The Use of Amitriptyline for Improving Hypoglycemia Course and Recognition

NCT03591458

Document Date: 04/24/2019

Study: The Use of Amitriptyline for Improving Hypoglycemia Course and Recognition

IRB # 00110853

Principal Investigator	Yu Kuei Lin, MD yu.lin@hsc.utah.edu
Sub-investigator(s)	Simon J. Fisher, MD, PhD simon.fisher@u2m2.utah.edu Michael Varner, MD michael.varner@hsc.utah.edu
Funding Organization	NIDDK/Washington University-University of Utah Diabetes Research Center Contact: Karen Muehlhauser kmuehlha@wustl.edu
Investigational Agent	Amitriptyline
IND Number	Pending – applying for IND exemption

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
BMI	Body Mass Index
BP	Blood Pressure
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CGM	Continuous glucose monitoring
CIOMS	Council for International Organizations of Medical Science
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCC	Data Coordinating Center
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ERICA	Electronic Research Integrity and Compliance Administration system
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1C
HIPAA	Health Insurance Portability and Accountability Act
HR	Heart Rate
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum Tolerated Dose
NIH	National Institutes of Health
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
PI	Principal Investigator
rtCGM	Real-time continuous glucose monitoring
SAE	Serious Adverse Event

STATEMENT OF COMPLIANCE

I confirm that I have read this protocol, and I will conduct the study as outlined herein and according to the ethical principles stated in the latest version of the Declaration of Helsinki, the U.S. code of federal regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312 and/or 21 CFR Part 812), and the applicable ICH guidelines for Good Clinical Practice (GCP).

I will promptly submit the protocol to the IRB for review and approval. Once the protocol has been approved by the IRB, I understand that any modifications made during the course of the study must first be approved by the IRB prior to implementation except when such modification is made to remove an immediate hazard to the subject.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study treatment, the conduct of the study, and the obligations of confidentiality.

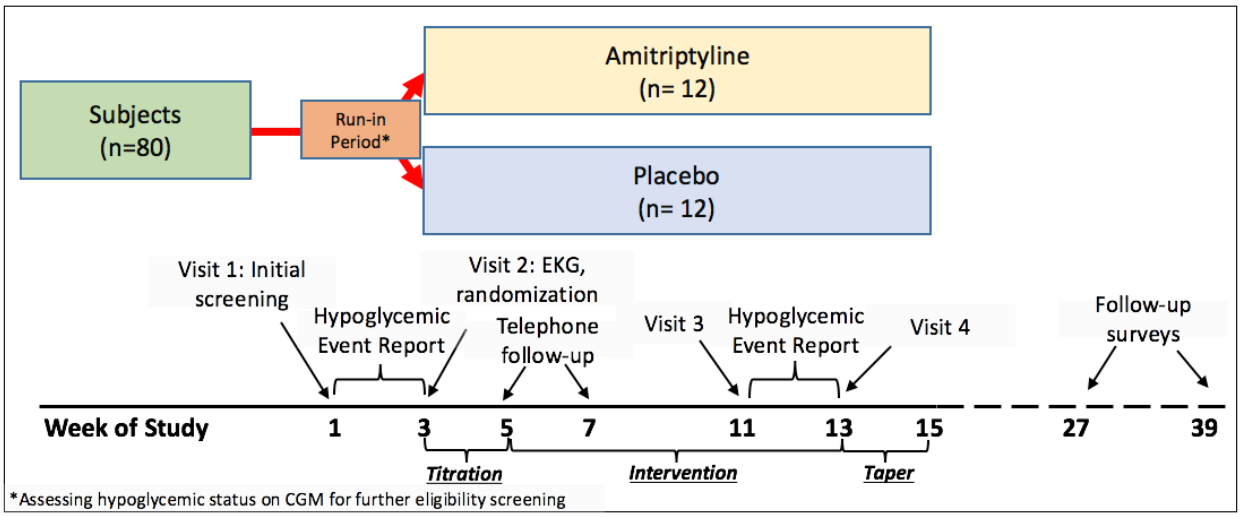
Note: This document is signed electronically through submission and approval by the Principal Investigator in the University of Utah IRB Electronic Research Integrity and Compliance Administration (ERICA) system.

STUDY SUMMARY

Title	The Use of Amitriptyline for Improving Hypoglycemia Recognition and Course
Short Title	Amitriptyline as an anti-hypoglycemic agent
Protocol Number	IRB # 00110853
IND	Pending – applying for IND exemption
Phase	Pilot, clinical phase II
Design	Double blind, randomized, placebo control, cross-over design
Study Duration	38 weeks
Study Center(s)	University of Utah Hospital and Clinics
Objectives	To evaluate whether amitriptyline improves the hypoglycemia course and the ability to recognize hypoglycemia in type 1 diabetes patients who are using real-time continuous glucose monitoring devices
Number of Subjects	Approximately 80 participants for Run-in Period, with a goal of randomizing 24 patients for drug intervention phase
Main Eligibility Criteria	Inclusion Criteria • Subjects with T1DM for one years or more • Age between 21 to 60 years old • HbA1c less or equal to 9% with the last measurement in the last three months • Ongoing use of real-time CGM for at least 3 months Exclusion Criteria • Ongoing or recent history of major depressive disorder, or other ongoing major psychiatric disorders • History of anti-depressant use within the last three months • History of advanced cardiac, liver, kidney and neurological disease • Active malignant or HIV diseases • Advanced diabetic retinopathy, neuropathy or nephropathy • Female in pregnancy or not able to practice effective contraception during the study period • Contraindication to amitriptyline use

	• < 70% of CGM readings available over the last 2-week period • Time spent in hypoglycemia (i.e., < 70 mg/dL) for < 5% over a 2-week period on based on CGM reading
Study Product, Dose, Route, Regimen	Amitriptyline 25 mg and 50 mg oral daily at bedtime
Duration of Administration	Up to 12 weeks
Reference Therapy	Placebo
Statistical Methodology	The Wilcoxon rank sums test as adapted to determine study outcomes. Hodges-Lehman estimates and associated exact 95% confidence intervals will provide estimates of the size of the treatment effect.

STUDY SCHEMA



1. OBJECTIVES

The overall goal of the current study is to evaluate whether amitriptyline improves the hypoglycemia course and the ability to recognize hypoglycemia in type 1 diabetes patients who are using real-time continuous glucose monitoring (rtCGM) devices.

1.1 Primary Objectives and Endpoints

- The area-under-curve (AUC) of glucose <70 and 54 mg/dL on continuous glucose monitoring (CGM).
- The ratio of recognized-to-total hypoglycemic episodes.

