METFORMIN THERAPY FOR OVERWEIGHT ADOLESCENTS WITH T1D

A Randomized Trial of Metformin as Adjunct Therapy for Overweight Adolescents with Type 1 Diabetes

PROTOCOL

Version 2.0
09/03/14
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CHAPTER 1: BACKGROUND

The study is being conducted by the T1D Exchange Clinic Network and is being coordinated by the Jaeb Center for Health Research in Tampa, Florida.

The study is designed to evaluate the efficacy and safety of metformin as an adjunct therapy for overweight adolescents with type 1 diabetes (T1D).

1.1 Rationale for the Study

There is increasing evidence that individuals with T1D have not escaped the general population trend toward overweight and obesity despite the traditional phenotype of T1D being normal or underweight. From the 1980s to the 1990s there have been reports of a tripling in overweight prevalence at disease onset. Roughly 25-30% of children with T1D were reported in 2003 to have a BMI in the 85th percentile or above at onset (1). More recent data from the Pediatric Diabetes Consortium including children 2 to 19 years showed the prevalence of overweight and obesity at the time of T1D diagnosis to be 21% (2). These results are similar to the SEARCH study (3) and a recent study including a large sample of Italian children (4). In adolescents, at enrollment into the T1D Exchange, 37% of 8,192 12 to 19 year olds with T1D for >1 year were overweight or obese.

Despite the fact that intensive therapy is the standard of diabetes care it is often found to come with the limitation of increased weight gain. The Diabetes Control and Complications Trial (DCCT) found a 33% increase in the risk of becoming overweight (defined as a body weight >120% above the ideal) in the intensive group compared with the control group (5). Five years into the trial, patients being treated intensively had gained a mean of 4.6 kg more than those receiving conventional therapy. Among participants in the top quartile of weight gain, changes in plasma lipids, blood pressure and body fat distribution were observed that were similar to patients with the metabolic syndrome, a macrovascular disease risk factor (5). Thus this raises the critical concern of the potential detrimental impact of obesity in young children with T1D who are already at increased morbidity and mortality given their existing disease.

SEARCH investigators have reported that the prevalence of hypertension in obese youth with T1D was 11% and that 6% of children with T1D already had elevated blood pressure after 5 years duration (6). The Italian study also reported nearly 18% of children had systolic blood pressure levels >130 mmHg after 8 years duration (4).

Preliminary data from our Pittsburgh site (7) suggest that overweight T1D children, with a mean age of 15 years and diabetes duration of 8 years, have a worse lipid profile than their lean counterparts as well as decreased insulin sensitivity as measured by the euglycemic hyperinsulinemic clamp technique. Similarly, data from our Denver site show that while all adolescent participants are more insulin resistant than non-diabetic controls as measured by hyperinsulinemic euglycemic clamp, lean T1D participants typically lack components of the metabolic syndrome, as well as ectopic liver, muscle, and visceral fat (8). In contrast, preliminary data from our Denver site in T1D participants with obesity have more of a metabolic syndrome phenotype. Among the T1D Exchange clinic registry participants, age 12~<20 yrs and T1D duration ≥1 year, who were overweight/obese (37%), 8% had a diagnosis of dyslipidemia and 3% had clinically diagnosed hypertension compared with 4% and 1%, respectively, of participants who were normal weight.

Identified cardiovascular disease (CVD) risk factors in patients with diabetes include hyperglycemia (9, 10), hypertension (11), dyslipidemia (12), albuminuria (13, 14), obesity (15), and low adiponectin (16). However, traditional CVD risk factors (17) do not fully explain the increased morbidity and mortality from CVD seen in individuals with T1D (18-21). Insulin resistance (IR) has a well-defined role in atherogenesis, but is more difficult to quantify in individuals with T1D. Despite the relative lack of dyslipidemia and obesity in T1D patients, studies using a euglycemic clamp have demonstrated decreased global insulin sensitivity in T1D patients when compared to non-diabetic persons, including studies in youth with T1D (8, 22-25).

Our Denver site used venous plethysmography and found reduced forearm reactive blood flow in T1D and T2D adolescents compared to lean and obese controls (26). Plethysmography correlated with IR, not HbA1c, thus non-glycemic factors may contribute to vascular function. T1D youth also had significantly reduced VO2 peak (8) that independently correlated with vascular reactivity in multivariate analysis (8, 27). Endothelial dysfunction using flow mediated dilation (FMD) has been reported in T2D adults at our Denver site (28), one potential cause of the
reduced limb blood flow we report in youth. Vessel stiffness or reduced capillary density may also contribute to abnormal vascular reactivity. The SEARCH study, which includes T1D Exchange investigators, found peripheral vascular stiffness (BrachD), in T1D youth, especially boys, by Dynapulse (29, 30). Our Gainesville site used reactive hyperemia–peripheral artery tonometry (RH-PAT) by the EndoPat device (Itamar Medical Ltd., Caesarea, Israel) to assess endothelial function in T1D adolescents and found endothelial dysfunction as evidenced by lower mean RH-PAT scores (1.63 ± 0.5) when compared with children without diabetes (1.95 ± 0.3, p= 0.01)(31). Children with T1D underwent a second RH-PAT study 4 wks after their initial study to determine the intrapatient variability of the technique and repeat RH-PAT scores were predicted by initial RH-PAT scores (p= 0.0025). Mean intrapatient standard deviation of RH-PAT score was 0.261 and mean coefficient of variation was 14.8.

Overweight adolescents with T1D often have a higher total daily dose of insulin per kg of body weight due to a higher degree of insulin resistance (32). Insulin resistance has been associated with poor glycemic control (22).

Metformin, an oral agent commonly used in treating T2D, acts primarily to reduce hepatic glucose production but also has been shown to increase sensitivity to insulin (33, 34). Optimal glycemic control remains difficult in T1D, and even more challenging in the context of obesity, highlighting a need for additional approaches to therapy. Further research is needed on the potential benefits and possible risk of metformin use in adolescents with poor glycemic control and insulin resistance.

Metformin has been used extensively in obese non-diabetic and T2D patients with PCOS based on improvements in insulin sensitivity and lowering of plasma insulin levels (35). Data in the literature to date shows that women with T1D have a higher testosterone level than controls women without diabetes, which may be driven by hyperinsulinemia overstimulating the ovary, or by changes in sex hormone binding globulin due to hepatic insulin resistance, and could impact insulin sensitivity or cardiovascular disease. In addition, preliminary data from the Denver site show that testosterone levels tend to be higher in adolescent girls with T1D (57.5 ng/dl ± 25, n=41) vs. normal controls (41.4 ng/dl ± 16.8, n=17), and vs. nondiabetic obese patients (42 ng/dl ± 20.8, n=15). The impact of metformin in overweight/obese adolescent girls with PCOS and T1D has not been evaluated. We plan to assess the effect of metformin on androgen levels in our obese females and the relationship between changes in testosterone and changes in insulin sensitivity and endothelial function as exploratory outcomes.

Adiponectin tends to be higher in subjects with T1D vs. controls, yet still correlates with insulin sensitivity. A recent study assessing metformin in obese children and adolescents did not report significant changes in adiponectin, resistin, and leptin concentrations but did observe improved adiponectin to leptin ratios with metformin therapy (36). We will be able to assess changes in adiponectin and other adipocytokines as exploratory outcomes that may serve as surrogate biomarkers of improvements in insulin sensitivity (37) in a larger sample size than used in the Kendall et al study.

Since glucose homeostasis depends upon both insulin resistance and insulin secretion, metformin may also have indirect salutary effects on preservation of insulin secretion in those with T1D. As described below, some individuals with T1D have been treated with Metformin, but no formal measures of insulin secretion have been previously done. Thus, insulin secretion in response to a mixed meal tolerance test (MMTT) also will be measured in this study.

