A Pilot Study to Evaluate the Safety of Terbutaline in Children with Type 1 Diabetes

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CHAPTER 1
INTRODUCTION

1.1 Background Information

DirecNet is planning to conduct a randomized clinical trial to evaluate whether bedtime administration of the epinephrine simulating β_2-adrenergic agonist terbutaline can reduce the incidence of nocturnal hypoglycemia without compromising glycemic control in youth with type 1 diabetes (T1D). As a prelude to the trial, we will be conducting a small, short-term, inpatient-outpatient pilot study of 10 pediatric subjects with T1D.

1.1.1 Hypoglycemia in T1D

Iatrogenic hypoglycemia, the result of the interplay of therapeutic hyperinsulinemia and compromised physiological and behavioral defenses against falling plasma glucose concentrations, is the limiting factor in the glycemic management of T1D (1). It causes recurrent morbidity in most patients, and is sometimes fatal. It impairs defenses against subsequent falling plasma glucose levels and thus causes a vicious cycle of recurrent hypoglycemia. It precludes maintenance of euglycemia over a lifetime of diabetes and thus full realization of the long-term benefits of glycemic control. The latter will ultimately require plasma glucose regulated insulin replacement or secretion.

Many studies have reported the vulnerability of children to hypoglycemic episodes that result in seizures and coma (2-4). There are a number of factors that contribute to the risk of hypoglycemia in young children and adolescents, including irregular patterns of eating and physical activity, poor compliance with SMBG, the insulin resistance of puberty, as well as the inability to recognize, report and manage a low blood glucose by the very young child. Repeated episodes of hypoglycemia have been correlated with lower intellectual function (5-7) and brain MRI changes, especially in children with an early onset of diabetes (8).

Episodes of hypoglycemia, even if asymptomatic, increase the risk of subsequent hypoglycemia substantially in T1D (9-11). Because of β-cell failure the first two physiological defenses against hypoglycemia, a decrement in insulin and an increment in glucagon, are lost in T1D. Following an episode of hypoglycemia (or following exercise or during sleep) the sympathoadrenal (adrenomedullary and sympathetic neural) response is attenuated. Thus, the third physiological defense, an increase in epinephrine, is compromised (causing the syndrome of defective glucose counterregulation). In addition, the behavioral defense, carbohydrate ingestion, is compromised largely as a result of the attenuated sympathetic neural response (causing the syndrome of hypoglycemia unawareness). These syndromes – defective glucose counterregulation and hypoglycemia unawareness – are the components of hypoglycemia-associated autonomic failure (HAAF), and constitute the basis of the pathogenesis of iatrogenic hypoglycemia, in T1D.

Most episodes of hypoglycemia occur during the night, specifically during sleep, in T1D (11). That is typically the longest interprandial period and time between self plasma glucose monitoring. It is also the time of maximal sensitivity to insulin (12). Furthermore, sympathoadrenal responses to hypoglycemia are reduced further during sleep (13; 14) and, perhaps because of that, people with T1D are much less likely to be awakened by hypoglycemia than nondiabetic individuals (13; 15). Although nocturnal hypoglycemia can be symptomatic and even severe, it is often asymptomatic. However, even asymptomatic nocturnal hypoglycemia causes attenuation of the sympathoadrenal and resulting symptom responses to hypoglycemia the following day (16; 17). Thus, it follows that, all other factors being equal, reducing nocturnal hypoglycemia will also reduce daytime hypoglycemia. Furthermore, it follows from the pathophysiology (1; 18) that reducing hypoglycemia will improve defenses against subsequent hypoglycemia and therefore, allow

improved glycemic control.

1.1.2 Terbutaline

The use of terbutaline to prevent iatrogenic hypoglycemia is based on the pathophysiology of defense against hypoglycemia in T1D: an attenuated plasma epinephrine response to falling plasma glucose concentrations is a key feature of defective glucose counterregulation (1; 18) which is associated with a 25-fold (19) or greater (20) increased risk of severe hypoglycemia during aggressive glycemic therapy of adults with T1D. The plasma glucose raising actions of epinephrine – increased hepatic and renal glucose production, limited glucose clearance by insulin sensitive tissues such as muscle, and mobilization of gluconeogenic precursors from muscle and fat to the liver and kidneys – are mediated through β_2-adrenergic receptors in people with T1D (in whom α_2-adrenergic inhibition of insulin secretion is inoperative) (21). Terbutaline is a β_2-adrenergic agonist. Nonetheless, unlike endogenous epinephrine but like other putative preventive bedtime treatments, the glycemic actions of administered terbutaline are not plasma glucose regulated.