1.2 Secondary Objectives and Endpoints

- Count of severe hypoglycemic episodes.
- Hypoglycemic course, including episode count, total time, average time/episode, and percentage of glucose < 70, 54 and 40 mg/dL; AUC of glucose < 40 mg/dL; average nadir glucose.
- Nocturnal hypoglycemic course, including episode count, total time, average time/episode, percentage and AUC of glucose < 70, 54 and 40 mg/dL; average nadir glucose.
- Hypoglycemia awareness score (Gold [1], Clarke [2] and Pedersen-Bjergaard [3]).
- Other glucose regulation: Average glucose, glycemic variability, time in hyperglycemia with level above 180, 250 and 300 mg/dL, percentage of time in normal glucose, HbA1c.
- Hypoglycemia Fear Survey score [4].

2 BACKGROUND

Poorly controlled type 1 diabetes mellitus (T1DM) can lead to serious and devastating complications, including microvascular (retinopathy, neuropathy and nephropathy) and cardiovascular disease. Both diabetic microvascular and cardiovascular complications can be reduced by intensive insulin therapy and strict blood glucose control aiming for hemoglobin A1C (HbA1c) less or equal to 7%. [5, 6] However, a tighter glycemic control correlates with a higher incidence of hypoglycemia. [7] Recurrent episodes of hypoglycemia induce an attenuation or loss of catecholamine counter-regulatory responses (a condition termed hypoglycemia-associated autonomic failure) and the ability to recognize hypoglycemic episodes (impaired awareness of hypoglycemia). [8, 9] Hypoglycemia-associated autonomic failure and impaired awareness of hypoglycemia are associated with a 25 and six-fold increased risk of severe hypoglycemia, respectively. [9-11] Severe hypoglycemia leads to seizures, emergency room visits/hospitalization, fear of hypoglycemia, compromised quality of life and potentially death. [12] Thus, hypoglycemia-

associated autonomic failure and impaired awareness of hypoglycemia are major barriers to optimal glycemic control. [8]

Real-time continuous glucose monitoring (rtCGM) is a technique which measures interstitial glucose levels every five minutes to estimate coincidental blood glucose levels. [13] A rtCGM will alert patients of hyper/hypoglycemic events at set glucose thresholds and when the blood glucose levels are rapidly rising/declining. While rtCGM has demonstrated to significantly decrease the daily time spent in hypoglycemia, patients wearing rtCGM still spend approximately 3-7% of time in hypoglycemia in average, equivalent to 43-101 minutes in a day.[14-16] While the prevalence of T1DM using CGM is rapidly increasing, there has been no adjuvant therapy demonstrating its ability to further decrease the hypoglycemic burden for this patient population.

In the current study, **we propose to test amitriptyline, a tricyclic antidepressant, as an adjuvant treatment of rtCGM to further improve hypoglycemia course and T1DM patients' ability to recognize hypoglycemic episode**. Our lab has constructed a 2-Deoxy-D-glucose (2DG)-mediated impaired awareness model in rats, in order to identify therapies for rapid translational testing and clinical use. 2DG blocks normal glucose metabolism and causes cellular glucose deprivation. Repeated 2DG infusions thus assimilate repetitive "cellular hypoglycemia". [17] Based on this concept, our lab has developed a rodent model of repetitive 2DG infusion-mediated impaired hypoglycemia awareness. We use the amount of food intake in response to subsequent insulin-induced hypoglycemia as an objective measurement of impaired awareness in this model, as food intake is an important behavioral defensive mechanism and can reflect hunger (a hypoglycemic symptom).

In our model, rats decreased food intake during a subsequent insulin-mediated hypoglycemic episode after repetitive 2DG infusion (figure 1), evident for the development of impaired hypoglycemia awareness. After testing 50+ drugs, we observed that amitriptyline both prevented and restored the attenuated food intake response (figure 2). [18] These findings suggest that amitriptyline has a potential role in clinically improving hypoglycemic course. In addition, amitriptyline is a common and safe therapy for diabetic neuropathy. [19-21] We therefore propose that amitriptyline is a strong testing candidate for mitigating hypoglycemia burden in T1DM patients.

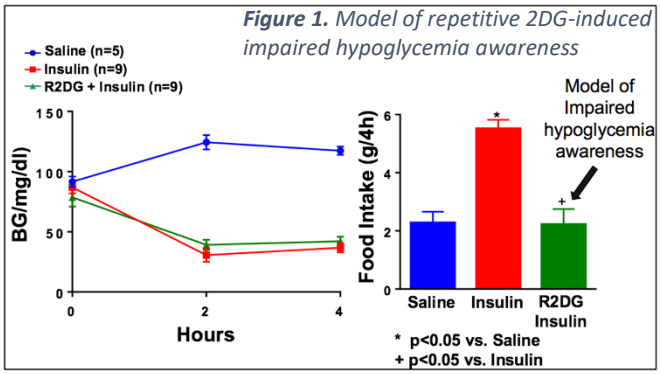


Figure 1. *Model of repetitive 2DG-induced impaired hypoglycemia awareness*

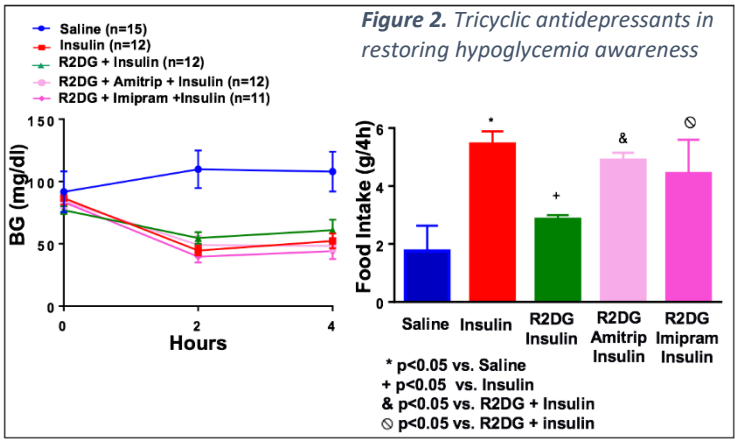


Figure 2. *Tricyclic antidepressants in restoring hypoglycemia awareness*

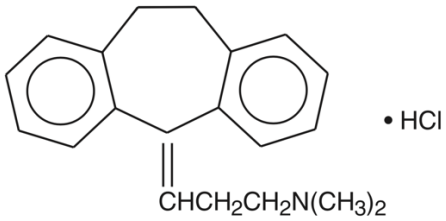
3 DRUG INFORMATION

Amitriptyline (investigational drug) has been approved by the FDA for indications unrelated to the current study. [22] In the current study, we will use amitriptyline as our investigational drug. A summary of the FDA label for amitriptyline has been provided in the following:

DESCRIPTION

Amitriptyline HCl, a dibenzocycloheptadiene derivative, is a white, or practically white, odorless, crystalline compound which is freely soluble in water and alcohol.