Endothelial dysfunction correlates with IR in T2D adults (28) and in obese youth (38), and we propose that IR is a similarly major contributor to vascular abnormalities in T1D youth. Therefore, improving IR should improve these abnormalities, as a study of rosiglitazone in T2D, improved IR, endothelial function and VO₂ max (39). In addition, muscle blood flow is a large determinant of muscle glucose uptake in response to insulin, and therefore blood flow abnormalities and abnormal vaso-reactivity could lead to IR. Unregulated lipolysis likely also accelerates atherosclerosis, but little data exists in T1D, thus examining adipose insulin sensitivity and response to metformin would provide novel data in T1D. Three months of metformin was recently shown to improve arterial stiffness and endothelial function in 30 young women with IR related to PCOS (40). Metformin improved blood flow by plethysmography and exercise capacity in 11 adults with PAD (41), arguing for potential benefits of metformin on CV abnormalities which may be common to T1D. Finally, and compared with placebo, metformin significantly improved endothelial function in 41 adults with T1D (42).

Endothelial dysfunction can be measured by several techniques, including flow mediated dilation by brachial artery ultrasound and RH-PAT by Endo-PAT. While the brachial artery ultrasound is considered by some to be the gold
standard technique, it requires extensive training and experience to perform and analyze correctly, and its user-
dependence introduces more variability for repeated measures and in the setting of a multi-center site. The Endo-
PAT device is much simpler to use and is performed and analyzed in a standard way that allows comparability
within subjects and across sites. For the proposed study we used Endo-PAT due to its availability at multiple of our
sites and its advantages for a multi-center study. Nitrate-mediated dilation (NMD) to assess non-endothelial
mediated dilation was not included due to our previous experience with difficulties in its approval for use in
pediatric studies.

1.2 Background on Metformin

Metformin acts predominantly on the liver to reduce hepatic gluconeogenesis and hepatic glucose output. It also
results in a slight increase in skeletal muscle glucose uptake, reduces intestinal glucose absorption and decreases
fatty acid oxidation. In studies of patients with type 2 diabetes, metformin is clearly associated with a reduction in
HbA1c level, weight stabilization/loss and modest reductions in serum triglycerides, VLDL and LDL levels,
reduced C-reactive protein, platelet activation and procoagulant factors (43). These metabolic effects of metformin
should translate into improved cardiovascular outcomes, albeit this has only been demonstrated in a sub-study of
participants with type 2 diabetes in the UK Prospective Diabetes Study (UKPDS) (44).

Although metformin is becoming more routinely used in adult patients with T1D, there are relatively few
randomized clinical trials in adults with T1D. A recent meta-analysis (45) found only 9 randomized studies of 197
reviewed studies. In this age group, metformin use was associated with a decrease in insulin dose requirement (5.7-
10.1 U/day in six of seven studies), HbA1c (0.6–0.9% in four of seven studies), weight (1.7–6.0 kg in three of six
studies), and total cholesterol (0.3–0.41 mmol/l in three of seven studies). Metformin also was found to be well
tolerated, with minimal gastrointestinal (GI) side effects, with only a trend towards increased hypoglycemia.
Analysis of the combined effects in the five trials which reported appropriate data demonstrated a significant
reduction in insulin dose (6.6 U/day, P<0.001) but no significant reduction in HbA1c or other measurements. The
effect of lower insulin dose implies that insulin sensitivity improved, although there is a paucity of data on the
mechanism of metformin’s action in T1D.

1.3 Prior Studies of Metformin Use in Adolescents with T1D

Whether metformin might be beneficial to diabetes control in adolescents with T1D is even less well understood.
Two small 3-month randomized controlled trials [Hamilton et al. 2003, (N=27) (33) and Sarnblad et al. 2003,
(N=30) (46)] in adolescents with insulin resistance found a significantly lower HbA1c in the metformin group
compared with the placebo group among adolescents (0.6% difference in change from baseline to 3 months in both).
They also found no significant differences in body mass index, insulin sensitivity, or serum lipids. Hamilton (33)
also demonstrated a decrease of mean daily insulin dose in the metformin group in comparison to the placebo group
after three months of metformin therapy of -0.14 (0.1) versus 0.02 (0.2), P=0.01 though, Sarnblad (46) did not find
any differences in insulin dose. Side effects were variable, as one study (33) reported a higher incidence of GI side
effects (60% vs. 33%) and mild hypoglycemia [mean 1.75 (0.8) versus mean 0.9 (0.4) events per patient and week
respectively (P=0.03)] in the metformin group compared with the placebo group, but this was not demonstrated in
the other study (46), which reported more side effects in the placebo group than the metformin group (43% vs.
19%). There were no episodes of lactic acidosis or ketoacidosis.

Our Denver site also performed a randomized, double blinded trial of “low dose” (500 mg BID) metformin in poorly
controlled T1D adolescents (17, 47). After 3 and 6 months, metformin significantly decreased insulin dose and
waist circumference, suggesting sustained improvement in insulin sensitivity, and possibly in fat distribution (17,
47), and a trend to decreased BMI at 6 months. Metformin, when blinded, was very well tolerated by youth in this
study. However, adherence was lower at the 6 month than 3 month time point. Of note, this study used a lower
metformin dose than the proposed study, so greater effects are anticipated with the full dose of metformin used in
the proposed study. In addition, the Denver study included lean and obese participants and an initial HbA1c level of
>8.5%. Therefore its results may not be directly applicable to obese participants in better diabetes control as in the
proposed study (18, 48).
Although these small studies suggest benefit for metformin as adjunctive therapy for T1D in adolescents, metformin is not widely used for these patients. In the T1D Exchange database, among 3,060 overweight or obese participants age 12 to <20 years, only 180 (6%) were being treated with metformin or other adjunctive therapy at enrollment.

1.4 Tolerability and Adverse Effects

Data are limited on the frequency of adverse effects of metformin as an adjunct treatment in people with T1D. Possible adverse effects include, hepatotoxicity, lactic acidosis, increased risk of severe hypoglycemia, and GI intolerance. Use of metformin is very rarely associated with anemia and appears to be rapidly reversible with discontinuation or vitamin B12 supplementation. In the TODAY study, a large study of 700 adolescents with type 2 diabetes who all took metformin, there was no meaningful change in vitamin B12 over the course of the study (49).

Metformin has not traditionally been thought to be intrinsically hepatotoxic. Past reports show that there are fewer than 10 cases of hepatotoxicity reported while taking metformin and all but one occurred in patients taking other potentially hepatotoxic drugs. There was a more recent case report of idiosyncratic hepatotoxicity in a 61 year-old male thought to be due to metformin (50). No cases of hepatotoxicity with metformin in youth have been reported. Moreover, a study in adolescents from our Denver site found that when compared at 6 months, participants with initial fatty liver who received metformin had significantly improved liver enzymes and liver fat by ultrasound than those who received placebo (51), arguing that metformin may improve liver health. Finally, in the TODAY study, a large study of 700 adolescents with type 2 diabetes who all took metformin, there was no metformin-related liver toxicity (48).

There are several case series that suggest that patients with either acute or chronic hypoxemic conditions who are on metformin therapy are at risk of lactic acidosis (about 0.03 cases per 1,000 person years), and then only when used in persons with renal or hepatic insufficiency, with administration of IV contrast, or during episodes of hypoxia or circulatory failure. However, a recent Cochrane review of 347 prospective comparative trials or observational cohort studies revealed no evidence that metformin is associated with an increased risk of lactic acidosis, or with increased levels of lactate, compared with other anti-hyperglycemic treatments (52). Nevertheless, many providers continue to stop metformin therapy when patients develop either dehydration or other conditions which could lead to hypoxemia. During the TODAY study there was only 1 case of lactic acidosis in a participant who was hospitalized for a severe asthma exacerbation (48). However, the lactic acidosis was felt to be secondary to the hypoxia and severe illness, not the metformin, and was transient and nonfatal.