Terbutaline (also known as Brethine®) has been primarily used for the treatment of asthma, priapism and preterm labor. It has been FDA approved in children for the treatment and prophylaxis of asthma and bronchospasm for more than 3 decades (1974). Its mechanism of action in asthma is by relaxing smooth muscle by action on β_2 receptors with less cardiac effect. Terbutaline has been used in oral, inhaled and subcutaneous forms. The oral form is less bioavailable and is associated with fewer side effects. The half life of the oral form is ~5.7 hours (range 2.9 -14 hours). It comes in 2.5 mg and 5 mg scored tablets. The dose of oral terbutaline for the treatment of asthma in children older than 15 years old and adults is 5mg PO TID; for those children between 12 and 15 years old, it is dosed 3 times a day at a usual dose of 2.5 mg PO/dose, not to exceed 7.5 mg PO QD; and in children 6 to 12 years old it is prescribed at 0.05 - 0.15 mg/kg/dose 3 times a day to a maximal dose of 5 mg/24 hours (6). It also seems that children have a shorter terminal half life than adults and a slightly higher weight corrected clearance than adults (7).

The use of this medication should be avoided in patients with glaucoma, hyperthyroidism, cardiovascular disease, hypokalemia or seizure disorders. Its action interacts with MAO inhibitors tricyclic antidepressants and β-blockers. The common side effects of its continuous use are: (>10%) nervousness, restlessness, high blood glucose, trembling, decreased potassium. (1-10%): tachycardia, hypertension, dizziness, insomnia, headache, diaphoresis, muscle cramps. (<1%): arrhythmias, paradoxical bronchospasm.

Terbutaline does not raise plasma glucose concentrations in nondiabetic individuals because they secrete insulin (22; 23). In adults with T1D, however, terbutaline raises plasma glucose concentrations substantially when administered 1) to insulin infused, initially euglycemic patients (23), 2) during hypoglycemia induced by injection of regular insulin (24), 3) at bedtime following injection of NPH insulin (25), and 4) at bedtime in patients treated aggressively with contemporary methods (CSII or MDI with insulin analogues) (26).

A shift of the sympathoadrenal response to hypoglycemia to lower plasma glucose concentrations, rather than reduced tissue sensitivity to the actions of epinephrine, norepinephrine and acetylcholine, is the common mechanism by which antecedent hypoglycemia, exercise or sleep contribute to HAAF. There is substantial evidence that whole body metabolic (and hemodynamic) sensitivity to epinephrine is not reduced in patients with T1D (27). Similarly, local adipose and skeletal muscle metabolic sensitivity to a β_2-adrenergic agonist does not appear to be reduced (28; 29). Berk and colleagues (27) confirmed that glycemic sensitivity to epinephrine is increased in

patients with T1D, but found it to be comparable in patients with T1D and nondiabetic individuals when the latter, like the T1D subjects, could not increase insulin secretion.

In a study of 21 adults with aggressively treated T1D (mean ± SD HbA_{1C}=7.1±1.0%), compared with no bedtime treatment, bedtime (2200h) terbutaline (5.0 mg orally) 1) raised the mean nadir nocturnal plasma glucose concentration (from 75±9 to 127±11 mg/dL, P<0.001) and 2) eliminated nocturnal glucose levels <50 mg/dL (P=0.038), reduced levels <60 mg/dL to a single measurement (P=0.005) and reduced those <70 mg/dL to five measurements, all at 2215h and 2230h (P=0.001) (26). Thus, for practical purposes, terbutaline prevented nocturnal hypoglycemia. (In contrast, neither a conventional bedtime snack nor bedtime administration of uncooked cornstarch raised the mean nadir nocturnal plasma glucose concentrations or reduced the number of glucose levels <40, <50, <60 or <70 mg/dL.) Therefore, efficacy of bedtime terbutaline in youth with T1D seems likely, at least initially. In this study, bedtime terbutaline (5.0 mg), compared with no bedtime intervention, raised mean (±SE) heart rates (79 ±2 vs.71+2 bpm,P=0.003) and blood lactate concentrations (1440 ±230 vs.740±80µmol/L, P=0.016) at 0700h the following morning (18). Blood pressure and levels of NEFA, β-hydroxybutyrate and counterregulatory hormones were unaltered. Symptoms were not assessed systematically, but none were noted.

Obviously, several issues remain to be clarified. First, in adults with T1D the 5.0 mg terbutaline dose, while it prevented nocturnal hypoglycemia, caused hyperglycemia the following morning (25; 26). Mean plasma glucose concentrations at 0700h were 37% higher than those at 2200h, just before terbutaline administration the previous night (26). Therefore, the optimal use of terbutaline will likely require lower, but still efficacious, drug doses, increased overnight insulin dosing, or both. Second, terbutaline has cardiovascular and nonglucose metabolic effects (23-25; 30). For example, mean heart rates were 11% higher and mean blood lactate concentrations were 95% higher at 0700h after bedtime terbutaline than after no bedtime intervention (30). While mean morning serum NEFA levels were not elevated significantly in that study (30), they were elevated following terbutaline administration in other studies (23-25); similarly, blood β-hydroxybutyrate levels were elevated in one study (23). Thus, careful attention to maintenance of metabolic control will be needed during long-term terbutaline administration. Third, to date the glucose raising effect of terbutaline has been studied only in single bedtime doses. Theoretically, daily terbutaline dosing could result in β_2-adrenergic receptor down regulation and, therefore, tachyphylaxis to its plasma glucose raising actions. However, that apparently did not limit use of the drug in the treatment of asthma, and it might be less likely with once daily (i.e., bedtime), rather than multiple daily, drug administration. Fourth, simply reducing insulin doses would reduce nocturnal hypoglycemia but that would compromise glycemic control. Our premise is that producing, in essence, a degree of resistance to insulin action during the night will, by reducing hypoglycemia, permit improved glycemic control. Obviously, that hypothesis remains to be tested.