It is designated chemically as 10,11-Dihydro-N,N-dimethyl- 5*H*-dibenzo[a,d] cycloheptene-Δ5, γ-propylamine hydrochloride. It has the following structural formula:



$C_{20}H_{23}N \bullet HCl$ M.W. 313.87

Each tablet for oral administration contains 10, 25, 50, 75, 100, or 150 mg amitriptyline hydrochloride.

CLINICAL PHARMACOLOGY

Amitriptyline HCl is an antidepressant with sedative effects. Its mechanism of action in man is not known. It is not a monoamine oxidase inhibitor and it does not act primarily by stimulation of the central nervous system.

Amitriptyline inhibits the membrane pump mechanism responsible for uptake of norepinephrine and serotonin in adrenergic and serotonergic neurons. Pharmacologically, this action may potentiate or prolong neuronal activity since reuptake of these biogenic amines is important physiologically in terminating transmitting activity. This interference with reuptake of norepinephrine and/or serotonin is believed by some to underlie the antidepressant activity of amitriptyline.

DOSAGE AND ADMINISTRATION

Oral Dosage

Dosage should be initiated at a low level and increased gradually, noting carefully the clinical response and any evidence of intolerance.

Initial Dosage for Adults

For outpatients, 75 mg of amitriptyline HCl a day in divided doses is usually satisfactory. If necessary, this may be increased to a total of 150 mg per day. Increases are made preferably

in the late afternoon and/or bedtime doses. A sedative effect may be apparent before the antidepressant effect is noted, but an adequate therapeutic effect may take as long as 30 days to develop.

An alternate method of initiating therapy in outpatients is to begin with 50 to 100 mg amitriptyline HCl at bedtime. This may be increased by 25 or 50 mg as necessary in the bedtime dose to a total of 150 mg per day.

Hospitalized patients may require 100 mg a day initially. This can be increased gradually to 200 mg a day if necessary. A small number of hospitalized patients may need as much as 300 mg a day.

Maintenance

The usual maintenance dosage of amitriptyline HCl is 50 to 100 mg per day. In some patients, 40 mg per day is sufficient. For maintenance therapy, the total daily dosage may be given in a single dose, preferably at bedtime. When satisfactory improvement has been reached, dosage should be reduced to the lowest amount that will maintain relief of symptoms. It is appropriate to continue maintenance therapy 3 months or longer to lessen the possibility of relapse.

Plasma Levels

Because of the wide variation in the absorption and distribution of tricyclic antidepressants in body fluids, it is difficult to directly correlate plasma levels and therapeutic effect. However, determination of plasma levels may be useful in identifying patients who appear to have toxic effects and may have excessively high levels, or those in whom lack of absorption or noncompliance is suspected. Because of increased intestinal transit time and decreased hepatic metabolism in elderly patients, plasma levels are generally higher for a given oral dose of amitriptyline hydrochloride than in younger patients. Elderly patients should be monitored carefully and quantitative serum levels obtained as clinically appropriate. Adjustments in dosage should be made according to the patient's clinical response and not on the basis of plasma levels. For this study, as we are using low amitriptyline dose, we will not conduct plasma level monitoring.

METABOLISM

Studies in man following oral administration of ^{14}C-labeled drug indicated that amitriptyline is rapidly absorbed and metabolized. Radioactivity of the plasma was practically negligible, although significant amounts of radioactivity appeared in the urine by 4 to 6 hours and one-half to one-third of the drug was excreted within 24 hours.

Amitriptyline is metabolized by N-demethylation and bridge hydroxylation in man, rabbit, and rat. Virtually the entire dose is excreted as glucuronide or sulfate conjugate of metabolites, with little unchanged drug appearing in the urine. Other metabolic pathways may be involved.

INDICATION, CLINICAL USE, ADVERSE EVENT, CONTRAINDICATIONS AND PREGNANCY IMPLICATION

Amitriptyline is indicated for depression/major depressive disorder. Prior studies also supported its effectiveness in treating diabetic neuropathy [23], chronic pain management [24], fibromyalgia [25], insomnia [26], interstitial cystitis [27], irritable bowel syndrome [28], postherpetic neuralgia [29], post-traumatic stress disorder [30] and sialorrhea (excessive production of saliva) [31], and preventing migraine [32].

The following adverse events were observed and have been reported in patients using amitriptyline:

- Cardiovascular: Atrioventricular conduction disturbance, cardiac arrhythmia, cardiomyopathy (rare), cerebrovascular accident, ECG changes (nonspecific), edema, facial edema, heart block, hypertension, myocardial infarction, orthostatic hypotension, palpitations, syncope, tachycardia
- Central nervous system: Anxiety, ataxia, cognitive dysfunction, coma, confusion, delusions, disorientation, dizziness, drowsiness, drug withdrawal (nausea, headache, malaise, irritability, restlessness, dream and sleep disturbance, mania [rare], and hypomania [rare]), dysarthria, EEG pattern changes, excitement, extrapyramidal reaction (including abnormal involuntary movements and tardive dyskinesia), fatigue, hallucination, headache, hyperpyrexia, insomnia, lack of concentration, nightmares, numbness, paresthesia, peripheral neuropathy, restlessness, sedation, seizure, tingling of extremities
- Dermatologic: Allergic skin rash, alopecia, diaphoresis, skin photosensitivity, urticarial
- Endocrine & metabolic: Altered serum glucose, decreased libido, galactorrhea, gynecomastia, increased libido, SIADH, weight gain, weight loss
- Gastrointestinal: Ageusia, anorexia, constipation, diarrhea, melanoglossia, nausea, paralytic ileus, parotid gland enlargement, stomatitis, unpleasant taste, vomiting, xerostomia
- Genitourinary: Breast hypertrophy, impotence, testicular swelling, urinary frequency, urinary retention, urinary tract dilation
- Hematologic & oncologic: Bone marrow depression (including agranulocytosis, leukopenia, and thrombocytopenia), eosinophilia, purpura
- Hepatic: Hepatic failure, hepatitis (rare; including altered liver function and jaundice)
- Hypersensitivity: Tongue edema
- Neuromuscular & skeletal: Lupus-like syndrome, tremor, weakness
- Ophthalmic: Accommodation disturbance, blurred vision, increased intraocular pressure, mydriasis
- Otic: Tinnitus
- Postmarketing and/or case reports: Angle-closure glaucoma, neuroleptic malignant syndrome (rare), serotonin syndrome (rare)

The contraindications of amitriptyline are hypersensitivity to amitriptyline or any component of the formulation; coadministration with or within 14 days of MAOIs; coadministration with cisapride; acute recovery phase following myocardial infarction.

Amitriptyline can be used as an antidepressant. Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18 to 24 years of age) with major depressive disorder and other psychiatric disorders. For the current study, patients with ongoing and recent history of depression or other major psychiatric disorders will be excluded from recruitment. Furthermore, short-term studies did not show an increased risk in patients >24 years of age and showed a decreased risk in patients ≥65 years.

