the following criteria are met:

1) The occurrence of any adverse event
2) Treatment with a prohibited concomitant medications as specified in the exclusion criteria
3) Concurrent drug or alcohol abuse (or relapse)
4) Pregnancy

In addition, the investigator may discontinue the subject at any time based on his/her clinical judgment which may include one of the following reasons:

1) Adverse event/reaction
2) Noncompliance with the requirements of the study
3) Major protocol violation
4) Lost to follow-up

Patients, who discontinue the study drug before completing the study, will be scheduled for a final study visit as soon as possible, at which time all of the assessment listed for the final visit will be performed. At a minimum all patients who discontinue the study drug, including those who refuse to return for the final visit, will be contacted for a safety evaluation by phone within one month following the last dose of the study drug. Every effort will be made to obtain follow-up amounting to the planned study duration. Subjects have the right to withdraw consent for study participation at any point. Additional subjects may be recruited taking into account these early withdrawn subjects if they withdrew prior to the second visit.

8. Sources of Research Material:

Sources of data from this study will include the laboratory values and anthropomorphic measurements taken from the study participants including lean:fat mass ratio as measured through whole-body DXA. Laboratory values to be studied include HbA1c, fasting glucose, C-peptide, lipid profile, and baseline and stimulated glucose, free fatty acid, and C-peptide values taken through a 4hr MMTT. No new clinical data should be generated. Because baseline data will be established at the first enrollment visit, no historical laboratory values will be needed from the patient's medical record, with the exception of the last HbA1c, creatinine and LFTs in order to determine eligibility for enrollment.

9. Recruitment Methods and Consenting Process:

Patients will be recruited through the UT Southwestern Clinical Diabetes Office. Advertising for the study will be done through flyers that will be distributed at the UT Southwestern and Parkland Hospital Outpatient Clinics. Because the investigator and sub-investigators perform clinical duties at both locations, potential study participants may be patients under the care of the investigator or sub-investigator. A flyer, detailing the study drug and outlining a study participation including directions for contacting the UT Southwestern Clinical Diabetes Office, will be distributed to patients who are attending regularly scheduled office visits for outpatient diabetes management. Patients who qualify based on the inclusion criteria listed above will be referred by their primary endocrinologist or PCP, and the sub – investigator or study coordinator will speak with the patient in the exam room following the regular diabetes

visit. After referral is made, the potential study participants will be approached either by the sub-investigators and/or study coordinator, several of whom are fluent in Spanish, and provided with basic information regarding the study.

Interested study participants will be asked to attend a screening visit during which the details of study participation will be provided, and if the patient is amenable, informed consent will be obtained. In the event that the patient is Spanish-speaking only, a bilingual study coordinator will conduct the informed consent process. The primary care or endocrinology physician involved in the ongoing management of the patient's diabetes will serve only to refer the patient for consideration in this study and will not play an active role in soliciting their participation. By maintaining this separation, the potential for undue influence or coercion should be eliminated.

10. Potential Risks:

Risks incurred through study participation include the physical discomfort associated with routine laboratory testing. While these patients would ordinarily be seen in a physician-led office visit every three months for ongoing care of their diabetes, patients enrolled in the study would be seen a total of five times over a six-month period and receive additional laboratory testing in the form of more frequent HbA1c and two 4hr MMTT performed at the initial and concluding visits during the study. DXA assessment for body composition is not expected to produce any physical pain or discomfort for the patient. Other inconveniences related to study participation include the logistical and economic challenges of coming to the Clinical Diabetes Office for more frequent visits, and the participants will receive nominal compensation ($35/visit) for these expenses.

Phase 3 safety studies provided to the FDA and included in the package insert, report that over a 52-week period the following symptoms were observed in patients taking QR-bromocriptine, compared to placebo-treated patients: Nausea-- 32.2%, (7.6% in placebo – treated patients); dizziness – 14.8% (9.2%); fatigue – 13.9%, (6.7%); headache –11.4%, (8.3%); vomiting –8.1%, (3.1%); diarrhea – 8.1%, 8.0%; constipation – 5.8% (5.1%). Anaphylaxis and allergic reaction was not readily observed in patients taking QR-bromocriptine. Given the prior clinical trials documenting the safety of QR-bromocriptine and the long clinical experience with bromocriptine, an independent safety and data monitoring board is not felt to be necessary.

With the addition of a second insulin-sensitizer, QR-bromocriptine, the patient may experience lower average SMBG readings and transient episodes of mild hypoglycemia (SMBG <70mg/dL). Patients will be asked to record these episodes in SMBG logs which will reviewed at each clinical encounter in person and by phone. Insulin will be titrated as a primary means to prevent recurrent hypoglycemia in the same manner that it would be titrated through regular office visits.