1.1.3 Safety of Terbutaline in Nondiabetic Children

Although among the known side effects of continuous use of terbutaline in adults are hypersensitivity reactions, elevation in serum glucose, blood pressure and heart rate, CNS stimulation with restlessness and insomnia, increased intraocular pressure, tremors, hypokalemia, and headaches (6), there are vast data and experience with the use of this drug in pediatrics that assures its safety in children.

A double blind parallel study in 32 children 7-14 years of age studied the safety and effectiveness of terbutaline 2.5 mg PO three to four times a day vs. ephedrine in children with chronic asthma and showed that there were no adverse effects including tachyphylaxis and tremor during the three month study period (8). A prospective double-blind crossover study in 24 asthmatic children using

terbutaline 5mg, theophylline 200 mg, the combination of both, or placebo, each given twice daily for 28 days, showed that the side effects were mild (Table 1) (11).

Table 1 4. Adverse Events During Study Period*

Adverse Events	Placebos	Terbutaline	Theophylline	Both Drugs
Sleep disturbance	0	0	4	1
Headache	0	4	4	1
Abdominal pain	0	3	0	1
Vomiting	3	1	0	4
Fever	1	5	2	2
Convulsion	0	0	1	0
Palpitation	0	0	1	0
Dizziness	2	1	0	2
Diarrhea	1	0	0	0
General malaise	1	0	1	0

* Results are numbers of events.

Although tremor is one of the main limiting side effects of oral therapy with terbutaline in adult patients (9; 10), it was not reported by any of the pediatric subjects studied (11). Furthermore, the Bambuterol Multicenter Study Group (14) evaluated the safety of terbutaline and bambuterol (a terbutaline prodrug) for a year in 141 children 2-12 years of age in an open, randomized, parallel group design, and found that both drugs were well tolerated and tremor was not reported by any of the subjects 5-12 years old on terbutaline at 2.5 mg PO TID or in those 2-5 years of age receiving terbutaline at a dose of 0.075 mg/kg/TID. Despite the mean plasma terbutaline concentrations being above the therapeutic levels 10.6-15.2 nmol/L, the most frequently reported adverse events in the terbutaline group were not drug related: otitis media (42%), respiratory infection (28%) and conjunctivitis (19%). This multicenter study group also evaluated the safety in 155 children 2-5 years old with asthma over a 3-month period (13), and noted that although both treatments showed good tolerability and safety profile with respect to clinical and laboratory tests, restlessness was the most frequent adverse event, (86% of the patients in the terbutaline group). In most of these studies blood pressure did not change relative to baseline and heart rate increased minimally (4-8bpm) (8; 11; 13; 14). Tremor, as well as other of the side effects noticed with this drug tends to disappear within a few days or within 1-2 weeks of its use in adults (12). For this reason, we anticipate that terbutaline will be well tolerated and safe in children, but believe that a study with outpatient dosing of terbutaline over a period of time is critical to determine the adverse events and tolerability of bedtime administration of the drug in the diabetic population.

1.2 Study Objectives

This pilot study is being conducted as a prelude to conducting a randomized trial. The purpose of the study is to gain experience with the use of terbutaline in children with T1D and to determine that there is not a frequent serious, unexpected, uncontrollable effect on short-term glycemic control. Some information also will be obtained with regard to whether terbutaline, in the dosing being used in the study, is sufficiently well tolerated to expect that adherence will be satisfactory in a large randomized trial. In addition, this pilot study will provide data on the accuracy of a continuous glucose monitor during terbutaline use to verify that the drug does not impact on sensor function.

1.3 Synopsis of Study Protocol

1.3.1 Study Design/Sample Size: Pilot study including 10 subjects with type 1 diabetes for at least one year using daily basal:bolus insulin therapy, age 12 to <18 years, HbA1c $\leq$8.0%.