Amitriptyline is Pregnancy Category C. Adverse events have been observed in some animal reproduction studies. Amitriptyline crosses the human placenta; CNS effects, limb deformities, and developmental delay have been noted in case reports (causal relationship not established). Tricyclic antidepressants may be associated with irritability, jitteriness and convulsions (rare) in the neonate. Crying, constipation, problems with urinating, and nausea may also occur in neonate exposed during pregnancy. For the current study, pregnancy will be ruled out before initial recruitment and before study drug intervention. Consultation for contraception will also be provided.

4 STUDY DESIGN

4.1 Description

The current investigation is a pilot phase II clinical trial with placebo control, randomization and double-blinding design.

After the initial recruitment (Visit 1), the study participants will enter a two-week "Run-in Period", during which the participants will be asked to continue their CGM use and record their symptom(s) on Hypoglycemic Event Reports for all their hypoglycemic events. For the participants who meet the criteria to be initiated on study drug (see recruitment criteria), they will then be randomized to be initiated either on daily amitriptyline or a matching placebo (Visit 2). All participants will undergo a two-week drug "Titration Period", and at the end of this period (i.e., the end of Week 4), the amitriptyline dose will be titrated up with a matching placebo and continued until Visit 4. During this "Intervention Period", the patient will receive telephone follow-ups at Week 5 and Week 7, and undergo a return visit (Visit 3). After Visit 3, the participants will again start to record their hypoglycemic symptoms, and then return to Visit 4 at the end of the Intervention Period. The participants will then undergo a two-week study drug "Tapering Period" to complete the study drug intervention. At week 27 and 39 of the study, the participants will be assessed with follow-up questionnaires.

4.2 Number of Subjects

Up to 80 participants are expected to be enrolled into the study for the Run-in Period assessment. For the study drug testing phase, 24 participants will be randomized and equally divided into two arms (i.e., 12 participants in the amitriptyline arm and 12 participants in the matching placebo arm).

4.3 Number of Study Centers

This study will be a single-center study conducted at the University of Utah.

4.4 Study Duration

The pilot study is expected to last for two years, and will help provide the estimated time for the final study. The duration of each patient's participation in the study will be 39 weeks, with 15 weeks of active assessment/intervention and 24 weeks of distant follow-up.

5 ELIGIBILITY CRITERIA

This checklist is used to determine subject eligibility; it should be completed for each subject, including review and signature by the enrolling investigator and filed in the subject research chart.

Subject ID: _____

Subject Initials: _____

5.1 Inclusion Criteria

Yes/No (a response of 'No' indicates the subject is **ineligible**)

1. _____ Subjects with T1DM for ≥ five year or more
2. _____ Age between 21 to 60 years old
3. _____ HbA1c less or equal to 9% with the last measurement in the last three months
4. _____ Use of rtCGM providing continuous glucose data points for at least 3 months with ≥ 80% of CGM readings over the last 2-week period
5. _____ Able to provide informed consent and willing to sign an approved consent form that conforms to federal and institutional guidelines.

5.2 Exclusion Criteria

Yes/No (a response of "Yes" indicates the subject is **ineligible**)

1. _____ Ongoing or recent history of major depressive disorder, or other ongoing major psychiatric disorders
2. _____ History of anti-depressant use within the last three months
3. _____ Insulin pump linked to a CGM with programmed automatic insulin adjustment/suspension

4. _____ History of advanced cardiac, liver, kidney and neurological disease
5. _____ Active malignant
6. _____ Uncontrolled HIV diseases
7. _____ Advanced diabetic retinopathy, neuropathy or nephropathy
8. _____ Frequent acetaminophen use which can disrupt CGM accuracy
9. _____ Pregnancy or female of child-bearing potential unable to practice effective contraception during the study period
10. _____ Breastfeeding female or female with prospective plan to initiate breastfeeding
11. _____ Ongoing history of alcohol abuse
12. _____Contraindication to amitriptyline use, including hypersensitivity to amitriptyline or any component of the formulation, coadministration with or within 14 days of MAOIs and coadministration with cisapride
13. _____ Inability to understand or cooperate with study procedure, including taking study drugs and record hypoglycemic symptoms

The participants meeting the above criteria will enter "Run-in Period". At the Visit 2, the following additional exclusion criteria will be applied before study drug randomization:

14. _____ < 80% of CGM readings available over the last 2-week period
15. _____ Time spent in hypoglycemia (i.e., < 70 mg/dL) for < 5% over a 2-week period on based on CGM reading.

I verify that this subject meets all eligibility criteria for enrollment onto this study

_____ _____

Investigator Signature Date

6 TREATMENT PLAN

6.1 Administration Schedule

6.1.1 Treatment Arm 1

After randomization at Visit 2, participants of the Treatment Arm 1 will be initiated on Amitriptyline 25 mg daily (to be taken at bedtime) for two weeks during the "Titration Period". Starting at Study Week 5, the amitriptyline dose will be titrated up to 50 mg (two capsules of amitriptyline 25 mg) when entering the "Intervention Period". For those participants who report intolerance to the 50 mg dose due to the adverse effect, the dose will be tapered down to 25 mg dose for three to five days, before another trial for the 50 mg dose. For those who still do not tolerate amitriptyline 50 mg, they will be asked to continue the 25 mg dose for the rest of the Intervention Period.

At the end of the Intervention Period, the participants who take amitriptyline 50 mg will be reduced to amitriptyline 25 mg daily for another one to two weeks ("Taper Period"), and discontinue the 25 mg daily dose as tolerated. For the participants who are taking amitriptyline 25 mg at the end of the Intervention Period, they will discontinue treatment with the study drug at that time.

6.1.2 Treatment Arm 2

After randomization at Visit 2, participants of the Treatment Arm 2 will be initiated on the matching placebo of Amitriptyline 25 mg daily (to be taken at bedtime) for two weeks during the "Titration Period". Starting at Study Week 5, the matching placebo of amitriptyline 50 mg (two capsules of matching placebo of amitriptyline 25 mg) will be initiated when entering the "Intervention Period". For those participants who report intolerance to the matching placebo of amitriptyline 50 mg dose due to the adverse effect, the matching placebo will be switched back to that of the amitriptyline 25 mg for three to five days, before another trial for the matching placebo for amitriptyline 50 mg. For those who still do not tolerate the matching placebo for amitriptyline 50 mg, they will be asked to continue the matching placebo of amitriptyline 25 mg dose for the rest of the Intervention Period.

At the end of the Intervention Period, the participants who take the matching placebo of amitriptyline 50 mg will be asked to take the matching placebo of amitriptyline 25 mg for another one to two weeks ("Taper Period"), and discontinue the matching placebo as tolerated. For the participants who are taking matching placebo of amitriptyline 25 mg at the end of the Intervention Period, they will discontinue treatment with the study drug at that time.

6.2 Treatment (include name of each treatment as section header)

6.2.1 How Supplied, Stored, Packaged and Labeled

Amitriptyline 25 mg: Over-encapsulated for blinding.