Routine phlebotomy precautions will be taken during the collection of blood samples so as to minimize patient discomfort. All standard sterile procedures will be followed to reduce risk of infection. Patients will be contacted with greater frequency during the dose escalation period, so as to intervene quickly in the event of adverse reactions.

12. Procedures to Maintain Confidentiality:

Patient records collected during the study will be stored in a password – protected computerized database. All patient data will be de-identified using a unique patient ID number assigned at randomization, and the study will be HIPAA-compliant. All research records will be de-identified prior to publication. No data/specimens will be disclosed to outside persons or entities. Oversight and regulatory agencies such as the IRB, will be afforded access to data when needed. There are no plans to file for a Certificate of Confidentiality from the NIH.

13. Potential Benefits:

Participants in the study will gain by having more frequent visits with the subspecialty physician investigators and study coordinators specializing in the care of patients with diabetes. These visits, in conjunction with more frequent blood work and insulin titration, will enable study participants to reach a goal HbA1c faster than had they received routine care through the outpatient primary care or endocrinology provider. Even if randomized to receive placebo therapy, intensive outpatient management may translate to a higher proportion of patients achieving target HbA1c goal.

Patients will also be offered the opportunity to augment their existing diabetes care through the use of QR-bromocriptine, an FDA – approved therapy not yet available on many hospital formularies or pharmaceutical benefit plans.

All patients will receive additional testing in the form of a 4hr MMTT and DXA body composition analysis which is not ordinarily provided in the scope of routine diabetes care. In combination these factors may improve the patient's awareness of their diabetes and ability to self-manage their disease following completion of the trial.

14. Biostatistics:

The sample size of 72 was determined using the PS-Power and Same Size Calculation (version 2.1.31) program. To measure a minimum HbA1c difference of 0.5% with a standard deviation of 1.0, α= 0.5%, and a power of 80%, 72 patients would need to be recruited and allocated 1:1 to the intervention and treatment groups. We estimate a conservative attrition rate of 30% in light of the incidence of nausea reported in previous studies and our prior experience working with this challenging patient population from Parkland Hospital. Likewise, patients initiating on metformin frequently report nausea which subsides after the first 2-3 weeks of use, therefore, this study will clarify whether the incidence is heightened for patients on dual therapy with metformin and QR-bromocriptine. Therefore, an additional 22 patients will be recruited for a total of 94 patients.

Due to resource constraints, a pilot study consisting of 10 patients in the active study drug group will be performed. An additional 5 unblinded patients receiving no treatment will complete the study visits and testing to serve as a comparator for the treatment arm. Should additional funding become available, we will proceed with the full 94 patients.

<u>Randomization</u>
A minimization strategy will be used to randomize patients in order to reduce intergroup variability for factors including age, gender, race, BMI, duration of type 2 diabetes, and pre-enrollment HbA1c.

Statistical Analysis

The primary analysis will be an intention-to-treat and this analysis will include all randomized subjects who received study medication and have at least one post-randomization visit. Descriptive statistics will be used to summarize responses for each group and evaluation and 95% confidence intervals will be computed for differences between groups or visits within groups. Geometric means will be used to summarize data with log-normal distributions.

HbA1c (primary endpoint) and other continuous variables (secondary endpoints, *e.g., body weight, waist circumference, BMI, fasting plasma glucose, HOMA-IR, daily insulin dose, fasting glucose, fasting lipid profile, fasting c-peptide)* will be analyzed with a mixed model repeated measures analysis (MMRM) to compare treatment responses between the randomized treatment groups. The repeated measures model will have a between treatment group factor, a repeated factor for study evaluation visits, and a group x visit interaction term. Pairwise comparisons will be made using least square contrasts derived from these MMRM models. Baseline covariates such as age, gender, race, BMI, duration of type 2 diabetes and pre-enrollment HbA1c, will be assessed and incorporated into the models as warranted. The MMTT area under the curve (AUC) will be computed using the trapezoidal rule. MMTT c-peptide AUC (primary endpoint) will also be assessed with MMRM analysis.

Categorical variables, including as hypoglycemic event occurrence, will be compared between groups with the Fisher's Exact test. Multiple hypoglycemic event occurrences will be evaluated with correlated binary regression via generalized estimating equations (GEE). Model assumptions such as normality and covariance structure adequacy will be carefully assessed. Data transformations or nonparametric tests may be employed if needed to meet analysis assumptions. SAS (SAS Institute, Cary, NC) statistical software will be used for most analyses. If appropriate, Bonferroni type adjustments (i.e., Bonferroni-Hochberg) for multiple testing will be implemented to control Type I errors.

