Study Protocol: Efficacy of Mifepristone in Males with Type 2 Diabetes Mellitus

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The prevalence of type 2 diabetes mellitus (T2DM) continues to increase to epidemic proportions, particularly among low-income, racial minorities who are disproportionately affected as compared to Caucasian populations. Hypercortisolism is known to adversely affect glucose homeostasis through a number of different mechanisms, and blockade of glucocorticoid action through inhibition of the glucocorticoid receptor by mifepristone can favorably reverse these actions. Given that milder degrees of hypercortisolism may also contribute to worsening of glycemic control in T2DM, we hypothesize that mifepristone may have favorable and clinically meaningful effects on "common-variety" T2DM, in the absence of classical states of hypercortisolism.

Specific Aim: To determine the effects of mifepristone compared to placebo on overall glycemic control, static and dynamic measures of insulin sensitivity and insulin secretion, in male type 2 diabetic patients without evidence for Cushing's disease.

Background and Rationale: Type 2 diabetes mellitus (T2DM) affects almost 26 million individuals in the U.S., and with the ongoing progression of obesity, the prevalence of T2DM is continuing to increase despite the growing availability of newer treatment options acting through novel mechanisms of action. Clinically significant hypercortisolism (e.g., Cushing's disease) is a well-known contributor to insulin resistance and other adverse effects on glucose homeostasis, acting through several mechanisms, including direct inhibitory actions on skeletal muscle insulin signaling, glucose-stimulated insulin secretion from pancreatic β cells, and adverse hepatic effects on glucose output, but also indirectly via effects on adipose tissue lipolysis and increasing fatty acid flux. However, more subtle derangements of cortisol metabolism may also be involved with milder degrees of glucose derangements.

The glucocorticoid and progesterone antagonist, mifepristone, has been shown to reduce many of the adverse metabolic effects mediated by glucocorticoids. Pre-clinical *in vitro* and *in vivo* studies have shown that mifepristone can reverse the development of obesity in animal models, increase adiponectin, inhibit the expression of lipoprotein lipase (LPL) and the increases in glucocorticoid-mediated lipolysis in adipose tissue, normalize the high expression of genes controlling gluconeogenesis and hepatic glucose output in db/db mice, inhibit the dexamethasone-dependent reduction of glycogen synthesis in 3T3-L1 adipocytes and the dexamethasone-dependent reduction in synthesis of the critical insulin signaling messenger, insulin receptor substrate-1 (IRS-1), substantially attenuate high fat diet-induced skeletal muscle insulin resistance, enhance basal insulin secretion and reduce glucocorticoid-induced inhibition of insulin secretion from cultured islets, and reduce overall glucose and insulin levels in mouse models of insulin resistance and diabetes.

In addition to its anti-glucocorticoid actions, mifepristone's anti-progesterone actions may additionally provide beneficial effects on glucose homeostasis. Picard, et al. showed that mifepristone can reduce glucose in db/db mice, and that progesterone receptor-knockout animals displayed lower glycemia and higher insulin responses than wild-type animals. Furthermore, mifepristone may exert direct and favorable actions in brown adipose tissue, and interestingly, it may also act as a weak agonist of peroxisome proliferator-activated receptor-gamma (PPARγ), the molecular target of thiazolidinedione (TZD) agents used for treating T2DM.

In humans, mifepristone is typically used for its anti-progesterone activity in women for post-coital pregnancy termination, but its anti-glucocorticoid actions have also been shown to improve metabolic abnormalities. Mifepristone can reduce cortisol-induced increases in human adipose tissue lipoprotein lipase (LPL) activity and fasting triglyceride levels. Dynamic studies have shown that mifepristone blocks multiple adverse effects of cortisol on glucose and amino acid metabolism, and even induces transient reductions in hepatic glucose

production and glucose levels in the absence of a cortisol challenge. Most notably, in non-diabetic individuals with adrenal incidentalomas and evidence of autonomous cortisol secretion, treatment with mifepristone improved measures of insulin resistance. These and other studies have led to clinical trials demonstrating improved clinical outcomes along with acceptable safety and tolerability in cases of Cushing's syndrome refractory to traditional treatments, in selected patients with psychotic depression, as well as for patients with unresectable meningiomas. As a result, mifepristone was recently approved by the FDA (Korlym ™, Corcept Therapeutics, Menlo Park, CA) for use in controlling hyperglycemia in endogenous Cushing's syndrome refractory to surgical therapy (NDA #202107; approved February 17, 2012).