1.3.2 Summary of Protocol

1. After eligibility is determined, informed consent and assent are obtained from the parent/guardian and subject.
2. An unblinded CGM will be used and blood ketones will be checked each morning by the subject for at least one week. Subjects may be asked to wear an Actiwatch monitor each night.
3. Terbutaline will be initiated during a CRC admission and continued following the CRC stay for 21-28 days.
   - Subjects weighing between 25 and 45 kg will be treated with a nightly oral dose of 2.5 mg and subjects who weigh more than 45 kg will be treated with 3.75 mg.
4. The CRC admission will last approximately 18-20 hours and include the following:
   - Monitoring of effects of terbutaline by measurement of heart rate, blood pressure, blood and interstitial glucose, lactate, ketones, NEFA, B-OH butyrate
   - Assessment of the accuracy of the CGM by comparing sensor glucose values to blood glucose values
5. The outpatient phase will last 21-28 days and include the following:
   - Nightly use of terbutaline as described above
   - Use of an unblinded CGM on a daily basis to monitor the glucose levels
   - Subjects may be asked to wear the Actiwatch monitor overnight
   - Measurement of blood ketones each morning
   - Phone calls to each subject on the first outpatient day of terbutaline use and then approximately every 3 days (twice a week) until the end of the subject's follow up.
6. Second CRC admission to mirror the first admission between 21 and 28 days after initiation of terbutaline
7. Follow up for 1-2 weeks after discontinuation of terbutaline until glucose control is back to prestudy level.

CHAPTER 2
SUBJECT ELIGIBILITY AND ENROLLMENT

2.1 Study Population

Ten subjects will be enrolled in this study at five clinical centers with 2 enrolled at each center.

2.2 Eligibility and Exclusion Criteria

2.2.1 Eligibility

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

1) Clinical diagnosis of type 1 diabetes and using daily insulin therapy for at least one year
   The diagnosis of type 1 diabetes is based on the investigator's judgment; C peptide level and antibody determinations are not needed.
2) Age 12.0 years to less than 18.0 years
3) HbA1c $\leq$8.0%
   - Measured with DCA2000 or equivalent device
4) Use of basal: bolus insulin therapy with either an insulin pump or glargine with MDI of a short-acting insulin for at least 6 months (approximately 5 pump and 5 MDI users will be enrolled)
   - For subjects using MDI, NPH and Lente cannot be part of the insulin regimen.
5) Availability of home computer to download the CGM
   - Subjects will be required to have internet access to email the files or the ability to print and fax the files
6) For females: not currently pregnant, negative pregnancy test, and not intending to become pregnant during the next 3 months
7) Parent/guardian and subject understand the study protocol and agree to comply with it
8) Informed Consent Form signed by the parent/guardian and Child Assent Form signed by the subject if required by IRB

2.2.2 Exclusion

The presence of any of the following is an exclusion for the study:

1) Severe hypoglycemic event (seizure or coma) or diabetic ketoacidosis in the past 6 months
2) Cardiac disease, including prolonged QT interval on EKG or pathologic arrhythmia
   - An EKG will be done either prior to the CRC admission or during the CRC admission prior to the first dose of terbutaline
3) Treatment for hypertension orblood pressure exceeding the 90^{th} percentile for age and height
4) Current treatment for a seizure disorder
5) Asthma if treated with systemic or inhaled corticosteroids in the last 6 months or with a beta adrenergic agonist more than once a month
6) Cystic fibrosis
7) Use of MAO inhibitors, tricyclic antidepressants, or beta blockers
8) Current use of oral/inhaled glucocorticoids or other medications, which in the judgment of the investigator would be a contraindication to participation in the study.
9) Inpatient psychiatric treatment in the past 6 months for either the subject or the subject's primary care giver (i.e., parent or guardian).
10) Medical condition that in the judgment of the investigator might interfere with the completion of the protocol

- *Adequately treated thyroid disease and celiac disease do not exclude subjects from enrollment*

2.3 Patient Enrollment and Baseline Data Collection

Potential subjects 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 Historical Information and Physical Exam

A history will be elicited from the subject and parent and extracted from available medical records with regard to the subject's diabetes history and current diabetes management. A standard physical exam (including vital signs and height and weight measurements) will be performed by the study investigator or his or her designee (a pediatric endocrinologist, pediatric endocrine fellow, or a pediatric endocrine nurse practitioner).

An EKG will be performed either before or during the CRC admission (prior to the first dose of terbutaline).

2.3.2 Informed Consent

For eligible subjects, the study will be discussed with the subject and parent/legal guardian (referred to subsequently as 'parent'). The parent will be provided with the Informed Consent Form to read and will be given the opportunity to ask questions. If needed based on local IRB requirements, subjects will either be given the Child Assent Form to read or it will be read to the child. If the parent and child agree to participate, the Informed Consent Form and Child Assent Form (if necessary) will be signed. A copy of the consent form will be provided to the subject and his/her parent and another copy will be added to the subject's clinic chart.

Written informed consent must be obtained from the parent or guardian prior to performing any study-specific procedures that are not part of the subject's routine care.

2.3.2.1 Authorization Procedures

As part of the informed consent process, each subject will be asked to sign an authorization for release of personal information. The investigator, or his or her designee, will review what study specific information will be collected and to whom that information will be disclosed. After speaking with the subject and their parent, questions will be answered about the details regarding authorization.