Metformin is generally not associated with increased risk of hypoglycemia when given to patients with type 2 diabetes or polycystic ovary syndrome (PCOS). However, it is possible that metformin may increase the risk of hypoglycemia in patients with T1D, as its effect on hepatic gluconeogenesis and hepatic glucose output may result in decreased insulin requirement; if insulin is not adjusted accordingly, hypoglycemia may result. Hamilton (33) demonstrated a mild increase in both severe and mild hypoglycemia in adolescents with T1D who are on metformin therapy as well as insulin compared with those taking only insulin. In the Denver T1D metformin study, metformin was not associated with a significant increase in hypoglycemia. In addition, in the HbA1c range proposed and with close monitoring, hypoglycemia is less likely.

Finally, GI side effects are commonly reported in patients who take metformin therapy, including diarrhea, stomach cramping, and nausea. These effects have been shown to be reduced when the dose is titrated up slowly, given with food, and when blood sugars are followed closely as described in the Study Design section. In TODAY, adherence to the medication regimen was 84% at month 8, showing that it was tolerated well in adolescents (48). The Denver nondiabetic metformin study, a double blinded placebo-controlled study in 100 adolescents, found that about 29% of participants on metformin reported side effects (nausea 14%, diarrhea 14%, abdominal pain 1%) vs. 22% of participants on placebo (nausea 11%, diarrhea 11%) (51). Thus when blinded, GI side effects did not differ significantly between placebo and metformin. In addition, in this latter study, no participants had side effects to the point of requiring metformin dose reductions (51).

1.5 Objective

Primary: The objective of the proposed research is to evaluate the efficacy and safety of metformin in combination with standard insulin therapy in overweight children and adolescents (12-<20 years of age) with type 1 diabetes.
Secondary Objectives:
1. Assess the effect of metformin on C-peptide among participants with detectable C-peptide (≥0.017 nmol/L) at baseline.
2. Assess the effect of metformin on vascular function in participants at sites with an Endo-PAT machine.

1.6 Synopsis of Study Design

1.6.1 Study Design
1. Randomized, double-blind, placebo-controlled, 1:1 multi-center clinical trial

1.6.2 Major Eligibility Criteria (see Section 2.2 for a complete listing)
1. Diagnosis of presumed autoimmune T1D as indicated by age of diagnosis <10 years or documented positive diabetes-related autoantibodies
2. Age: 12-<20 yrs
3. Duration of T1D: ≥1.0 year
4. HbA1c: 7.5%-<10.0% (7.0%-<10.0% for ancillary clamp study enrollments after August 18, 2014 following IRB approval) from point of care measurement or local lab on day of screening visit or within 1 month prior
5. BMI: ≥85th percentile
6. Total daily dose of insulin per kg: ≥0.7 units per kg per day
7. Self-monitoring of blood glucose ≥3 times per day
8. Participation in the ancillary clamp protocol for patients enrolled after August 18, 2014

1.6.3 Treatment Groups
Random assignment 1:1 to one of the following 2 treatment groups:
• Group A: Placebo plus standard care basal-bolus insulin.
• Group B: Metformin up to 2000 mg per day (see 4.1.1 for titration) plus standard care basal-bolus insulin.

1.6.4 Total Sample Size (see 7.1 Sample Size Estimation)
Approximately 136 participants (68 per group).

1.6.5 Visit and Phone Contact Schedule
• Screening visit to assess eligibility, obtain informed consent and obtain blood samples for safety labs, non-fasting c-peptide, diabetes-related autoantibody measurements and place blinded continuous glucose monitor (CGM).
• Randomization/Baseline visit after screening eligibility is determined.
• Follow-up visits at 6, 13, and 26 weeks. Phone calls weekly for the first month and at 20 weeks.
  o Participants in the clamp ancillary study will end the study at 13 weeks (see 2.3.4).
• Post-treatment visit or phone contact 4-6 weeks after study treatment phase is completed.

1.6.6 Main Efficacy Outcomes
Primary: Change in HbA1c from baseline to 26 weeks, adjusted for baseline HbA1c.
• Change from baseline to 13-weeks for participants in the ancillary clamp study.
Secondary:
• Change in sensor data (% of time 71 to 180 mg/dl, % of time ≤70 mg/dl, % of time >180 mg/dl).
• Change in total daily dose of insulin (TDI) per kg, change in long-acting insulin dose in Multiple Daily Injection (MDI) and basal insulin dose in Continuous Subcutaneous Insulin Infusion (CSII) patients
• Change in Body Mass Index (BMI), waist circumference and body composition
• Change in serum lipids
• Change in blood pressure
• Change in measures of insulin resistance

Exploratory:
• Change in adipocytokines
• Change in androgen levels in females
• Change in C-peptide for participants with MMTT performed at baseline and 26-weeks
• Change in pro-insulin:C-peptide ratio and pro-insulin:insulin ratio for participants with MMTT performed at baseline and 26-weeks
• Change in vascular dysfunction at sites with an Endo-PAT machine

1.6.7 Main Safety Outcomes
• Liver enzymes and serum creatinine
• Lactic acidosis
• Frequency of severe hypoglycemia
• Frequency of diabetic ketoacidosis
• GI side effects

1.6.8 Flow Chart of Study Visits

*Participants enrolled in the ancillary clamp study will end follow-up at 13-weeks.
## 1.6.9 Schedule of Study Visits and Procedures

<table>
<thead>
<tr>
<th>Visit Window</th>
<th>Screening</th>
<th>Day 0</th>
<th>Phone Call At 7, 14, 21, 28 days*</th>
<th>6 wk</th>
<th>13 wk</th>
<th>Phone call at 20 weeks</th>
<th>26 wk</th>
<th>Post Treatment Visit¶</th>
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<td>(+/- 3 days)</td>
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<td>(+/- 1w)</td>
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<td>Vascular function assessment in participants at a site with Endo-PAT machine</td>
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*Phone call to assess treatment side effects in both treatment groups and adjust dose until up to 2000 mg per day.

*A Mixed Meal Tolerance Test (MMTT) may be performed at the baseline (0 week) and 26 week visits for participants who presented with detectable C-peptide (≥0.017 nmol/L) on the screening non-fasting C-peptide test. Participants enrolled in the ancillary clamp protocol after August 18, 2014 will not have a baseline MMTT performed. Insulin and pro-insulin levels will be assessed in participants with an MMTT at baseline and 26-weeks.

§Sample will be frozen and run in the metformin treatment group to evaluate compliance (after participant has completed the study) if needed.

¶Post-treatment visit completed 4-6 weeks after the participant completes the 26-week (13-week for clamp participants) blinded CGM wear and has stopped taking the study drug.

£ DEXA, Waist circumference and tanner staging will be measured at 13-weeks for participants in the ancillary clamp protocol.

β Clamp participants will have samples collected for storage at 13-weeks instead of 26-weeks.

∑ Urine sample for storage in T1D Exchange Biobank will be obtained at 13-weeks if obtained at baseline.

The volume of blood drawn will vary depending on the participant’s age and weight and study procedures. For children <18 years the maximum blood volume will not exceed 5 ml/kg body weight over a 1 month period and 9.5 ml/kg over eight weeks. The exact blood volumes collected may vary according to local IRB regulations. The maximum blood volume collected from adults >18 years will not exceed 250 ml at each visit.