We now propose to test the potential clinical benefits of mifepristone for glycemic control and other associated metabolic derangements in adults with "common-variety" T2DM, i.e., diabetes unrelated to states of clinically significant hypercortisolism. No study has yet systematically examined the multiple actions of mifepristone in humans using a properly designed, placebo-controlled, randomized clinical trial design, as we are proposing here. Thus, we propose this proof-of-concept, pilot study to test our hypothesis that mifepristone may also benefit glycemic control in non-Cushingoid adults with "common-variety" T2DM (i.e., diabetes unrelated to states of clinically significant hypercortisolism). If successful, this study may have substantial implications for the management of T2DM. A positive finding will set the stage for further clinical trials examining the clinical utility and safety of mifepristone as a pharmaceutical agent, alongside and/or in combination with other currently available anti-hyperglycemic agents; additional studies of mifepristone's efficacy and safety in specific sub-populations; and long-term follow-up studies to assess its sustained efficacy and/or late-occurring side effects; all of which may lead glucocorticoid antagonism being accepted as another complementary mechanism of treating T2DM. The study's mechanistic outcome measures may open up numerous opportunities for additional investigations into how normal physiological levels of glucocorticoids adversely affect multiple aspects of usual glucose homeostasis, at the molecular, cellular, organ system and/or whole organism levels. The relative contributions of mifepristone's actions on restoring insulin sensitivity and improving insulin secretion can all be compared using multiple isotopic tracer models of substrate kinetics, more refined intravenous challenge tests, and/or in vitro examination of signal transduction pathways.

Design & Setting: We propose a double blind, placebo-controlled, randomized trial of mifepristone 600 mg daily in adult males with T2DM not optimally controlled on insulin, with or without metformin. Being only a pilot study, we will restrict enrollment to male subjects to avoid the potential gynecological and pregnancy-associated complications associated with mifepristone's anti-progesterone actions; replication of this study in female subjects will be a critical follow-up study if we determine the risk-benefit ratio to be favorable in males. Participants will be identified from the Diabetes Specialty Clinic at the Martin Luther King Jr., Outpatient Center (MLK), an urban inner city clinic that serves a very large racial minority (Hispanic and African-American) population with a disproportionately high prevalence of T2DM, its affiliated clinical sites across the Los Angeles Department of Health Services, and the general communities across South Los Angeles.

Inclusion Criteria:

- Males, age 18-65 inclusive, with established T2DM for ≥ 1 year, on stable doses (defined as ≤ 20% change in total daily dose within 2 months prior to screening) of basal insulin, with or without prandial insulin (total daily dose must be ≤ 300 units); with or without maximally tolerated doses of metformin (metformin must stay at a constant dosage during the study, except for safety medication adjustments, below); baseline hemoglobin A_{1c} (HbA_{1c}) 8.0%-11.5%

Exclusion Criteria:

- Use of any anti-hyperglycemic agents (oral or injectable) other than metformin and insulin; any history or clinical suspicion of type 1 diabetes mellitus; known contraindications to metformin e.g., metabolic acidosis,

dehydration, alcohol abuse, impaired renal or hepatic function (new onset of any such conditions during the study should justify the withdrawal of the subject, as determined by the investigators)