2.3.2.2 Special Consent Issues

The study population for this study includes children and adolescents. The consent form and study procedures will be discussed with each subject at a level in which they can understand. The study staff will ask questions of each subject to assess the autonomy and understanding of the study. Each subject will be asked to sign an assent form, if appropriate for the subject's age and required by the local IRB. Additionally, the parent(s) and/or guardian(s) of each subject will be asked to sign the consent form. They will be given the opportunity to ask questions throughout the study on all study related procedures.

2.4 Enrollment Procedures

Subjects will be enrolled by the entering of data on the DirecNet website where eligibility will be confirmed.

2.5 Initiation of CGM Use

The subject and parent will be instructed on use of the CGM and will be provided with a manual describing its calibration and use. A CGM sensor will be placed. The CGM will be used unblinded until the time of the CRC admission in 7 to 14 days.

The subject also will be provided with a study home glucose meter (HGM) and test strips to be used during the study and a blood ketone meter and strips for morning testing for the week prior to the CRC admission.

Subjects may be asked to wear an Actiwatch each night. The Actiwatch is a device that is the size of a standard wrist watch and measures movement.

The subject will be asked to download the CGM from home prior to the CRC admission to verify that the sensor is working and sufficient baseline data are available.

The subject will be asked to insert a new sensor on the day prior to the CRC admission.

Subjects who are unable to successfully use the CGM on at least 5 of 7 days prior to the CRC admission will not be continued in the study.

CHAPTER 3
INITIAL INPATIENT CRC ADMISSION

3.1 Overview

The CRC admission will occur 7 to 14 days after the visit at which the CGM use was initiated.

- Subject will arrive in the CRC prior to dinner time.
- The CGM will be downloaded and the data evaluated to verify that there are at least 96 hours of data.
- A second CGM sensor will be inserted.
- An intravenous catheter will be inserted for reference glucose measurements.
- Dinner and dinner-time insulin will be given.
- At 9 p.m., an oral dose of terbutaline will be given (see section 5.1).
- Blood glucose measurements will be made every 30 minutes from 9 p.m. to 12 noon the next day.
- Monitoring of effects of terbutaline will include measurement of heart rate, blood pressure, blood and interstitial glucose, lactate, ketones, NEFA, B-OH butyrate.
- The subject will be discharged the next day prior to lunch at approximately 12 noon.

3.2 CGM Management and Procedures

At the time of CRC admission, the CGM and HGM will be downloaded.

- If there are fewer than 96 hours of sensor data, the subject will either need to repeat the baseline CGM use or be discontinued from the study.
- If the sensor has been used for fewer than 5 out of the 7 days preceding the CRC admission, the subject will not be continued in the study unless there is a reason for lack of use that is not related to compliance and the likelihood that the subject will use the sensor regularly during the outpatient phase.

A second CGM will be inserted and calibrated after admission to the CRC.

The CGMs will be downloaded before the subject is discharged from the CRC. One of the sensors will be removed and the other will remain in place for start of the outpatient phase.

If a CGM sensor stops functioning during the evening prior to bedtime, it will be replaced. Otherwise, it will not be replaced as long as there is one functioning sensor.

3.3 Blood Glucose Measurements

Venous blood samples will be obtained for central laboratory glucose measurements. An intravenous catheter will be inserted in an arm vein. The area where the catheter will be inserted may be numbed with Elamax or EMLA cream prior to catheter insertion.

A home glucose meter, YSI, Beckman, or other device will be used to measure the blood glucose for immediate management decisions.

The blood samples for glucose measurements will be collected on the half-hour from 9 p.m. to 12 noon.

If a subject reports symptoms of hypoglycemia, a CGM hypoglycemia alarm occurs, or the CGM value is <60 mg/dL, the blood glucose will be checked. When the blood glucose is <60 mg/dL, the subject will receive treatment for hypoglycemia. Additional glucose measurements will be made as needed until the blood glucose is >70 mg/dL.

3.4 Diabetes Management, Activity, and Diet

Insulin management will follow the same routine that the subject was following at home prior to the hospitalization.

Subjects will be permitted to perform their usual indoor activities during the hospitalization.

The prescribed diet will be at the discretion of the investigator. The same diet for dinner and breakfast will be given during both CRC admissions.

3.5 Monitoring of Effects of Terbutaline

Terbutaline will be given orally at 9 p.m.

Blood pressure and pulse will be measured at the time of admission, prior to breakfast the next morning and prior to discharge.

Blood samples will be drawn and saved for possible measurement of terbutaline, lactate, NEFA, and B-OH at the following times: 9 p.m. (prior to the dose of terbutaline), 9:30 p.m., 1 a.m., and 7 a.m. (prior to breakfast).

CHAPTER 4
OUTPATIENT PHASE

4.1 Terbutaline

Terbutaline will be taken orally each day prior to bedtime. Further details are provided in chapter 5.