Matching placebo capsules: Capsules identical to the ones used to encapsulate amitriptyline for blinding.

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) (See USP Controlled Room Temperature). Dispense in a tight, light-resistant container.

6.2.2 Preparation and Administration

At Visit 2, participants will be given a 10-week supply of amitriptyline sufficient for 2 weeks of 25 mg daily and 8 weeks of 50 mg (i.e., two capsules of 25 mg) daily. At Visit 3, the participants will then be given a 2-week supply of amitriptyline 25 mg, if needed.

The matching placebo will be provided in a similar fashion.

6.2.3 Accountability and Compliance

Participants will be asked to return medication bottles and any unused study drugs at the end of the Interventional Periods (i.e., Visit 3) for reconciliation. For participants who will require amitriptyline 25 mg or matching placebo for the Taper Periods, Guide of Safe Medicine Disposal following the FDA and Utah State regulations, including returning the unused study drugs to the study team, will be provided.

6.3 Duration of Therapy

The total duration of the treatment period will last about 12 weeks.

Subjects must be withdrawn or discontinued from the clinical trial for the following reasons:

- Subject withdraws consent from participation in the clinical trial. A subject must be removed from the study at his/her own request or at the request of their legally authorized representative. At any time during the trial and without providing reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.
- Subject is lost to follow-up despite efforts to contact
- Death

Subjects may be withdrawn or discontinued from the clinical trial for the following reasons:

- The subject is non-compliant with study treatment requirements and/or protocol procedures, including the use of prohibited concomitant medications.
- The occurrence of an AE, laboratory abnormality, or other medical condition or situation such that in the investigator's opinion, continued participation in the study would not be in the best interest of the subject.

Discontinued or withdrawn subjects may be replaced for each treatment arm.

7 TOXICITIES AND DOSE MODIFICATION

Toxicities will be monitored in each study subject according to the study calendar and Section 9.11, Safety Measurements. Serious Adverse Events and intolerable toxicities determined by the PI to be related to study medication will result in discontinuation of treatment and withdrawal of the subject from the trial. Treatment may be reduced and resumed if adverse events resolve to a tolerable level as determined by the investigator.

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) version 4.0 for adverse event and serious adverse event reporting.

7.1 Dose Modification

For those participants who report intolerance to the 25 mg dose due to the adverse effect, the amitriptyline will be stopped for three to five days before another trial. Similarly, for those participants who report intolerance to the 50 mg dose after up-titration from 25 mg, the dose will be tapered down to 25 mg dose for three to five days, before another trial for the 50 mg dose. For those who still do not tolerate amitriptyline 50 mg, they will be asked to continue the 25 mg dose for the rest of the Intervention Period.

7.2 Supportive Care

All supportive measures consistent with optimal subject care will be given throughout the study.

8 STUDY CALENDAR

Period	**Screening**[1] **/Run-in**	**Treatment**					**Follow-up**	
Visit No.	1	2	-[2]	-[2]	3	4	-[3]	-[3]
Week[4]	-4 to 1	3	5	7	11	13	27	39
Assessments								
Informed consent	X							
Inclusion/Exclusion criteria	X							
Demographics	X							
Vital signs	X	X			X	X		
Physical Examination	X	X[5]			X[5]	X[5]		
Pregnancy Test	X	X						
ECG		X[1]						
Comprehensive Metabolic Panel[6]	X							
HbA1c		X				X		
AE Assessment		X	X	X	X	X		
Concomitant Medications	X	X			X	X		
Investigational Drug Treatment		X	X	X	X	X		
Primary Objective Assessment	X[7]	X			X	X		
Secondary Objective Assessment	X[7]	X			X	X	X	X

1. All screening procedures should be completed within 4 weeks of study enrollment, except that an ECG and laboratory evaluation completed within 3 months will be considered as valid.
2. Telephone call follow-up to assess participants' adverse events, and to remind study drug titration/adherence.
3. Telephone call follow-up to assess participants' general well-being, and to complete questionnaire surveys for Secondary Objective Assessment.
4. All visits/telephone calls can occur within +/- 3 days of the anticipated dates based on the schedule calendar
5. Follow-up physical exam to be conducted at the discretion of PI/Sub-investigator based on reported adverse events.
6. Comprehensive Metabolic penal include Albumin, Alkaline Phosphatase, Aspartate Aminotransferase, Alanine Aminotransferase, Total Bilirubin, Calcium, Carbon Dioxide, Creatinine, Chloride, Glucose, Potassium, Protein, Sodium and Urea Nitrogen.
7. Including instructions about Hypoglycemic Event Reports and conducting questionnaires surveys to assess baseline status. Will only be provided only after obtaining the consent.

9 STUDY PROCEDURES

Detailed descriptions of subject evaluations required for this protocol are described in this section. These evaluations will be performed during the indicated visits/weeks of the study as described in the Study Calendar and in this section.

All data collected are to be recorded on source documents and entered into the appropriate CRF page.

The PI is responsible for maintaining a record of all subjects pre-screened, screened, and enrolled into the study. All subjects must provide written informed consent before the performance of any study procedures.

9.1 Participant Identification/Recruitment Process

Describe the recruitment/participant identification process in detail (e.g. who will review charts or records, who can refer participants to the study, where will flyers be posted, how often will recruitment letters be sent, when will follow-up phone calls be made, etc.):

2) Study flyers which include the study survey web link/address will be printed. These printed study flyers will be placed in patient encounter rooms of the University of Utah Endocrinology clinics. The study flyers will also be placed/distributed at the front desk for interested patients. Information about the current study will be distributed to clinical providers, including University of Utah Endocrinologists and diabetes educators.

3) The study investigator(s) and coordinator(s) may approach the potential candidates after visits for clinical and research purposes and to discuss with potential candidates about the current research opportunity.

For each recruitment route, the candidates may "optout" for no further contact to be made for this study. On the myChart message/email/mail/flyer/study survey, contact information will be provided for candidates' inquiries.

The PI will work with the University of Utah Enterprise Data Warehouse (EDW) for initial candidate screening with based on the elements of inclusion/exclusion criteria (e.g. type 1 diabetes, age, recent HbA1c, etc) on the Human Subject Recruitment tool. The Human Subject Recruitment tool is a computer software managed by the EDW for subject recruitment with a constantly updating database, and this tool is commonly utilized for clinical investigations at the University of Utah. The study team will then review of these candidates' medical charts for further candidate selection. The study team will also review the medical charts of the patients with recent/upcoming visits scheduled with University of Utah Endocrinology Clinics for potential candidates screening. A list

of potential candidates will be generated and used to recruit subjects in the following routes:

1) Care providers (including primary care physicians, Endocrinologists or Diabetes Educators) with established clinical relationships with the potential candidates may discuss the research opportunity with the candidates, to obtain the permission of contact for interested candidates, and/or offer recruitment letters.