Note: Coordinators should contact participants 1-2 days prior to a clinic visit to review procedures as applicable.
CHAPTER 2: SCREENING VISIT

2.1 Study Population

A minimum of 136 participants are expected to be enrolled. As the enrollment goal approaches, sites will be notified of the end date for primary study recruitment. Participants who have signed an informed consent form can be randomized up until the study end date. Clinical sites participating in the clamp ancillary study may continue enrolling patients after the recruitment goal for the main protocol has been reached to achieve the target enrollment for the ancillary study. The maximum number of randomized participants will be 190.

2.2 Eligibility and Exclusion Criteria

2.2.1 Eligibility

To be eligible for the study, all participants must meet the following criteria:

1. Clinical diagnosis of presumed autoimmune T1D as indicated by age of diagnosis <10 years or documented positive diabetes-related autoantibodies
   
   i. Note: For randomization, presence of at least one of the diabetes-related autoantibodies (Insulin autoantibodies (IAA) at diagnosis prior to initiation of insulin, Islet cell antibodies (ICA), Anti-GAD (GAD65), Anti-IA2 (IA2), Zinc Transporter 8 (ZnT8)) must be documented either from medical records or new laboratory measurement (IAA and ICA not measured by central lab) sent to central lab for participants who were ≥10 years old at diagnosis.

2. Age: 12 to <20 years

3. Duration of T1D: ≥1 years

4. Current insulin regimen involves either use of an insulin pump or multiple daily injections of insulin (at least 3 shots per day) for the last three months, with no plans to switch the modality of insulin administration during the next 6 months (e.g., injection user switching to a pump, pump user switching to injections)

5. Hemoglobin A1c: 7.5% - <10.0% (7.0% - <10.0% for ancillary clamp enrollments after August 18, 2014 pending IRB approval) from point of care measurement or local lab on day of screening visit or within 1 month prior

6. BMI: ≥85th percentile adjusted for age and sex

7. Total daily dose of insulin: ≥0.7 units per kg per day

8. Average of ≥3 Self-Monitoring Blood Glucose (SMBG) tests per day prior to initiating study and from download of study-provided blood glucose meter following screening visit

9. Available for at least 6 months of follow-up, has home phone (or access to phone), and willing to be contacted by clinical site staff

10. Expected to comply with protocol in investigator’s judgment

11. Participation in the Insulin Clamp Ancillary Study for assessment of insulin resistance if enrolled after August 18, 2014

12. Use of non-insulin medications for blood glucose control within prior 6 months or planning to use within next 6 months (other than study drug)

13. Use of medications for weight reduction (such as: Belviq (lorcaserin), Qsymia (Phentermine + topiramate), Orlistat (xenical)) within the prior 6 months or planning to use within next 6 months

14. Use of a medication such as stimulants, psychotropic agents and oral/inhaled glucocorticoids that could affect weight gain or glycemic control of T1D or planning to use within the next 6 months

15. Any condition that in the judgment of the investigator will adversely affect the completion of the protocol.

16. Females: pregnant, lactating, or intending to become pregnant within the next 34 weeks
   
   a. A negative urine pregnancy test will be required for all females An effective contraceptive method or abstinence will be required for all females who have experienced menarche

   b. Requirements regarding pregnancy testing prior to enrollment and monitoring for pregnancy over the course of the study may be further defined by each individual Institutional Review Board (IRB)

17. Clinical diagnosis of celiac disease that is in poor control as defined by most recent tissue transglutaminase (tTG) that is in the abnormal range

18. History of ≥1 DKA events in the past 3 months
19. History of ≥1 severe hypoglycemic events (cognitive impairment that required assistance to treat) in the past 3 months
20. History of anemia or vitamin B12 deficiency in the past 2 years
21. Participation in an intervention study in the past 3 months. Participants who complete the main study but were not given the opportunity to be in the ancillary clamp study may be enrolled again into the ancillary clamp study if they were previously randomized to the placebo group.

2.2.3 Exclusions Based on Screening Lab Results
22. Serum creatinine level greater than the upper limit of normal for an adult
   i. Normal limit: 1.2 mg/dL (Male), 1.1 mg/dL (Female)
23. Liver enzymes (ALT and AST) greater than 2.5 times upper limit of normal
   i. Normal limits:
      • Aspartate transaminase (AST): 65 U/L (Male), 46 U/L (Female)
      • Alanine transaminase (ALT): 65 U/L (Male), 50 U/L (Female)

2.3 Participant Enrollment
Potential participants will be evaluated for study eligibility through the elicitation of a medical history and performance of a physical examination by a study investigator.

2.3.1 Informed Consent
For eligible participants, the study will be discussed with the potential participant and, for those <18 years old, with the parent/legal guardian (referred to subsequently as ‘parent’).
Informed consent and assent will be obtained from the potential participant (and parent for minors) according to IRB requirements prior to performing any study-specific procedures that are not part of the potential participant’s routine care.
For participants who turn 18 years old during the course of the study, IRB requirements will be followed with respect to reconsenting.

2.3.2 T1D Exchange Clinic Registry
If a participant is not already enrolled in the T1D Exchange clinic registry, they will become part of the registry when joining this study. As a registry participant, information from their medical record may be entered into the registry database at least once a year and they will have an opportunity to provide their email address to be contacted in the future about other studies for which they may be eligible. Participants also may be asked to complete a questionnaire(s) either on a computer, paper, or via telephone. Participants may be given the option to have questionnaires emailed to them and may decide whether or not to complete a questionnaire each time they are asked.

2.3.3 T1D Exchange Biobank
The T1D Exchange Biobank is designed to support ongoing and future research by qualified investigators by collecting information and biosamples from people with T1D. Samples will be used only for the study of T1D and its complications. Within this overarching purpose, multiple T1D Exchange studies will collect blood samples specifically for the T1D Exchange Biobank, whose policies and procedures will govern the release of data and samples to investigators. The T1D Exchange Biobank is directed by the Biobank Operations Center at Benaroya Research Institute, Seattle, WA and the Jaeb Center for Health Research (JCHR) who are responsible for the oversight of the operations of this database and biosample repository. Specifically, the JCHR IRB reviews and approves specific protocols under which data and samples may be obtained and shared, and ensures that adequate provisions protect the privacy and confidentiality of participants and data.
Enrolled participants will have blood and urine samples collected for storage in the T1D Exchange Biobank. Blood will be drawn at randomization, 13-weeks (for clamp participants only following IRB approval), and 26-weeks and may include DNA, RNA, peripheral blood mononuclear cells (PBMC), serum and plasma. Urine will be obtained at randomization and 13-weeks for participants enrolled after August 18, 2014 following IRB approval.
2.3.4 **Insulin Clamp Ancillary Study for Assessment of Insulin Resistance**

An ancillary study involving a 2-stage hyperinsulinemic euglycemic clamp procedure will be conducted to assess if metformin will improve tissue-specific insulin resistance. Clamps will be performed at baseline and after 13-weeks of treatment with metformin versus placebo. Details regarding the ancillary clamp study are outlined in a separate ancillary protocol. Recruitment for the ancillary clamp study will continue after recruitment for the main study is completed. Ancillary clamp participants will end follow-up at 13-weeks when the primary outcome for the ancillary study is completed and will not be included in the primary analysis for the main study.

2.4 **Historical Information and Physical Exam**

A history will be elicited from the participant/parent and extracted from available medical records with regard to the participant’s diabetes history and current diabetes management, current medications, and current medical conditions.