4.2 CGM Use

Each subject will continue to use a CGM, with instructions to use it as close to 24/7 as possible.

Prior to each phone call, the subject will be instructed to download the CGM and either email or fax the file to the clinic so that the glucose data can be reviewed during the phone contacts.

4.3 Home Glucose Meter and Ketone Meter

Each subject will be provided with an HGM and test strips. The HGM will be used for calibration of the CGM and to confirm high and low values on the CGM prior to acting on them. It will be downloaded at the end-of-study CRC admission.

The subject will be asked to measure blood ketones each morning using the meter and strips that will be provided.

4.4 Actiwatch Monitor

Each subject may be asked to wear an Actiwatch each night to measure movement while the subject is sleeping.

4.5 Adjustments in Diabetes Management

The use of terbutaline may produce hyperglycemia. Frequent phone calls will be made to the subject to review the glucose profile and make changes as needed in insulin management.

Subjects will be advised to contact the clinical center at any time should the glucose be uncontrollable with their usual approach.

4.6 Phone Contacts

Phone calls to each subject will be made after the first outpatient day of terbutaline use and then approximately every 3 days (twice a week) until the end of the subject's follow up plus an about 7 days after terbutaline is discontinued.

The primary purpose of the calls will be to review the subject's glycemic control and any side effects that are occurring that could be attributable to terbutaline.

On each phone call, the subject will be asked to verify that the CGM is working properly.

4.7 Follow-up Visits

Prior to the end-of-study CRC admission, follow-up visits can occur at any time at the discretion of the investigator.

CHAPTER 5
TERBUTALINE

5.1 Dose

Each subject will be treated with terbutaline for 21-28 days following the initiation of treatment during the CRC admission.

Subjects weighing between 25 and 45 kg will be treated with a nightly oral dose of 2.5 mg and subjects who weigh more than 45 kg will be treated with 3.75 mg.

The standard 2.5 mg terbutaline tablets available in a pharmacy will be used in the study, with subjects taking either 1 or 1.5 tablets nightly.

5.2 Monitoring of Side Effects

The occurrence of side effects will be solicited during each phone contact and at the follow-up visit.

5.3 Changes in Dose

If in the investigator's judgment the terbutaline dose is not being tolerated, it can be reduced or discontinued for an individual subject.

If the terbutaline side effect profile indicates that the dose is not being sufficiently tolerated before all 10 subjects have been enrolled, the dose may be decreased for subsequent subjects with the approval of the Data and Safety Monitoring Board (DSMB).

If none of the first 4 subjects have an overnight elevation of blood sugar, which is the initial expected effect of terbutaline, during the initial CRC admission, consideration will be given to increasing the dose of subsequent subjects to 3.75 mg for the subjects weighing 25-45 kg and to 5.0 mg for subjects weighing >45 kg. An increase in dose will require approval of the DSMB prior to implementing.

CHAPTER 6
END-OF-STUDY CRC ADMISSION

6.1 Overview

The end-of study CRC admission will occur after 21-28 days of the outpatient phase.

The protocol will be identical to the protocol for the first CRC admission described in chapter 3.

The dinner and breakfast meals will be identical to the meals given during the first admission.

6.2 Study Completion

The sensors will be removed prior to discharge, unless the investigator decides it would be beneficial to continue a CGM for 1-2 weeks to assist in the maintenance of glucose control after terbutaline has been stopped.

There will be a phone contact approximately 7 days after discharge to review diabetes management and collect any additional adverse event data. Additional contacts will be made, if necessary, until the prestudy level of glucose control is achieved.

CHAPTER 7
ADVERSE EVENTS

7.1 Definition

An adverse event is any untoward medical occurrence in a study subject, irrespective of whether or not the event is considered treatment or device-related.

Adverse events will be reported that occur up to 30 days after discontinuation of study treatment and device use.

7.1.1 Reporting of Hypoglycemic and Hyperglycemic Events as Adverse Events

Hypoglycemic events are recorded as adverse events if the subject required assistance from another person to administer carbohydrate, glucagon or other resuscitative actions. This means that the subject 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. The hypoglycemic event is classified as a serious adverse event if it resulted in seizure, loss of consciousness, coma, or hospitalization.

Hyperglycemic events are recorded as Adverse Events if the event involved DKA as defined by DCCT:

- Symptoms such as polyuria, polydipsia, nausea, or vomiting;
- Serum ketones >1.1 mM 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

7.2 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 subject, and appropriate medical intervention will be made.

The investigator will elicit reports of adverse events from the subject at each visit and complete all adverse event forms online. 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 study device or study procedures.

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 a serious adverse event. For example, itching for several days may be rated as severe, but would not be considered a serious adverse event.

Adverse events will be coded using the MedDRA dictionary.

Definitions of relationship and intensity are listed on the website data entry form.

Adverse events that continue after the subject'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.