2) A recruitment letter may be sent via mail or email or myChart message to the potential candidates. If no response is received in at least 7 days after the mail/message being sent, a phone call may be generated to discuss the study.

3) A research assistant/coordinator may present at the University of Utah Clinics to discuss with the potential candidates. Communication with the care providers will be done before the research assistant/coordinator approaches the potential candidates.

Other recruitment methods include the following:

1) Study flyers will be placed in patient encounter rooms, phlebotomy site and the front desk at the Endocrinology Clinics.
2) Information about the current study will also be distributed to clinicians, mostly primary care physicians and endocrinologists, and referrals for the current study may be made by these physicians.

For each recruitment route, the candidate may opt-out request for no further contact to be made for this study.

For interested candidates, we will proceed with further eligibility screening through telephone discussions and mailing/emailing surveillance of Personal Medical History and other questionnaires. A copy of the consent form will also be mailed/emailed to the candidates to look over for at least 1 day before obtaining consent.

9.2 Informed Consent

For candidates interested in the study, a copy of the consent form will be mailed to the candidates to look over for at least 1 day before obtaining consent.

The informed consent process is to be completed at the screening visit. Prior to conducting any study-related procedures, written informed consent must be obtained from the subject. The nature, scope and possible consequences, including risks and benefits, of the study will be explained to the subject by the PI or designee in accordance with the regulations and guidelines in the Statement of Compliance.

The recruiting investigators/coordinators will be trained to discuss the study with the potential participants only limited to the informed consent document, including that the potential participant will continue the receive the same medical care regardless whether he/she decide to participate in the study. The potential participant selection process will be independent of the potential participants' diabetes care provider.

To avoid the financial participant support/study compensation being an undue influence, we will not share the financial participant support information during screening telephone calls unless the subject asks or after they have verbally agreed that they would like to participate. We also will not disclose details in compensation before completion of consenting process.

As much time as needed will be used to allow adequate time to exchange information and questions during the recruitment. The subjects and the investigators should not feel rushed for the recruitment process.

9.3 Study Entrance Criteria

At Screening, each subject will be assessed for eligibility against the inclusion/exclusion criteria. Subjects who do not meet the study entrance criteria will not be allowed to enroll and participate in the study. Further recruitment criteria is to be applied prior to the randomization and study drug intervention. The reason(s) for ineligibility will be documented in the subject research chart.

9.4 Demographics and Medical History

Subject information including gender, age, date of birth, race, ethnicity, diagnosis of type 1 diabetes, and other relevant past medical history will be collected during the screening period and recorded in the appropriate CRF.

9.5 Laboratory Variables

Comprehensive Metabolic Panel, HbA1c and pregnancy test will be performed as indicated on the Study Calendar. Comprehensive Metabolic Panel and HbA1c Analyses of laboratory samples will be performed with ARUP Laboratories (500 Chipeta Way, Salt Lake City, UT) protocol and supplies or at ARUP Laboratories. Pregnancy test will be performed with Immunostics Inc. (1750 Brielle Avenue, Ocean Township, NJ) protocol and material.

9.5.1 Comprehensive Metabolic Panel

Phlebotomy will be conducted for the Comprehensive Metabolic Panel analysis, including Albumin, Alkaline Phosphatase, Aspartate Aminotransferase, Alanine Aminotransferase, Total Bilirubin, Calcium, Carbon Dioxide, Creatinine, Chloride, Glucose, Potassium, Protein, Sodium and Urea Nitrogen.

9.5.2 HbA1c

Phlebotomy will be conducted for the HbA1c assessment.

9.5.3 Pregnancy Testing

Urine collection will be conducted for Qualitative Beta-human chorionic gonadotropin assessment.

9.5.4 Specimen Collection, Preparation, Storage and Shipping

Specimen collection, preparation, storage and shipping will be conducted as the standard based on ARUP laboratory and Immunostics Inc. protocol.

9.6 Physical Examination

Physical examination, including respiratory, cardiovascular, abdominal and others as indicated based on medical history, will be conducted at the screening visit. For the follow-up visits, focused physical examination will be conducted at discretion of PI/sub-investigator based on reported adverse events.

9.7 Vital Signs

Vital signs, including measurement of systolic and diastolic blood pressure, pulse, heart rate are to be measured.

9.8 Electrocardiogram

An ECG will be completed during the screening period to assess for cardiac conduction abnormalities.

9.9 Concurrent Medications

All prescription and non-prescription medications including pharmacologic doses of vitamins, herbal medicines, or other non-traditional medicines, taken from 4 weeks prior to the first dose of amitriptyline through the last study visit must be documented and recorded in the CRF.

9.9.1 Prohibited Concurrent Medications

The following medications are prohibited during the study:

- Antidepressants, including monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, and tricyclic antidepressant other than the study drug.

9.9.2 Prohibited Procedure/Device

- Anticipation of changing CGM device or modifying CGM settings should be discussed with the study team to determine whether these changes will potentially interfere with the study.

9.10 Efficacy Measurements

On all Treatment visit days, dosing will occur after all safety and efficacy assessments scheduled for that visit are complete.

9.10.1 Primary Objective Assessment

The primary objective assessment will be done through the determining area-under-curve for CGM glucose level < 70/54 mg/dL and the total and recognized hypoglycemic episodes based on CGM data and hypoglycemic event reports, respectively.

A single CGM hypoglycemic episode will be defined by any CGM readings < 70 mg/dL lasting equal to or more than 20 minutes on the CGM data.

A participant will complete a hypoglycemic event report for all hypoglycemic events during the surveillance periods. A hypoglycemic event report will include information about whether the participants perceive symptom(s) for hypoglycemic episodes recorded based on CGM.

At each visits, CGM data will be downloaded into a secure system and exported into an Excel format, and the hypoglycemic event reports will be prepared for analysis.

9.10.2 Secondary Objective Assessment

In brief, the count of severe hypoglycemic episodes will be generated by participant surveillance at each Visit/telephone call. The hypoglycemic/nocturnal hypoglycemic courses, and other glucose regulation will be assessed with CGM data download and venous blood HbA1c assessment. A nocturnal hypoglycemia will be defined for all hypoglycemic episodes occur during 00:00-06:00 on CGM clock. Hypoglycemia awareness status and fear of hypoglycemia status will be assessed through hypoglycemia awareness questionnaires (Gold, Clark and Pedersen-Bjergaard) and Hypoglycemia Fear Survey Questionnaire. CGM data will be collected at Visit 1-4, and the questionnaires will be completed by study subjects at the first, second and the last Visit, and with the follow-up phone calls.

9.11 Safety Measurements

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) version 4.0 for AE and SAE reporting. An electronic copy of the CTCAE v.4 can be found at: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

9.11.1 Adverse Events

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. For the purposes of this study, the terms toxicity and adverse event are used interchangeably. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test

results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy

Collection of adverse events will begin following the initial treatment with amitriptyline and continue through the last follow-up visit. Adverse events will be documented in the study source record and recorded in the CRF.