Physical examination for measurement of:
- Body weight, height
- Pubertal assessment by tanner staging

2.5 **Screening Labs**

Blood or urine will be obtained for the following laboratory tests at the screening visit:

1. Diabetes-Related Autoantibodies (e.g. GAD65, IA2, ZnT8)
2. Serum creatinine levels – for eligibility and baseline assessment for safety outcome
3. HbA1c - measured using the DCA2000 or similar point of care device to assess eligibility. Measurement from local lab can be used if point of care not performed. Not needed if measurement within prior 30 days available.
4. Liver enzymes – for eligibility and baseline assessment for safety outcome
5. Non-fasting C-peptide – for an initial screen of residual C-peptide and subgroup analyses

A pregnancy test (urine, unless IRB has other requirements) for all female participants will be performed and repeated at every study visit.

2.6 **Log Book for Total Daily Insulin Assessment**

Participants using MDI will be provided with a log book to record the amount of insulin given each day for one week prior to clinic visits at randomization, 6 weeks, 13 weeks, and 26 weeks.

2.7 **Blinded CGM**

A blinded CGM sensor (iPro™2 digital recorder (“iPro2”) with Enlite™) will be worn for up to a week to obtain a baseline assessment of glucose data between the screening and randomization visit. The Enlite Sensor Serter ™ and overtape (Enlite Sensor Overtape) will be used for insertion and placement. The goal will be to achieve a minimum of 3 days of sensor glucose data. The CGM will be placed by a member of the study team and participant/parent will be instructed on the use and return of the device.

The Enlite™ Medtronic sensor has a retractable, smaller needle for inserting the sensor and has a smaller sensor that is inserted under the skin. The Enlite™ sensor and its components are currently approved by the FDA for use with another CGM. Therefore, use of the iPro2 CGM device with the Enlite sensor in this study will be considered investigational.

A blood glucose meter and test strips will be provided to all participants for use during CGM wear. The meter data will be used for calibration of the CGM device. Both the CGM and meter will be returned to the site after each use.
CHAPTER 3: RANDOMIZATION VISIT

3.1 Timing of Randomization Visit
Enrolled participants will have a visit at which treatment assignment will be determined after all baseline testing results affecting eligibility are available. In addition, if the participant is taking part in the ancillary study, this must be completed prior to randomization.

3.2 Review of Eligibility Requirements
Eligibility again will be assessed. The following are required for the participant to be eligible for randomization:
1) From download of study-provided blood glucose meter, an average of at least 3 SMBG measurements per day.
2) From pump download or review of daily insulin log, TDI $\geq$ 0.7 units/kg.
Lab results that are part of the exclusion criteria also will be reviewed including serum creatinine and liver enzymes.
Participants who do not meet the total daily insulin or fingerstick requirements or who have lab results out of the eligibility ranges will be withdrawn from the study and not randomized.

3.3 Randomization of Eligible Participants
The Jaeb Center will construct a Master Randomization List using a permuted block design, stratified by HbA1c groups of 7.5%<9.0% and 9.0%<10.0% based on the screening HbA1c, which will specify the order of treatment group assignments. Participants in the clamp ancillary study will have a separate randomization list that is not stratified by HbA1c due to small sample size.
   a. Participants will be randomized in a 1:1 ratio.
   b. Both the participant and the site will be masked to treatment group assignment.

3.4 Procedures at Randomization Visit
Participants will need to be fasting for at least 8 hours prior to coming in for the randomization visit. The following procedures will be performed in both groups at the randomization visit unless otherwise noted:
1. Review of insulin log data for injection users and pump data for recording of insulin doses
2. Blinded CGM and HGM download
3. Measurement of height, weight, waist circumference, and blood pressure
4. DEXA scan for body composition
5. Collection of blood samples to be sent to the central lab for assessment of:
   i. HbA1c
   ii. Serum Lipids
   iii. Testosterone panel in females
   iv. Adipocytokines assays
   v. Storage in the T1D Exchange Biobank
6. Collection of urine to be sent to the central lab for storage in the T1D Exchange Biobank
7. Mixed Meal Tolerance Test (MMTT)
   i. Participants who presented with detectable C-peptide ($\geq$0.017 nmol/L) on the screening non-fasting C-peptide test may have a MMTT performed at baseline, to compare change in residual C-peptide from baseline to 26-weeks between treatment groups. If a participant is unable to complete the MMTT, he/she will still be randomized into the study. Participants enrolled in the ancillary clamp study after August 18, 2014 following IRB approval will not have an MMTT at baseline.
   ii. Additional samples will be collected to assess pro-insulin and insulin levels in participants who have a MMTT performed.
8. Assessment of vascular function in participants at sites with an Endo-PAT machine.

iii. Endo-PAT is a non-invasive technique that combines the traditional flow-mediated dilatation with pneumatic fingertip probes to measure arterial pulse wave amplitude.

1. Prior to coming in for the Endo-PAT procedure participants will need to fast for 8 hours.

2. During the procedure, the participant will be seated and fingertip probes are placed on both index fingers. Blood flow will be restricted using an arm BP cuff for a short time during the procedure. Blood pressure and pulse will be measured and recorded.

3. Immediately following the Endo-PAT procedure, blood glucose will be measured to document the glucose level at the time of assessment.
CHAPTER 4: TREATMENT AND FOLLOW UP

4.1 Randomized Treatment

All participants will continue a standard basal/bolus insulin regimen. Participants will be randomly assigned 1:1 to one of two oral treatment regimens for approximately 27 weeks (approximately 14 weeks for ancillary clamp participants):

- Oral metformin up to 2000 mg per day (see 4.1.1 for titration)
- Oral placebo

Metformin has been approved by the Food and Drug administration (FDA) for use in adults and children greater than 10 years of age with type 2 diabetes but is currently not approved for use in individuals with type 1 diabetes. For this reason, use of metformin in this study is considered investigational.

A central pharmacy will compound a placebo to match the metformin tablets. Tablets will be dispensed in masked prescription bottles and will be shipped to study sites from the Jaeb Center.

The placebo product will contain the following components:

- Micosolle™, silica based excipient
- Silicified Micro Crystalline Cellulose, NF
- Safflower Oil, USP
- K-30 Povidone Powder
- Magnesium Stearate, NF (Vegetable source)
- Fumed Silica, NF

4.1.1 Study Medication Dosing

The strength of each tablet will be 500 mg. Participants will build up to a daily dose over four weeks by taking one tablet per day for 7 days, one tablet twice daily for 7 days, one tablet in morning and 2 tablets at night for 7 days, and then 2 tablets in the morning and 2 tablets at night, daily throughout the remainder of the study treatment period.

Study participants will continue to take the study drug for 1-week after the 26-week study visit (13-week visit for ancillary clamp participants) during blinded CGM use. A post study treatment follow-up visit will occur 4-6 weeks after the participant has stopped taking the study drug.

Participants who cannot tolerate a dose of 2000 mg (4 tablets per day) can be reduced to 1500 mg or 1000 mg if necessary per investigator discretion.

4.2 Compliance

Medication containers will be brought to all visits while on randomized treatment. The amount of remaining study drug will be recorded as a measure of treatment compliance. Blood samples will be drawn at 13 weeks and 26 weeks for possible analysis of metformin plasma levels.

4.3 Side Effects of Treatment

Reporting of adverse events is described in Chapter 6.

4.3.1 Discontinuation of Treatment

Study drug will be discontinued if significant safety concerns arise including the following: increase in liver enzymes, recurrent episodes of acidosis or any documented episode of lactic acidosis, renal impairment based on GFR. If there is a reason to unblind the treatment assignment for patient management, a request can be made to the medical monitor.
If a participant presents to the emergency room with symptoms of dehydration or ketoacidosis study medication will be discontinued and serum lactate measured when possible. Whether or not study drug is resumed following dehydration or ketoacidosis event will be at investigator discretion.

In the case of pregnancy during this study, study drug will be discontinued.

Study drug (metformin or placebo) will be temporarily discontinued if a participant needs to undergo contrast-based angiographic procedures for any reason.