- Concurrent chronic use of any corticosteroids by any route and for any indication, or concurrent conditions that may require the initiation of glucocorticoids during the study, as judged by the investigators
- Concurrent lipid-lowering medications whose levels are dependent on CYP3A pathway clearance (e.g., simvastatin, lovastatin, atorvastatin, fluvastatin and rosuvastatin) should either be washed out for at least one month prior to enrollment and/or switched to alternative LDL-cholesterol lowering agents (e.g., pravastatin or ezetimibe) for at least one month. If temporary discontinuation or switching (i.e., for 3 months) is deemed clinically unsafe, the subject should be excluded. If a substantial rise in LDL-cholesterol is anticipated, the subject should be re-screened with an updated lipid profile after the washout/switch.
- Contraindications or known intolerance to mifepristone; concurrent use of strong CYP3A inhibitors (e.g., cyclosporine, ergotamine, fentanyl, quinidine, sirolimus, tacrolimus, imidazole antifungals, HIV protease inhibitors, certain macrolide antibiotics, grapefruit juice) or CYP3A inducers (e.g., phenytoin, phenobarbital, carbamazepine, rifampin), including over-the-counter preparations or products contained within dietary supplements; concurrent use of medications that may prolong the QT interval (e.g., selected antipsychotics and antidepressants, quinolone antibiotics); daily use of warfarin or non-steroidal anti-inflammatory agents
- Baseline K^+ and Mg^{+2} outside the laboratory normal ranges, with or without oral K^+ and/or Mg^{+2} supplementation; if adjustment of any such supplementation fails to raise hypokalemia or hypomagnesemia into the normal range, the subject must be excluded from participation or withdrawn from the study
- Fasting plasma glucose (FPG) averaging ≥ 280 mg/dL with polyuria or polydipsia; persistent hyperglycemia ≥ 280 mg/dL with polyuria or polydipsia, or ≥ 300 mg/dL in the absence of any symptomatic polyuria or polydipsia, that occurs during the study on two or more consecutive FPG samples, or that is detected on self-glucose monitoring on 3 or more consecutive mornings, *and* that is not clearly attributable to major changes in adherence to concomitant insulin or usual dietary practices, should withdraw the subject from further participation; identifiable and remediable contributors to the hyperglycemia should be addressed (e.g., clinically significant concurrent infections) and the subject should be returned to their pre-study diabetes care providers.
- Symptomatic hypoglycemia averaging > once per day; subjects unable or unwilling to perform regular self-monitoring of blood glucose (SMBG), or a demonstrated history of unreliable SMBG, at the investigators' discretion
- Mean BP > 140 mmHg systolic or 90 mm Hg diastolic; baseline LDL-cholesterol ≥ 200 mg/dL if on lipid-lowering therapy or ≥ 250 mg/dL while not on lipid-lowering therapy; fasting triglycerides > 500 mg/dL; HDL-cholesterol < 25 mg/dL
- Known history of prostate cancer, or elevated level of prostate-specific antigen (PSA) at screening
- Estimated GFR < 30 mL/min; concurrent endocrinopathies that have not been stabilized with replacement or other definitive therapies (including known adrenal insufficiency regardless of replacement therapy, cortisol < 5 μg/dL at screening, or < 18 μg/dL at screening if a subsequent ACTH stimulation test fails to rule out adrenal insufficiency); active hemolytic anemias or hemoglobin variants that render the measurement of HbA_{1c} potentially unreliable; any other clinically significant hepatic, cardiovascular (including a history of heart failure, peripheral pitting edema, known personal or family history of, or risk factors for long-QT syndrome, QTcF prolongation on ECG > 500 ms; subjects with confirmed new onset QTcF prolongation > 60 ms from baseline during the study should also be withdrawn), infectious (including HIV or any viral hepatitis), inflammatory, neoplastic or other systemic disease that, in the investigators' opinion,

contraindicates the change of lipid-lowering therapy, renders mifepristone unsafe, or otherwise confounds data interpretation

- Subjects likely to start other drugs that may influence the study's outcomes (e.g., weight loss agents)
- Subjects who are unable or unwilling to comply with all components of the study protocol, attend all scheduled follow-up visits, or present other foreseeable barriers that, in the investigators' opinion, might make the implementation of the protocol problematic or confound data interpretation

Intervention: Double-blind, random assignment to mifepristone 600 mg daily taken with meals vs. matching placebo, for 3 months, followed by a 1-month post-treatment visit. Mifepristone will start at 300 mg daily (or matching placebo) for 2 weeks, increasing to 600 mg daily (or matching placebo) for the remaining 10 weeks.

Outcomes:

Primary: Between-group comparison of the change in HbA_{1c} from baseline to 3 months.