7.3 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
- Is a congenital anomaly/birth defect

An *Unanticipated Adverse Event* is defined as an adverse event caused by, or associated with, the study drug or device, if that effect or problem was not previously identified in nature, severity, or degree of incidence.

Serious or unexpected adverse events must be reported to the Coordinating Center immediately via completion of the online serious adverse event form.

The Coordinating Center will notify all participating investigators of any adverse event that is both serious and unexpected. Notification will be made within 10 days after the Coordinating Center becomes aware of the event.

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

7.4 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board will approve the protocol prior to its initiation and will be informed of all serious adverse events and any unanticipated, related adverse events that occur during the study.

The DSMB will be responsible for establishing monitoring guidelines for stopping the study due to safety concerns.

7.5 Risks And Discomforts

7.5.1 Terbutaline

Terbutaline is known to raise plasma glucose concentrations substantially in adults with T1D, to decrease this risk we will make subjects aware of this possibility and closely monitor blood glucose excursions overnight during a CRC admission and will contact patients every 3 days to determine the need for insulin dose adjustments.

Theoretically, daily terbutaline dosing could result in β_2-adrenergic receptor down regulation and, therefore, tachyphylaxis to its plasma glucose raising actions. However, that apparently did not limit use of the drug in the treatment of asthma, and it might be less likely with once daily (i.e., bedtime), rather than multiple daily, drug administration. To assess this risk we will be assessing symptoms and blood glucose trends on the patients by phone every 3 days. We will also measure terbutaline levels at the initiation of the study at 0 min, 30 min, 4 hours and 12 hours after the first dose of bedtime terbutaline and repeat these after 21-28 days of bedtime terbutaline administration.

Common side effects of multiple daily dosing and continuous use of terbutaline are nervousness, restlessness, tremor, insomnia, headache, diaphoresis, muscle cramps and paradoxical bronchospasm, we anticipate that with only once a day dosing at the doses studied these will not be very common, however, we will assess symptoms every 3 days by phone with the patients and depending on the severity of these we will decide continuation of patient in the study. (See Terbutaline Pilot Study Decision Table for Proceeding to RCT).

Terbutaline has the potential to aggravate arrhythmias, for this reason we plan to obtain an EKG at screening before initiation of first dose of terbutaline to assure no patient included in the study has an underling arrhythmia or prolonged QT.

Patient's blood pressure and heart rate will be monitored during both overnight stays to determine any tachycardia or hypertension. Patients will be instructed on how to measure heart rate at home and depending on the severity of the tachycardia and hypertension if these occur the decision to discontinue treatment will be made. (See Terbutaline Pilot Study Decision Table for Proceeding to RCT).

Terbutaline has potential nonglucose metabolic effects such as increase in blood lactate concentrations, serum NEFA levels and blood β-hydroxybutyrate levels, thus, careful attention to maintenance of metabolic control will be needed during long-term terbutaline administration of bedtime terbutaline. We plan to measure these during the overnight stays at the CRC at the beginning and end of the study. Patients will be asked to check blood ketones each morning on the meter provided by the study and will also be instructed to check for urine ketones if blood glucose is >300 mg/dL given the potential occurrence of ketosis and ketoacidosis while on terbutaline.

7.5.2 CGM

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. Minor skin reaction is to be expected. Severe skin reactions will be considered adverse events.

7.5.3 Fingerstick Blood Glucose and Blood Ketone Measurements

Fingersticks may produce pain and/or ecchymosis at the site.

7.5.4 IV Risks

In the CRC, a hollow needle/plastic tube will be placed in the arm for taking blood samples or giving fluids during the CRC admission. This will be left in for 16-20 hours. When the needle goes into a vein, it can cause pain. A special cream (Elamax or EMLA®) may be used to numb the area where the needle will be inserted. The most common risks related to putting the numbing cream on the skin are redness, blanching (temporary whiteness of the skin area), swelling, and itching. There will be the minor discomfort of having the needle/plastic tube taped to the arm. In about one in 10 cases a small amount of bleeding under the skin will produce a bruise. The risk of a blood clot forming in the vein is about one in 100, while the risk of infection or significant blood loss is one in 1000.

7.5.5 Risk of Hypoglycemia

As with any person having insulin-treated diabetes, there is always a risk of having a low blood sugar (hypoglycemia) and of ketoacidosis. Symptoms of hypoglycemia can include sweating, jitteriness, and not feeling well. Seizure and coma is possible. Death is extremely rare. When a severe low blood sugar does occur, it almost always goes away quickly with treatment to raise the

blood sugar. The risk of hypoglycemia in the study is no greater than it would be for the subject prior to and after the study.

7.5.6 Risk of Hyperglycemia

As noted in section 1.1, the objective of terbutaline use is to reduce the risk of overnight hypoglycemia. In doing so, the possibility of hyperglycemia is increased. Hyperglycemia, if not properly treated, could produce diabetic ketoacidosis or coma. Subjects will be made aware of this possibility and will be instructed on adjustments to make in insulin management throughout the course of the study if hyperglycemia occurs.