4.4 Phone and Visit Schedule in Randomized Trial

Protocol-specified contacts and follow-up visits will occur at the following times. All contacts and visits are timed from randomization.

Randomized Treatment Phase:

- 1-week phone call: 7 days (± 4 days)
- 2-week phone call: 14 days (± 4 days)
- 3-week phone call: 21 days (± 4 days)
- 4-week phone call: 28 days (± 4 days)
- 6 week follow-up visit (± 1 week)
- 13 week follow-up visit (± 1 week)*
- 20-week phone call (± 1 week)*
- 26 week follow-up visit (± 1 week)*

Post-Treatment study visit or phone contact will occur 4 to 6 weeks after the participant has completed the final treatment phase visit and has stopped taking the study drug.

Participants enrolled in the ancillary clamp protocol will end follow-up at 13-weeks when the primary outcome for that study is completed.

Additional visits and phone contacts may be completed at investigator discretion.

4.5 Testing and Study Procedures in Randomized Trial

4.5.1 Telephone Contacts

Each participant will be contacted by the physician's office via telephone 1, 2, 3, 4 and 20 weeks post-randomization (clamp participants will not have a 20-week phone contact). During each call, the participant/parent will be questioned about side effects and reminded of the importance of completing all aspects of the treatment. Participants/parents will be reminded to bring their study medication containers to the office visits. Participants also may be contacted prior to coming in to study visits to be reminded of visit requirements.

4.5.2 Procedures at Follow-up Visits – Treatment Phase

Follow-up visits will occur at 6±1 weeks, 13±1 weeks, and 26±1 weeks following randomization. Participants in the ancillary clamp protocol will not have a 26-week visit. Participants will need to be fasting for at least 8 hours prior to coming in for the 13-week and 26-week visits.

The following procedures will be performed in both groups at each visit, unless otherwise noted:

1. Medical history will be updated, including questioning about the occurrence of adverse effects of treatment and other adverse events, including the occurrence of diabetic ketoacidosis and severe hypoglycemia. Any concomitant medications will be recorded.

2. Evaluation of treatment compliance

3. Review of insulin log or pump download to determine average total daily insulin per day
4. Height and weight
5. Waist circumference and Tanner staging—26 wk visit only (13 wk visit for ancillary clamp participants)
6. Blood pressure—13 and 26 wk visits only
7. DEXA scan for body composition—26 wk only (13 wk visit for ancillary clamp participants)
8. Recording of SMBG per day
9. Urine pregnancy test for females, as indicated
10. HbA1c determination using the DCA2000 or similar point of care device for management decisions. Measurement from local lab can be used if point of care not performed.- 13 and 26 wk visits only
11. Collection of blood or urine samples at 13 wk and 26 wk visits to send to the central laboratory for:
   i. HbA1c
   ii. Serum lipids
   iii. Liver enzymes
   iv. Serum creatinine
   v. Testosterone panel – females only
   vi. Adipocytokine assays
   vii. T1D Exchange Biobank blood samples – 26 wk visit only (13 wk for ancillary clamp participants)
   viii. T1D Exchange Biobank urine samples – 13 wk visit for ancillary clamp participants only if obtained at baseline
   ix. Plasma metformin levels – 13 and 26 wk visits only
12. Mixed Meal Tolerance Test (MMTT):
   i. Participants who had a MMTT at baseline will have a MMTT performed at the 26 week visit.
   ii. Additional samples will be collected to assess pro-insulin and insulin levels in participants who have a MMTT performed.
13. Blinded CGM training and placement (at the 13 week visit and 26 week visit only)
14. Assessment of vascular function at sites with an Endo-PAT machine (at the 13 week visit and 26 week visit only)

4.5.3 Post Study Treatment Visit
Post-treatment study visit or phone contact will occur 4-6 weeks after the participant completes the 26-week blinded CGM wear (13-week for clamp participants) and has stopped taking the study drug. Remaining study drug will be collected from participant (if not previously mailed back) and the CGM data and insulin use will be reviewed and adjusted as needed. Medical history including collection of adverse events will be updated if needed. The participant may be prescribed metformin at the discretion of the investigator.
CHAPTER 5: MISCELLANEOUS CONSIDERATIONS

5.1 Benefits

There is the prospect of direct benefit to the individual participants for their participation in the study. These potential benefits include the recognized benefits of being in a clinical study, including close monitoring. Further, the intervention has the prospect of direct benefit to a given participant and is likely to yield general knowledge about T1D which is of importance for the understanding of T1D in children and young adults. Sensor data will be reviewed with participants after the study is completed, which may result in beneficial changes to diabetes management. Participants will be given some of the lab results including antibody testing, C-peptide levels, HbA1c, and lipids.

5.2 Participant/Parent Reimbursement

The study will be providing the participant with a $50 gift/merchandise card per completed protocol-required visit in lieu of travel and other visit-related expenses. A $50 gift/merchandise card will be provided for each MMTT performed. At the end of the study, participants may receive an additional:

- $25 gift/merchandise card for completing at least 4 of the 5 (3 of 4 for clamp participants) protocol-required study phone calls
- $25 gift/merchandise card for bringing in at least 75% of all study drug bottles to visits

Additional travel expenses may be paid in select cases for participants with higher expenses.

5.3 Participant Withdrawals

Participation in the study is voluntary, and a participant may withdraw at any time. The investigator may withdraw a participant who is not complying with the protocol.

Participants will not be withdrawn from the study if the study drug is discontinued due to adverse events (see section 4.3.1).

5.4 Study Costs

The following will be provided by the study at no charge:

- Blinded CGM and related supplies
- Metformin or placebo
- Study visits and procedures

5.5 Discontinuation of Study

The study may be discontinued by the investigators (with approval of the Data and Safety Monitoring Committee) prior to the preplanned completion of enrollment and follow-up for all participants.

5.6 Confidentiality

For security purposes, each participant will be assigned a coded identifier. All study data will be shared with the Jaeb Center for Health Research in Tampa, FL, which is the coordinating center for the study. Laboratories will receive specimens and certain study information, such as the assigned ID number and date of specimen collection. All laboratories and specimen storage facilities will sign agreements with the Jaeb Center that will require compliance with HIPAA/HITECH/future regulations. Protected Health Information (PHI) that does not directly identify a participant may be shared with Benaroya Research Institute in Seattle, WA, which is the Biobank Operations Center for the T1D Exchange.

Study data will be entered on the Coordinating Center’s secure website through an SSL encrypted connection. The Coordinating Center websites are maintained on Unix and Linux servers running Apache web server software and on a Windows server running IIS, all with strong encryption. The study website is password-protected and restricted.
to users who have been authorized by the Coordinating Center to gain access. No identifiable health information of
an enrolled participant will be released by the Coordinating Center.

During each visit, the CGMs and home glucose meters will be uploaded to a secured and password-protected website
called CareLink. The CareLink website was created by Medtronic, the company that makes the CGM for this study.
All data uploaded will include only the participant’s identifier; no names or personal information will be included.
The password for each center’s CareLink account will be provided to the Coordinating Center to retrieve the data.
The CGM and meter data will then become part of the study database at the Jaeb Center.
CHAPTER 6: ADVERSE EVENTS

6.1 Definition

An adverse event is any untoward medical occurrence in a study participant, irrespective of whether or not the event is considered to be related to treatment.