Secondary: Within-group changes from baseline to 3 months, and between-group comparisons of the change from baseline to 3 months, in:

- Anthropometry and body composition: weight, height, body mass index (BMI), waist circumference; percent fat and lean mass by DXA scanning
- Fasting plasma glucose (FPG), static insulin resistance and β-cell function estimates by the Homeostasis Model Assessment (HOMA); stimulated measures of glucose homeostasis using the 75 gram oral glucose tolerance test (OGTT) with determinations of insulin sensitivity based on the Matsuda index for insulin sensitivity (*Diabetes Care* 1999; 22:1462-70), β-cell secretion based on the insulinogenic index (*Diabetologia* 1984; 26:44-9), the Stumvoll index (*Diabetes Care* 2000; 23:295-301), and the OGTT disposition index (*Diabetes Care* 2007; 30:1544-8), and hepatic response based on the hepatic insulin sensitivity index (*Diabetes Care* 2007; 30:89-94); total daily insulin dosage
- Fasting lipid panel (total cholesterol, fasting triglycerides, LDL-, HDL-, and non-HDL-cholesterol); systolic and diastolic blood pressure; and cardiovascular risk scores based on the UKPDS Risk Engine (available at https://www.dtu.ox.ac.uk/riskengine)
- Serum cortisol, ACTH levels; safety measures: symptomatic hypoglycemia, CBC/diff, electrolytes (including magnesium), hepatic transaminases, uric acid, TSH, PSA, bilateral testicular volumes (estimated by orchidometer), clinical adverse effects (including the need for insulin and/or metformin down-titration, rescue BP medications, oral K+ or Mg^{+2} supplementation after randomization, and the need for down-titration or discontinuation of blinded study medication), and medication compliance

Schedule of Procedures: See **Table 1**. Screening laboratory test results older than 1 month (including HbA_{1c}) must be updated to confirm eligibility. Randomization will be stratified according to whether or not subjects agree to also participate in the euglycemic hyperinsulinemic sub-study (see below), and will, in either case, use a random number generator under the control of the Charles Drew University (CDU) research pharmacist, who will assign the appropriate randomization codes sequentially to each qualifying subject in a manner that keeps the investigators blinded. Randomized subjects will be followed at least every week throughout the treatment period. All subjects will also return for a follow-up visit 4 weeks after study completion/early termination to review any adverse events, hypoglycemia, compliance with concurrent medications, vitals and anthropometry, and optional safety lab tests. Diet and lifestyle, and regular SMBG will be reinforced at each visit, and adverse events, SMBG results, hypoglycemia, pill counts, and compliance with concurrent medications (via pill counts and/or reconciliation with pharmacy records, if available) will also be reviewed. The study medication supply will be collected, and a new supply will be dispensed as needed (except at end-of-treatment at V13/Wk12). At the investigator's discretion, additional visits or phone calls may be scheduled as needed to monitor for any adverse events or hypoglycemia.

Table 1: Study Procedures

Visit	Screen	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Week	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**16**
Consent, Screening	x														
Vitals, Anthropometry	x	(x)	x	x	x	x	x	x	x	x	x	x	x	x	x
Randomization		x													
Dispense Blinded Rx		x		x	x[a]	x[a]	x[a]	x[a]	x[a]	x[a]	x[a]	x[a]	x[a]		
Collect Unused Rx				x	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x	
12-Lead EKG	x			x		x		x		x		x		x	
Reinforce Diet/Lifestyle	(x)	x	x	x	x	x	x	x	x	x	x	x	x	x	
Basal Insulin Treat-to-Target		x	x	x	x	x									
Review AE, SMBG, Hypoglycemia	(x)		x	x	x	x	x	x	x	x	x	x	x	x	x
CBC, Chemistry, FPG	x		x	x	x	x		x		x		x		x	(x)
Lipids, Uric Acid, TSH, HbA_{1c}, Cortisol, ACTH, PSA	x													x	
Testicular Volumes, OGTT, HOMA-IR, DXA		x[c]												x	

(x) = Optional; [a] = Dispense additional blinded study medication as needed to last until the next scheduled visit; [b] = Collect and count remaining study medication if new supply is to be dispensed; [c] = Prior to starting study medication. AE, adverse event; CBC, complete blood count; FPG, fasting plasma glucose; HbA_{1c}, hemoglobin A_{1c}; OGTT, oral glucose tolerance test; PSA, prostate-specific antigen; SMBG, self-monitoring of blood glucose; TSH, thyroid stimulating hormone.