7.5.7 Actiwatch Monitor

There are no risks involved with use of the Actiwatch monitor.

7.6 Other Risks

The study may include other risks that are unknown at this time.

7.7 Risk Assessment

This protocol falls under DHHS 46.405 which is a minor increase over minimal risk. In addition, it is the belief of the investigators that this study also presents prospect of direct benefit to the subjects and general benefit to others with diabetes as described in Section 8.1.

7.8 Blood Volume Requirements

At the time of CRC admission the maximum number of blood draws that can be performed based on a subject's weight will be determined so that the maximum blood volume in the blood draws will not exceed 5% of the subject's blood volume (calculated by multiplying the subject's weight in kilograms by 70 [70cc / kg blood volume] and then multiplying by .05). The maximum number of blood draws is then determined by dividing this maximum blood volume by the amount of blood in each blood draw at the center.

CHAPTER 8
MISCELLANEOUS CONSIDERATIONS

8.1 Benefits

Terbutaline may be beneficial for the subject in reducing nocturnal hypoglycemia. The information collected on the subject during the study in this regard may be useful for the subject's subsequent management. In addition, the use of the CGM may provide important information that will benefit the subject's subsequent diabetes management.

8.2 Subject/Parent Reimbursement

The study will provide the CGM and sensors, HGM and test strips, and terbutaline tablets.

A payment of $225 will be made after the subject completes the study, $25 for the Enrollment visit and $100 for each CRC admission. In addition subjects will be paid $10 for downloading the CGM at home prior to the initial CRC admission and up to $10 per week during the outpatient phase for downloading the CGM two times each week as instructed by the clinic personnel. Payments for downloading will not exceed $50. Payment for partial completion of the study will be prorated.

8.3 Subject Withdrawal

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

8.4 Confidentiality

For security and confidentiality purposes, subjects will be assigned an identifier that will be used instead of their name. Protected health information gathered for this study will be shared with the coordinating center, the Jaeb Center for Health Research in Tampa, FL. Information also may be provided to laboratories involved in the study.

Chapter 9
Statistical Considerations

9.1 Sample Size

The sample size of 10 for this pilot trial is a convenience sample and is not based on statistical principles.

9.2 Analysis Plan

There will be no formal statistical analyses as this study is not formally testing any hypotheses. The data collected on each subject will be tabulated regarding terbutaline dosing, side effects, tolerability, hypoglycemic events, hyperglycemic events, other adverse events, and other laboratory testing.

Glucose data from the CGM will be plotted for each subject and summarized as the percentage of values each day (separately for day and overnight) in the target range of 70 to 180 mg/dL and the percentage of values above and below this, plus the percentage of values <50 mg/dL and above 300 mg/dL.

Accuracy of the CGM will be evaluated by comparing CGM values with paired blood glucose values from both the inpatient and outpatient phases. For each sensor-reference glucose pair the following accuracy measurements will be calculated:

- Difference (sensor glucose minus reference glucose)
- Absolute Difference (absolute value of the Difference)
- Relative Difference (Difference divided by reference glucose, expressed as a percentage)
- Relative Absolute Difference (absolute value of the Relative Difference)
- ISO criteria (binary assessment of accuracy: sensor within ± 15 mg/dL if reference ≤ 75 mg/dL or sensor within ± 20% if reference > 75 mg/dL)

Mean and 95% confidence interval, median and quartile values will be given for the first four accuracy measures listed above as well the percentage of pairs meeting the ISO criteria with 95% confidence interval.

The sensor will be considered to be sufficiently accurate during terbutaline use if the median relative absolute difference (RAD) is <15%. The effect of terbutaline on accuracy will be questioned if the median RAD is >20%. Between 15% and 20% will require review to determine if the accuracy is less than expected.

9.3 Decision to Proceed to Randomized Trial

The data collected in this pilot study will be used to determine whether to proceed to a randomized trial using the dose of terbutaline being used in the pilot study or the need for additional pilot testing with a lower dose of terbutaline.

The following table provides a priori decision rules.

Terbutaline Pilot Study
Decision Table for Proceeding to RCT

Event	**Proceed to RCT**	**Uncertain**	**Don't Proceed with This Dose ***
	# of subjects with event out of 10		
Discontinuation of terbutaline due to nonglycemic side effects	2	3-4	5
Tachycardia >120 beats/min (resting) at 21-28 day follow up visit	0		1
DKA (not due to another cause)	0	1-2	3
Increase from baseline in time per day with BG > 300 mg/dL, measured with CGM, by an average of 2 or more hours per day in the 7 days prior to 3-4 week follow up visit	1	2-3	4
Severe hypoglycemia (seizure, coma)	1	1	2
2 or more nights <50 mg/dL for 2 or more hours during the 7 days prior to the 3-4 week follow up visit	1	2	3
Other unexpected adverse effect**			

* May consider repeating pilot study with lower dose
**will need to evaluate on case by case basis.

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