Hypoglycemic events are recorded as Adverse Events if the event required assistance of another person due to altered consciousness to actively administer carbohydrate, glucagon, or other resuscitative actions. This means that the participant was impaired cognitively to the point that he/she was unable to treat his or herself, was unable to verbalize his or her needs, was incoherent, disoriented, and/or combative, or experienced seizure or coma. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. If plasma glucose measurements are not available during such an event, neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

Hyperglycemic events are recorded as Adverse Events if the event involved DKA, as defined by the DCCT, and had all of the following:
- Symptoms such as polyuria, polydipsia, nausea, or vomiting,
- Serum ketones or large/moderate urine ketones,
- Either arterial blood pH <7.30 or venous pH <7.24 or serum bicarbonate <15, and
- Treatment provided in a health care facility.

6.2 Recording of Adverse Events

Throughout the course of the study, all efforts will be made to remain alert to possible adverse events or untoward findings. The first concern will be the safety of the participant, and appropriate medical intervention will be made.

The investigator will elicit reports of adverse events from the participant at each visit and complete an adverse event form if necessary. Each adverse event form is reviewed by the Coordinating Center to verify the coding and the reporting that is required.

The study investigator will assess the relationship of any adverse event to be related or unrelated by determining if there is a reasonable possibility that the adverse event may have been caused by the treatment.

The intensity of adverse events will be rated on a three-point scale: (1) mild, (2) moderate, or (3) severe. It is emphasized that the term severe is a measure of intensity: thus, a severe adverse event is not necessarily serious. For example, itching for several days may be rated as severe, but may not be clinically serious.

Adverse events that continue after the participant’s discontinuation or completion of the study will be followed until their medical outcome is determined or until no further change in the condition is expected.

6.3 Reporting Serious or Unexpected Adverse Events

A serious adverse event is any untoward occurrence that:

- Results in death
- Is life-threatening; (a non-life-threatening event which, had it been more severe, might have become life-threatening, is not necessarily considered a serious adverse event)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in significant disability/incapacity (e.g., sight-threatening)

Unexpected adverse events are those that are not identified in nature, severity, or frequency in the package insert for metformin.
Serious, related adverse events must be reported to the Coordinating Center within 24 hours.

A Medical Monitor will review all adverse events as they are reported and will evaluate the clinical investigator’s assessment with respect to coding, severity, relationship to study drug, expected/unexpected, and whether the event constitutes a serious adverse event. If there is a reason to unblind the treatment assignment for patient management, a request can be made to the Medical Monitor.

The Coordinating Center will notify all participating investigators of any adverse event that is serious, related and unexpected. Notification will be made within 7 days after the Coordinating Center becomes aware of the event.

Each principal investigator is responsible for informing his/her IRB of serious, unexpected study-related adverse events and abiding by any other reporting requirements specific to their IRB.

### 6.4 Data and Safety Monitoring Committee Review of Adverse Events

A Data and Safety Monitoring Committee (DSMC) will provide independent monitoring of study data including adverse events. Cumulative adverse event data are tabulated semi-annually for review by the Data and Safety Monitoring Committee (DSMC). Following each DSMC data review, a summary will be provided to IRBs.

The DSMC Chair or designee will be notified within 24 hours of the coordinating center being notified of a treatment-related serious adverse event.

### 6.5 Risks

#### 6.5.1 Risks of Examination Procedures

The blood draws and IV placement could result in discomfort or bruising, or rarely an infection or a blood clot. Fainting may also occur. The volume of blood drawn at each visit will vary depending on the participant’s age and weight. However, for children <18 years the maximum blood volume will not exceed 5 ml/kg body weight over a 1 month period and 9.5 ml/kg over eight weeks. The exact blood volumes collected may vary according to local IRB regulations. The maximum blood volume collected from adults >18 years will not exceed 250 ml at each visit.

There are no known risks to the MMTT. However, participants may not like the taste of the Boost drink, and some may also experience nausea. If the participant’s blood glucose is high at the end of the MMTT, he/she will receive help with the insulin dosing.

The DEXA scan will measure the percentage of fat and muscle in the participant’s body. This procedure will deliver the following amounts of radiation exposure: approximately 10 µSv total body equivalent dose per measurement. The amount of radiation that the participant will be exposed to during the DEXA test is approximately equal to the amount of radiation they would receive being outdoors for one to two days in a high altitude city, such as Denver. Because T1D and sedentary and obese participants are at increased risk of reduced bone mineral density, the results of the DEXA are of potential benefit to these participants.

There is a low risk for developing a local skin infection at the site of the sensor needle placement. Itchiness, redness, bleeding, and bruising at the insertion site may occur, as well as local tape allergies.

There may be slight discomfort when the cuff is inflated for the Endo-PAT test. There will also be slight discomfort when the fingerstick glucose is measured, but this is a standard procedure done multiple times daily in people with T1D.

#### 6.5.2 Risks and Side Effects of Treatment

Serious adverse effects are rare with metformin administration. Known adverse effects associated with metformin are primarily gastrointestinal (diarrhea, nausea, vomiting, abdominal bloating, flatulence, anorexia). Other rare effects are hematologic (reduced vitamin B12 levels and anemia), increased risk of hypoglycemia, and the very rare possibility of lactic acidosis. Metformin-induced hematologic risks are more associated with long-term use of the drug and appear to be rapidly reversible with discontinuation and vitamin B12 supplementation. Hematologic risks are not expected to occur with short-term use and are minimized by excluding patients with a history of anemia or B12 deficiency. Hypoglycemia risks are minimized by excluding participants with very low HbA1c levels and by
carefully following glucose levels. Serum lactate will be measured if a participant becomes sick and an assessment is deemed necessary by the clinic investigator (See section 1.4 for review of literature on side effects). Lactic acidosis is minimized by excluding participants with renal or liver dysfunction and by stopping metformin for severe illness, hypoxia, or administration of IV contrast. Participants will be advised to not drink alcohol while taking the study treatment.

6.5.3 Overdosage
With mild to moderate toxicity, nausea, vomiting, abdominal pain, low blood sugar, malaise, and myalgias may occur. With severe toxicity, severe lactic acidosis, confusion, mental status depression, hypothermia, hypotension, and renal failure may develop. Rarely, ventricular dysrhythmias, respiratory insufficiency, and death will occur.

6.5.4 Other Risks
There is the unlikely chance that your information is viewed by someone outside the research team who is not authorized to see your health information. However, we make special efforts to make sure that this does not happen.

6.5.5 Risk Assessment
It is the investigators’ opinion that this protocol falls under DHHS 45 CFR 46.405 and 21 CFR 50.52, which involves greater than minimal risk presenting the prospect of direct benefit to the individual participant. In addition, it is the belief of the investigator that this study also presents prospect of general benefit to others with T1D who are overweight and have reduced insulin sensitivity.
The approach to sample size and statistical analyses are summarized below. The analysis plan synopsis in this chapter contains the framework of the final analysis plan.

7.1 Sample Size Estimation

Primary outcome: Mean change in HbA1c at 26-weeks, adjusted for baseline HbA1c.

Data from the Sarnblad 2003 (46) study in adolescents and the T1D Exchange clinic registry were used to estimate the standard deviation of HbA1c. Data from the JDRF CGM study (53) was used to estimate the correlation between baseline HbA1c and 26-week HbA1c. In the Sarnblad 2003 (46) study on metformin use in adolescents, the 3-month mean±SD HbA1c for the control group (n=13) was 9.2±1.3%. When limiting the T1D Exchange clinic registry population to participants age 12-<20 yrs with duration of T1D ≥1 year, a BMI >85th percentile and HbA1c 7.5% - <10.0% at enrollment (N=1820) the mean±SD HbA1c was 8.6±0.6. When limiting the JDRF CGM (53) study population to control group participants age 12-<20 yrs with an HbA1c ≥7.5% at baseline (N=31), the mean±SD of the 26-week HbA1c was 8.1%±0.8%. The estimated correlation between baseline and 26-week HbA1c using data from the JDRF CGM study is 0.56.