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FIGURE 1
Flowchart of Study Activities

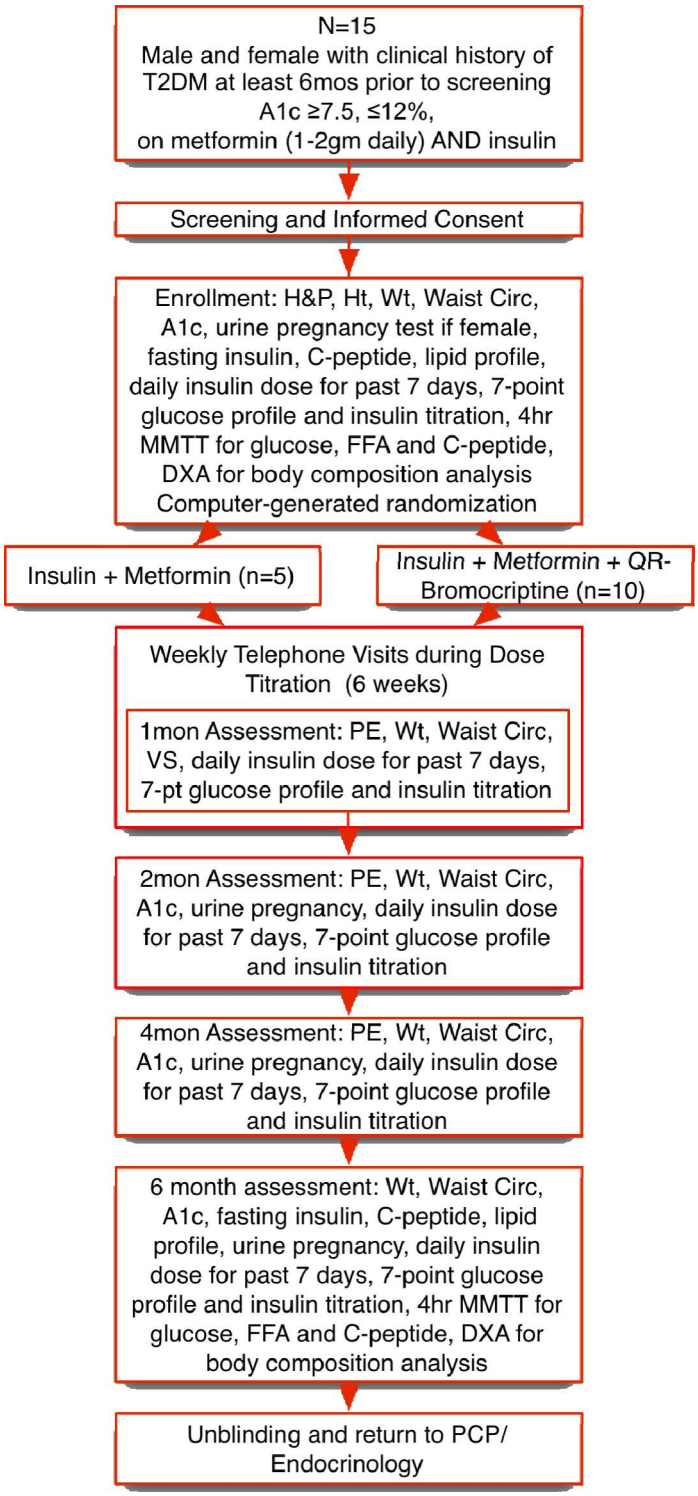

Table 2
Planned Study Visit Evaluations

Visit	Baseline/ Screening	1 mon	2 mon	4 mon	6 mon
Informed Consent	X				
HIPAA	X				
Inclusion Criteria	X				
Exclusion Criteria	X				
Randomization	X				
Medical History	X				
Height	X				
Weight/Hip and Waist Circ/Vital Signs	X	X	X	X	X
Comprehensive physical exam	X				
Basic physical exam		X	X	X	X
Urine pregnancy	X				
Fasting Lipid Panel	X				X
Fasting Insulin	X				X
HbA1c	X		X	X	X
Seven-point Glucose Profile	X	X	X	X	X
Glucose profile review and Insulin titration	X	X	X	X	X
Calculation of average total daily insulin dose	X	X	X	X	X
Basal (fasting) and 4hr MMTT stimulated glucose, FFA and c-peptide	X				X
DXA for body composition	X				X
Adverse Events		X	X	X	X

Based upon information provided to UT Southwestern and the Investigators by various sources including VeroScience, the outlined research protocol contained herein is believed to be appropriate. It is the intent of the undersigned to perform a pilot study consistent with the aforementioned protocol on ten patients using study drug provided by VeroScience and funding provided by the Endocrine Fellows Foundation. Should further funding become available from a third party source or through VeroScience, the undersigned may complete enrollment and study activities for the remaining 84 patients.

Co-Investigator Date

Principal Investigator Date