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit or phone contact during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade based on CTCAE v.4
2. The relationship of the event to the study drug(s): definite, probable, possible, unlikely, not related. [For multi-drug regimens, relationship will be assessed for each drug].
3. The duration: start and end dates, or continuing at final follow-up visit
4. Action taken: (e.g. study drug interrupted or dosage modified, concomitant medication taken, non-drug therapy, hospitalization, or no action taken)
5. Whether the event constitutes a Serious Adverse Event (SAE)

All adverse events will be treated appropriately. Such treatment may include changes in study drug treatment as listed in the dose modification section of this protocol (see section 7 for guidance). Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

9.11.2 Serious Adverse Events

Information about all serious adverse events will be documented in the study source record and recorded in the CRF. A serious adverse event is an undesirable sign, symptom or medical condition which:

- Is fatal or life-threatening
- Results in persistent or significant disability or incapacity
- Requires inpatient hospitalization or prolongation of existing hospitalization (unless the hospitalization is for routine treatment or

monitoring of the studied indication, or elective or pre-planned treatment of a pre-existing condition unrelated to the indication under study)

- Causes a congenital anomaly or birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

Toxicities which fall within the definitions listed above must be documented as an SAE regardless if they are felt to be treatment related or not.

9.11.3 Serious Adverse Event Reporting Requirements

An event determined to be an SAE must be reported to the IRB and the FDA according to the requirements described below:

IRB Notification:
The PI is responsible to report SAEs that meet the definition of an Unanticipated Problem through the ERICA system within 10 working days from the time the investigator learns of the event. An Unanticipated Problem is an event that is:

- **Unexpected** – unforeseen by the investigator in terms of nature, severity, or frequency, given the research procedures and the subject population being studied
- **Related or Probably Related** – determined by the investigator to be related or probably related to participation in the clinical trial
- **Greater Risk** – the severity or scope of the event suggests that the research places subjects or others at greater risk of harm than was previously known or recognized

FDA Notification:
FDA regulations require the PI to report any serious and unexpected adverse event for which there is a reasonable possibility that the drug caused the event. Fatal or life-threatening events that meet these criteria must be reported within 7 calendar days from the time the investigator learns of the event. All other reportable events must be reported within 15 calendar days. The SAE should be reported on a MedWatch form and submitted as an amendment to the IND. For studies without an IND, the MedWatch report should be submitted to the FDA through the voluntary reporting method.

9.11.4 Reporting of Pregnancy

Although pregnancy is not considered an adverse event, it is the responsibility of the PI or their designee to report any pregnancy or lactation in a subject, including the pregnancy of a male subjects' female partner as an SAE. Pregnancies or lactation that occurs during the course of the trial or within 30 days of completing the trial or starting another new therapy, whichever is earlier, must be reported to

the IRB, FDA, and the funding sponsor as applicable. All subjects and female partners who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events.

9.12 Study Protocol Modification or Study Termination

The study protocol will be modified if:

- If the adherence/recruitment is below expectation or not meet grant timelines

The study protocol will be stopped if:

- The funding is exhausted, or
- The risk to benefit ratio is higher than expected

10 STATISTICAL CONSIDERATIONS

The statistical analyses of the pilot study will evaluate feasibility and address questions concerning trial conduct and outcomes, as well as power analysis for sample size which must be resolved in order to develop a rigorous design for the full scale trial of the final study. These analyses will be primarily descriptive.

The statistical analyses to evaluate the effects of the intervention on the primary and secondary outcomes will be conducted in both the pilot and final studies. For the pilot study, we will apply the exact Wilcoxon rank sums test as adapted to compare the primary outcome defined by the ratio of recognized-to-total (i.e. CGM) hypoglycemic events between the amitriptyline and placebo treatments under the assumption of no-carry over effects. Hodges-Lehman estimates and associated exact 95% confidence intervals will provide estimates of the size of the treatment effect. Other outcomes will be analyzed using either a similar nonparametric approach or mixed effect models parameterized to estimate the effects of treatment and period.

11 DATA HANDLING AND RECORD KEEPING

Data collection is the responsibility of the clinical trial staff under the supervision of the PI. The investigator is ultimately responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. Do not erase, overwrite, or use correction fluid or tape on the original source data.

Case Report Forms (CRFs) will be utilized to capture data in the clinical study. Data collection processes and procedures will be reviewed and validated to ensure completeness, accuracy, reliability and consistency.

The PI and study team will conduct periodic reviews of the source data records and CRF database for completeness, consistency and accuracy. Study data will be collected and reported to the DSMB as required by the data and safety monitoring plan.

11.1 Records Retention

FDA investigational drug and device regulations, and GCP guidelines state that clinical trial records and essential documents should be retained for a minimum of 2 years after the last approval of a marketing application, or if no application is to be filed or if the application is not approved, at least 2 years have elapsed since the formal discontinuation or conclusion of the clinical trial. Refer to SOP #CTO-04 for maintenance and archiving of clinical trial records.

11.2 Disclosure and Publication Policy

This study will comply with the FDAAA regulations and NIH policy for registration and results reporting in the ClinicalTrials.gov database, as applicable. The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. Registration of the study in the ClinicalTrials.gov database prior to study initiation will comply with this policy.

The principal investigator will be responsible for developing publication procedures and resolving authorship issues.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 Institutional Review

The Institutional Review Board will review the application, protocol and all appropriate documentation in order to safeguard the rights, safety, and well-being of study subjects. The study will only be conducted at study centers where IRB approval has been obtained. The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by the IRB. If the protocol is amended, changes will not be implemented without prior review and approval from the IRB, except where necessary to eliminate an immediate hazard to study subjects.

12.2 Data and Safety Monitoring Plan

A review will take place of any adverse events that have occurred after every sixth subject has completed the study. Meetings/conference calls with members of the research team will be used as needed to discuss problems and make recommendations as an ongoing process throughout the study.

The clinical trial may be selected for audit within the scope of the Internal Audit Program. The purpose of an audit is to determine and evaluate adherence to applicable

federal regulations, to the study protocol and to GCP principles. The PI is responsible for working with the auditor in providing all needed study records and for developing corrective actions where necessary and ensuring complete and adequate responses to internal audit findings.

If the study is selected for an FDA or other federal agency inspection, the PI will make requested study records and study personnel records available for review (refer to SOP REG-01: FDA Inspections).

12.3 Protocol Deviations

A protocol deviation (or violation) is any departure from the defined procedures and treatment plans as outlined in the protocol version submitted and previously approved by the IRB. Protocol deviations have the potential to place participants at risk and can also undermine the scientific integrity of the study thus jeopardizing the justification for the research. Protocol deviations are unplanned and unintentional events.