Study Medication: Corcept Therapeutics, Inc. (Menlo Park, CA) will provide a supply of mifepristone 300 mg tablets and matching placebo ("*investigational product*", or IP). Bottles containing an appropriate 30-day supply of IP will be assigned to randomization codes under the oversight of the CDU research pharmacist. Each randomized subject will begin taking one tablet once daily with food (300 mg po daily or matching placebo, to be dispensed at V1/Wk0, containing 30 tablets to last a 2-week interval - the excess to accommodate variations in scheduling or potential missed visits), and then from V3/Wk2 onwards, two tablets once daily with food (600 mg po daily or matching placebo, to be dispensed at V3/Wk2 and then as needed to accommodate variations in visit scheduling through V12/Wk11, each bottle containing 60 tablets). If mild intolerance (that does not require IP discontinuation) occurs at the initial 300 mg dose level and the subject wishes not to increase to 600 mg, dose escalation may be postponed to the subsequent visit, but every attempt should be made to escalate to the 600 mg dose level as soon as possible after V3/Wk2. Each randomization code will correspond to one set of 8 bottles (i.e., 2 extra bottles of 60 tablets each for each randomized subject, to serve as backup in case of lost medications, etc.). At each follow-up visit from V4/Wk3 onwards, the next sequential bottle of the same code may be dispensed as needed, and the remaining pills from the existing bottle will be counted and collected. At visits where the existing supply is still more than sufficient to last until the next scheduled visit, pills will be counted but the subject will continue to use the same bottle until the subsequent visit.

Basal Insulin Treat-to-Target: Between V1/Wk0 and V5/Wk4, the subject's dose of basal insulin will be adjusted at each weekly visit to target the mean of all daily fasting SMBG readings obtained since the prior visit to below the American Diabetes Association-recommended pre-prandial upper limit of 130 mg/dL; as follows:

If the mean of all daily fasting SMBG readings since the prior visit is:

< 80 mg/dL:	Decrease basal insulin dose by 2-4 units (investigators' discretion)
80-130 mg/dL:	No change
131-150 mg/dL:	Increase basal insulin dose by 2 units
151-180 mg/dL:	Increase basal insulin dose by 4 units
181-220 mg/dL:	Increase basal insulin dose by 6 units
221-260 mg/dL:	Increase basal insulin dose by 8 units
≥ 261 mg/dL:	Increase basal insulin dose by 10 units or at investigators' discretion

At any time, if the indicated dose change is deemed to be excessive by the investigators (e.g., skewed by explainable outlier readings that are not representative of the subject's typical fasting status), the investigators' individualized judgment to make a smaller dose change should prevail. At no time should any of the subject's prandial insulin doses (if any) be up-titrated to try to achieve the fasting SMBG target. *From V6/Wk5 onwards, all insulin doses must be held constant* (subjects performing carbohydrate counting for prandial insulin dose adjustments should continue to follow their usual prandial dose adjustment scheme unchanged), unless down-titration is necessary for hypoglycemia (below).

Safety Medication Adjustments: Dosages of all other concurrent medications that can affect the study's outcome measures (e.g. anti-hypertensive, lipid-lowering, and anti-hyperglycemic medications-metformin) must remain at constant dosages throughout the study, except as permitted below. Whenever possible, cross-referencing pill counts of concurrent medications with the subject's pharmacy dispensing records, if available or accessible, should be applied to objectively verify adequate adherence to any concurrent medications that can potentially affect the study's outcome measures. Subjects will be appropriately counseled whenever any medication adherence that is less than optimal is noticed.

Hypoglycemia: Hypoglycemia will be defined as *a) classic symptoms on at least 2 occasions that cannot be attributed to erratic eating or other lifestyle behaviors; or b) documented evidence by SMBG readings < 60 mg/dL on at least 2 occasions that cannot be attributed to erratic eating or other lifestyle behaviors*. In the event of hypoglycemia, insulin down-titration (below) should be the first course of action.