Assuming two-tailed test with type I error rate of 5%, power of 90% and a correlation between baseline and outcome of 0.56 gives the following sample size estimates:

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Difference in Mean HbA1c</th>
<th>Total Sample Size* for various Standard Deviations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.7%</td>
</tr>
<tr>
<td>1.0%</td>
<td>18</td>
<td>32</td>
</tr>
<tr>
<td>0.5%</td>
<td>60</td>
<td>118</td>
</tr>
<tr>
<td>0.3%</td>
<td>160</td>
<td>324</td>
</tr>
</tbody>
</table>

*Sample size is adjusted for correlation between baseline and 26-week HbA1c

The sample size needed to detect a difference in HbA1c between groups, assuming that the true population value is 0.5%, with 5% type I error rate and 90% power is 118. After increasing the sample size by 15% to account for loss to follow up, the required number of participants per treatment group is 68 for a sample size of 136 participants.

7.2 Efficacy Analysis Plan

7.2.1 Primary Analysis

The primary analysis will be a treatment group comparison of mean change in HbA1c obtained at the 26 week primary outcome visit adjusted for baseline HbA1c in an analysis of covariance (ANCOVA) model. Participants enrolled in the ancillary clamp protocol will not be included in the primary analysis.

The primary analysis will follow the intent-to-treat principle. The data of all randomized patients will be included in the analysis regardless of whether the assigned treatment was actually received, according to randomization group.

A per-protocol sensitivity analysis also will be performed. The per-protocol analysis will only include participants in both treatment groups who were able to tolerate at least 1000 mg of metformin per day over the entire 26 weeks and were still using metformin at the 26 week visit.

Imbalances between groups in important covariates are not expected to be of sufficient magnitude to produce confounding. However, the presence of confounding will be evaluated in regression models for baseline characteristics that are not balanced between treatment groups.

Multiple imputation using Rubin’s method (54) will be used to impute the HbA1c outcomes that are missing. The primary analysis will be repeated including data from participants with no imputation for missing data. The results will be compared with those using imputation to verify that conclusions are not sensitive to the method for handling missing data.
7.2.2 **Secondary Efficacy Analyses**

Secondary analyses will include treatment group comparisons of the following:

1. Sensor data.
   - Treatment group comparisons of the mean change from baseline to 26-week visit will be made for the following CGM outcomes:
     - % of time glucose is in range 71-180mg/dl
     - Coefficient of variation and AUC
     - % of time glucose is ≤70 mg/dl
     - % of time glucose is >180 mg/dl

2. Change in total daily dose of insulin per kg
3. Change in BMI percentiles, waist circumference, and body composition (as measured by DEXA scan)
4. Change in serum lipids
5. Change in blood pressure
6. Change in insulin sensitivity
   - A treatment group comparison of the change in insulin sensitivity from baseline to the 26-week visit will be assessed using the following formula to estimate insulin sensitivity: \( \log_{10} IS = 4.64725 - 0.02032 \times (\text{waist, cm}) - 0.09779 \times (\text{HbA1c, %}) - 0.00235 \times (\text{Triglycerides, mg/dl}) \) (55).

7. PCOS:
   - The mean change in levels of the following testosterone panel results will be compared between treatment groups among females:
     - Total testosterone
     - Percent free testosterone
     - Free testosterone
     - Sex hormone-binding globulin

8. Change in adipocytokines
9. Change in C-peptide measured through MMTT on participants with detectable C-peptide on non-fasting C-peptide (expected that between 25% and 50% of participants will have an MMTT performed)
10. Change in pro-insulin:C-peptide ratio and pro-insulin:insulin ratio for participants with MMTT performed at baseline and 26-weeks
11. Change in vascular function among participants enrolled at sites with an Endo-PAT machine (expected that approximately 70 participants will have Endo-PAT test performed)

   - RH-PAT score will be used to assess changes in endothelial function. The augmentation index also may be collected for assessment of change in vascular stiffness.
   - Correlations between change in vascular function and change in other outcomes of interest will be assessed.

Both the primary and secondary efficacy analyses will be conducted at 13 week visit, if assessments were performed, and will mirror the analyses at the primary outcome visit.

7.2.3 **Treatment Effect in Subgroups/Assessment of Interaction**

The treatment effect at the primary outcome visit, in subgroups based on baseline factors, will be assessed in pre-planned secondary analyses. These analyses will be conducted to determine whether a similar trend of the overall treatment effect is seen in these subgroups. The study is not expected to have sufficient statistical power for definitive conclusions in subgroups and statistical power will be low to formally assess for the presence of interaction.

The general approach for these exploratory analyses will be to perform analyses within each subgroup similar to the methods described earlier for the overall primary and secondary efficacy analyses.

The planned subgroups for analyses are as follows:

1. HbA1c at time of randomization (7.5%-<9.0% vs. 9.0% -<10.0%)
2. Age (12-<15 yrs vs. 15-<20 yrs)
3. Gender (male vs. female)
4. Race/Ethnicity (‘white non-Hispanic’ vs. ‘non-white or Hispanic’)
5. BMI (overweight 85th -<95th percentile vs. ≥95th percentile)
6) Total daily insulin per kg
7) Tanner staging

7.2.4 Additional Tabulations and Analyses

The following will be tabulated according to treatment group unless otherwise stated:

1) Baseline demographic and clinical characteristics
2) Visit and phone contact completion
3) Baseline HbA1c data for completers vs. non-completers of the primary outcome visit
4) Compliance with study drug as evidenced by pill counts and investigator impression over follow-up visits
5) Protocol deviations

7.3 Safety Analysis Plan

7.3.1 Specific Safety Outcomes

The following safety outcomes will be tabulated and compared between the metformin and placebo group for analysis of safety:

1) Liver enzymes
   - The proportion of participants with >2.5 times the upper limit of normal:
     a) Normal limit: Aspartate transaminase (AST): 65 U/L (Male), 46 U/L (Female)
     b) Alanine transaminase (ALT): 65 U/L (Male), 50 U/L (Female)
2) Serum Creatinine
   - The proportion of participants who are above the upper limit of normal for an adult:
     a) Normal limit: 1.2 mg/dL (Male), 1.1 mg/dL (Female)
3) Lactic acidosis
   - Proportion of participants with detected lactic acidosis (measured if a participant becomes ill)
4) Severe hypoglycemia
   - Proportion of participants with a severe hypoglycemic event defined as an episode requiring assistance or involving seizure/loss of consciousness
5) DKA
   - Proportion of participants with DKA defined as having hyperglycemia and meeting ALL of the following criteria:
     a) Symptoms such as polyuria, polydipsia, nausea, or vomiting
     b) Serum ketones or large/moderate urine ketones
     c) Either arterial blood pH <7.30 or venous pH <7.30 or serum bicarbonate <15
     d) Treatment provided in a health care facility

7.3.2 Adverse Events

Adverse events will be tabulated by treatment group.

An estimate and 95% confidence interval by treatment group of the following proportions will be obtained using the exact binomial method and a Fisher’s exact test will be used to evaluate whether there is a treatment group difference in the proportion of participants with events, although the power for some of the comparisons is expected to be low.

- Proportion reporting at least one event
- Proportion with an adverse event thought by investigator to be related to study drug
- Proportion who stopped study drug in response to an adverse event

The mean, standard deviation, and median for the following will be tabulated by treatment group and an exact Wilcoxon-Rank-Sum Test will be used to evaluate whether there is a difference between groups.

- Total number of events reported
- Total number of new events reported
- Number of serious events reported
- Number of non-serious adverse events reported
CHAPTER 8: REFERENCES


38. Steinberg HO, Baron AD. Vascular function, insulin resistance and fatty acids. Diabetologia. 2002;45:623-34.