Insulin Down-Titration: At any time during the study, down-titration of insulin is permitted for hypoglycemia (as defined above). For subjects receiving basal insulin without prandial insulin, the basal insulin dose should be reduced by 20%. For subjects receiving both basal and prandial insulin, the insulin dose that is most likely responsible for the hypoglycemic event(s), based on the time of occurrence, should be reduced by 20% (for subjects performing carbohydrate counting for prandial insulin dose adjustments, a decrement of approximately 20% in the overall prandial dose adjustment scheme, if the prandial insulin is deemed to have caused the hypoglycemia). If hypoglycemia was severe (i.e., requiring the intervention of another individual), the applicable dose decrement may exceed 20%, at the investigators' discretion. A reassessment of SMBG readings and for persistence or resolution of hypoglycemic symptoms must be made *within no more than 4 days* (phone contact between scheduled visits are permissible in lieu of in-person visits). If hypoglycemia (as defined above) persists, a further down-titration of the applicable insulin dose (basal or prandial) by another 20% should be made and followed-up within no more than 4 days; this process should be repeated until hypoglycemia has been alleviated. For any single insulin dose (basal or prandial) of 10 units or less that is deemed to be the cause of hypoglycemia (as defined above), the decrement may exceed 20%, at the investigators' discretion. For any single insulin dose of 6 units or less that is deemed to be the cause of hypoglycemia (as defined above), the applicable insulin dose may also be discontinued altogether, at the investigators' discretion.

Metformin Down-Titration: Down-titration of background metformin will be permitted only for hypoglycemia that continues after the patient has down-titrated and discontinued all concurrent insulin. Down-titration should be a 500-1000 mg reduction in the total daily metformin dose. After each dose reduction, ongoing hypoglycemia should be reassessed within one week; if it persists, the dosage should be reduced further until hypoglycemia is alleviated or until the metformin is discontinued. Once alleviated, the metformin dose should be held constant, unless hypoglycemia recurs. If hypoglycemia persists after complete discontinuation of the metformin, the subject should be withdrawn and the hypoglycemia further investigated.

Rescue BP Medications: In the event of BP elevations to > 160 mm Hg systolic or > 100 mm Hg diastolic (despite adequate compliance with any concurrent anti-hypertensive medications), or any symptoms or signs suggestive of evolving end-organ damage due to a hypertensive crisis, anti-hypertensive medications may be prescribed or adjusted. The choice of agents is at the investigator's discretion (including mineralocorticoid antagonists if there is concern regarding concurrent hypokalemia despite supplementation and if these agents are

not otherwise contraindicated). Agents should be added stepwise and dosages increased in reasonable increments to achieve a target of < 140/90 mm Hg along with the alleviation of any symptoms or signs of end-organ damage, based on a reassessment of BP no less than once each week. Once BP is controlled, doses should be held constant, unless the BP again rises unacceptably. If uncontrolled hypertension persists despite the use of all accessible anti-hypertensive agent classes, the subject should be withdrawn from the study.

New-Onset Peripheral Pitting Edema: As the IP may exacerbate fluid retention (independent of BP control), if there is new development of peripheral pitting edema that persists despite appropriate interventions (including but not limited to diuretic therapy) for 2 weeks or more, the subject should be withdrawn from the study.

Potassium or Magnesium Supplementation: In the event of new-onset hypokalemia or hypomagnesemia after randomization, oral K^+ or Mg^{+2} supplements, as appropriate, may be prescribed or increased as needed to maintain levels within the respective laboratory normal ranges, using dosages or rates of dosage increase as judged to be appropriate by the investigators. The adequacy of K^+ and Mg^{+2} replacement should be reassessed at least at each subsequent scheduled visit until stabilized. Once levels are controlled, supplementation doses should be held constant. If maximum tolerated dosages of supplementation, at the investigators' discretion, fail to raise levels into the normal range, the subject should be withdrawn for safety reasons.

Adrenal Insufficiency and IP Down-Titration: Because plasma cortisol levels are not decreased with mifepristone treatment, a biochemical diagnosis of excessive GR blockade (adrenal insufficiency) is not possible and must rely on clinical assessment (i.e., the presence of headache, malaise, fatigue, lethargy, weakness, anorexia, nausea, vomiting, abdominal pain, hypoglycemia, and, uncommonly, hypotension; hyperkalemia is not part of the presentation of excessive GR blockade secondary to mifepristone treatment because of to retained mineralocorticoid receptor activation). At each study visit, subjects will be evaluated for these signs and symptoms of excessive GR blockade. In the event of any of the above symptoms (or any other constellation of non-specific clinical symptoms) that, in the judgment of the investigators, might be attributable to adrenal insufficiency or the administration of the IP at the 600 mg dose level (i.e., from V3/Wk2 onwards) and is of sufficient severity to warrant intervention, a reduction of the IP dose back to the 300 mg dose level may be considered. If the reduction leads to improvement of the clinical symptom to a level that is tolerable to the subject and acceptable to the investigators, the subject may continue in the study at the 300 mg dose level for the remainder of the study. If the reduction does not lead to improvement of the clinical symptom after an appropriate time interval (as judged by the investigators), then an alternate explanation for the symptom should be considered; in such cases, continuation of the IP back at the 600 mg dose level may also be considered (provided that adrenal insufficiency is not suspected), but standard good clinical practice (GCP) decision-making with respect to adverse events should still be applied to the symptom(s) in question, including the possibility of complete discontinuation of the IP (see below), if it is warranted in the judgment of the investigators. If the investigators judge that the symptom(s) may be a manifestation of adrenal insufficiency, discontinuation of IP and administration of high-dose corticosteroids may also be considered; in such cases, the subject must be withdrawn after resolution of the symptoms. Subjects will be provided with appropriate identification materials to carry on their person, as well as a medical alert bracelet to indicate the possibility of hypoadrenalism in the event of severe illness or injury, during their participation in the study.

Adverse Event Reporting: All adverse events (serious and non-serious) will be reported to the IRB within applicable time frames as per usual clinical trial procedures and good clinical practice. In addition, specific adverse events of special interest (AESI) will be reported as expedited safety reports to the IRB, Corcept Therapeutics Inc., and the FDA, as applicable. These include: 1) Major cardiovascular events including death related to coronary or cerebrovascular disease, acute myocardial infarction, stroke, and revascularization (coronary or cerebral); 2) Retinopathy; 3) Suspected or confirmed adrenal insufficiency, according to the clinical definition stated above.

Early IP Termination and Withdrawals: At the investigators' discretion, *subjects may be permitted to discontinue the IP at any visit, but only in discussion with the investigators, and for reasons of safety or intolerable side effects as judged to be appropriate by the investigators; such IP discontinuation will not automatically constitute withdrawal from the study*. Subjects permitted to discontinue the IP at a given visit should complete all requirements of the visit in question (with the exception of the clamp procedure, see below), and then should be scheduled to attend and complete all requirements of V14/Wk16, to take place 4 weeks after taking the final dose of the IP; only upon completion of V14/Wk16 and adequate resolution of any relevant clinical symptoms or laboratory abnormalities, as judged by the investigators, should the subject be formally withdrawn from the study. Subjects requesting discontinuation of the blinded study medication prior to attending a scheduled visit should also do so only in discussion with the investigators; in such cases, the subject and investigator should agree upon a specific date of the last dose of the IP, and the subject should then be scheduled to attend V14/Wk16 to take place 4 weeks after the agreed-upon date. *At any time, investigators may require additional (unscheduled) visits for follow-up of any adverse events or clinically significant symptoms.* With respect to subjects who completed a baseline clamp procedure and are then permitted to discontinue the IP prematurely, performance of the clamp procedure normally scheduled for V13/Wk12 should still be considered *prior to the final dose of the IP, if it is possible and clinically feasible, based on a discussion between the subject and the investigators.* Notwithstanding any of the above, subjects may still be free to voluntarily withdraw from the study, or may still be withdrawn by the investigators. Any subject who withdraws from the study for any reason will be referred back to their original diabetes provider to continue their diabetes care after their study participation is terminated. Reasons for study withdrawal by the research team will include, but will not be limited to, excessive non-adherence with the IP or concurrent medications that influence study outcomes, repeated failure to attend scheduled visits, substantial use of any other medications known to affect glucose or lipid control without initially consulting with the investigators, adverse effects that cannot be controlled by the investigators (including using the allowable changes to concurrent medications outlined above), or any other clinical situation which, in the opinion of the investigators, may jeopardize the subject's safety.

Lab Methodologies (see Table 1): The CTRC's contract commercial laboratory, Quest Diagnostics, will perform all lab assays (i.e., CBC/differential, complete metabolic panel, liver transaminases, FPG, HbA_{1c}, fasting lipids, insulin, TSH, uric acid, cortisol, ACTH (to rule out obvious hypercortisolemia), and PSA. The oral glucose tolerance test (OGTT) will be 75 grams of glucose administered orally in the fasting state with blood sampling for glucose and insulin at 0, 30, 60, 90 and 120 minutes while subjects remain sedentary with only minimal activity.

Statistical Analyses: Baseline characteristics between groups and within-group (pre & post) changes will be compared using unpaired Student's t-test (or an equivalent non-parametric test if data are not normally distributed) for continuous variables, or the χ^2 test for discrete variables. Between-group comparisons of changes over time will be made using repeated measures ANOVA for outcome measures that were taken at multiple time points, and paired Student's t-test for measures with only two time points. All outcomes will be analyzed with and without multiple adjustment for the confounders of baseline level, age, diabetes duration, race, and medication compliance rate; all secondary outcomes will be additionally adjusted for the baseline HbA_{1c} level. Outcomes will be principally analyzed by intent-to-treat (ITT), with imputation of any missing data using the last observation carried forward for 1) the full cohort; 2) based on race; 3) based on age tertile; and 4) stratified for baseline HbA_{1c} of 8.0-9.0% vs. 9.1-10.5%. Secondary analyses will also be carried out using a per-protocol approach for: A) All outcome measures among the subset of subjects who completed the full follow-up period and were ≥ 80% compliant with the study medication (to determine any biases from non-compliant/dropout subjects in the ITT cohort); B) BP outcome measures among the subset of subjects not requiring rescue BP medications (to determine any biases due to added anti-hypertensive therapy); and C) All outcome measures among the subset of subjects who did not require any down-titration of IP (to determine any biases from IP intolerance).

Power: Based on our previous study at MLK in the same population, the treatment effect of add-on oral agent therapy produced an absolute response in HbA_{1c} of -2.0% ± 1.7% from a baseline level of 9.4%. Assuming this same SD of treatment effect, to target a between-group treatment difference in absolute HbA_{1c} of 1.0%, by paired t-test, at $p<0.05$, we will have 90% power using a total sample size of 40 subjects. Estimating a 33% non-completion rate, we will target the enrollment of 60 subjects (30 per group).

Data Safety Monitoring Board (DSMB): Analyses of all accumulated safety data will be conducted every 4 months, to include analyses of: a) all accumulated clinical adverse events; and b) all accumulated laboratory test abnormalities that occur after subjects have initiated their first dose of the IP, *and* that are deemed by the investigators to represent either i) potentially clinically meaningful yet asymptomatic adverse events, or ii) clinically significant changes from baseline laboratory values that potentially represent clinically meaningful adverse events. Data collected from all enrolled subjects will be compiled by the study coordinator and reviewed and verified by the principal investigator. These cumulative data will then be presented to the CDU DSMB, and concurrently to the IRB. The DSMB will then review the submission independently, according to their established procedures, and report their conclusions and recommendations independently to the IRB, with a copy to the PI. Usual reporting requirements for serious and non-serious adverse events to the IRB will continue to apply throughout the study, and all such instances will also be included within each DSMB report. If on any review, the cumulative safety data indicates a possible *systematic and clinically harmful* risk that a) is plausibly and likely causally related to the IP and cannot be otherwise explained by subjects' concurrent circumstances, and b) cannot be mitigated by minor adjustments to the manner by which the investigators conduct or monitor subjects in the study, then consideration may be given for temporary or permanent study stoppage, with or without appropriate amendments to the protocol to mitigate the risk, as deemed necessary by the DSMB and/or IRB in consultation with the PI. Permanent study stoppage shall also be reported to the study's granting agency and IP supplier (Corcept Therapeutics, Inc.) as appropriate.