Because some protocol deviations pose no plausible threat to participant safety or scientific integrity, reporting is left to the discretion of the PI within the context of the guidelines below. The IRB requires the **prompt reporting** (within 10 working days) of protocol deviations which are:

- Exceptions to eligibility criteria
- Intended to eliminate apparent immediate hazard to a research participant
- Harmful – caused harm to participants or others, or placed them at increased risk of harm, including physical, psychological, economic, or social harm
- Possible serious or continued noncompliance

12.4 FDA Annual Reporting

If this study requires IND approval, within 60 days of the anniversary date that the IND went into effect, a brief report of the progress of the investigation will be submitted to the FDA following the requirements set out in 21 CFR Part 312.33.

12.5 Clinical Trials Database

The clinical trial will be registered at initiation and study results will be reported on the ClinicalTrials.gov database as required per 42 CFR Part 11.

13 REFERENCES

1. Gold, A.E., K.M. MacLeod, and B.M. Frier, *Frequency of severe hypoglycemia in patients with type I diabetes with impaired awareness of hypoglycemia.* Diabetes Care, 1994. **17**(7): p. 697-703.
2. Clarke, W.L., et al., *Reduced awareness of hypoglycemia in adults with IDDM. A prospective study of hypoglycemic frequency and associated symptoms.* Diabetes Care, 1995. **18**(4): p. 517-22.

3. Pedersen-Bjergaard, U., S. Pramming, and B. Thorsteinsson, *Recall of severe hypoglycaemia and self-estimated state of awareness in type 1 diabetes.* Diabetes Metab Res Rev, 2003. **19**(3): p. 232-40.
4. Gonder-Frederick, L.A., et al., *Psychometric properties of the hypoglycemia fear survey-ii for adults with type 1 diabetes.* Diabetes Care, 2011. **34**(4): p. 801-6.
5. *The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group.* N Engl J Med, 1993. **329**(14): p. 977-86.
6. Nathan, D.M., et al., *Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes.* N Engl J Med, 2005. **353**(25): p. 2643-53.
7. *Hypoglycemia in the Diabetes Control and Complications Trial. The Diabetes Control and Complications Trial Research Group.* Diabetes, 1997. **46**(2): p. 271-86.
8. Cryer, P.E., *The barrier of hypoglycemia in diabetes.* Diabetes, 2008. **57**(12): p. 3169-76.
9. Cryer, P.E., *Mechanisms of hypoglycemia-associated autonomic failure in diabetes.* N Engl J Med, 2013. **369**(4): p. 362-72.
10. Geddes, J., et al., *Prevalence of impaired awareness of hypoglycaemia in adults with Type 1 diabetes.* Diabet Med, 2008. **25**(4): p. 501-4.
11. White, N.H., et al., *Identification of type I diabetic patients at increased risk for hypoglycemia during intensive therapy.* N Engl J Med, 1983. **308**(9): p. 485-91.
12. Leese, G.P., et al., *Frequency of severe hypoglycemia requiring emergency treatment in type 1 and type 2 diabetes: a population-based study of health service resource use.* Diabetes Care, 2003. **26**(4): p. 1176-80.
13. Klonoff, D.C., *Continuous glucose monitoring: roadmap for 21st century diabetes therapy.* Diabetes Care, 2005. **28**(5): p. 1231-9.
14. Rickels, M.R., et al., *Continuous Glucose Monitoring for Hypoglycemia Avoidance and Glucose Counterregulation in Long-Standing Type 1 Diabetes.* J Clin Endocrinol Metab, 2018. **103**(1): p. 105-114.
15. van Beers, C.A., et al., *Continuous glucose monitoring for patients with type 1 diabetes and impaired awareness of hypoglycaemia (IN CONTROL): a randomised, open-label, crossover trial.* Lancet Diabetes Endocrinol, 2016. **4**(11): p. 893-902.
16. Beck, R.W., et al., *Effect of Continuous Glucose Monitoring on Glycemic Control in Adults With Type 1 Diabetes Using Insulin Injections: The DIAMOND Randomized Clinical Trial.* Jama, 2017. **317**(4): p. 371-378.
17. Sanders, N.M. and S. Ritter, *Repeated 2-deoxy-D-glucose-induced glucoprivation attenuates Fos expression and glucoregulatory responses during subsequent glucoprivation.* Diabetes, 2000. **49**(11): p. 1865-74.
18. Abreu AV, A.R., Fisher SJ, *Prevention of Hypoglycemia Unawareness with Tricyclics [Abstract].* Diabetes, 2017. **66 (suppl 1)**: p. A96.
19. Kaur, H., et al., *A comparative evaluation of amitriptyline and duloxetine in painful diabetic neuropathy: a randomized, double-blind, cross-over clinical trial.* Diabetes Care, 2011. **34**(4): p. 818-22.
20. Max, M.B., et al., *Amitriptyline relieves diabetic neuropathy pain in patients with normal or depressed mood.* Neurology, 1987. **37**(4): p. 589-96.
21. Bansal, D., et al., *Amitriptyline vs. pregabalin in painful diabetic neuropathy: a randomized double blind clinical trial.* Diabet Med, 2009. **26**(10): p. 1019-26.

22. Administration, U.S.F.a.D. *Drugs@FDA: FDA Approved Drug Products - Abbreviated New Drug Application (ANDA): 085966* [cited 2018 March 15]; Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=085966.
23. Bril, V., et al., *Evidence-based guideline: Treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation.* Neurology, 2011. **76**(20): p. 1758-65.
24. McQuay, H.J., D. Carroll, and C.J. Glynn, *Low dose amitriptyline in the treatment of chronic pain.* Anaesthesia, 1992. **47**(8): p. 646-52.
25. Macfarlane, G.J., et al., *EULAR revised recommendations for the management of fibromyalgia.* Ann Rheum Dis, 2017. **76**(2): p. 318-328.
26. Srisurapanont, M. and N. Jarusuraisin, *Amitriptyline vs. lorazepam in the treatment of opiate-withdrawal insomnia: a randomized double-blind study.* Acta Psychiatr Scand, 1998. **97**(3): p. 233-5.
27. Hanno, P.M., et al., *AUA guideline for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome.* J Urol, 2011. **185**(6): p. 2162-70.
28. Vahedi, H., et al., *Clinical trial: the effect of amitriptyline in patients with diarrhoea-predominant irritable bowel syndrome.* Aliment Pharmacol Ther, 2008. **27**(8): p. 678-84.
29. Rowbotham, M.C., et al., *Treatment response in antidepressant-naive postherpetic neuralgia patients: double-blind, randomized trial.* J Pain, 2005. **6**(11): p. 741-6.
30. Davidson, J., et al., *Treatment of posttraumatic stress disorder with amitriptyline and placebo.* Arch Gen Psychiatry, 1990. **47**(3): p. 259-66.
31. Squires, N., A. Wills, and J. Rowson, *The management of drooling in adults with neurological conditions.* Curr Opin Otolaryngol Head Neck Surg, 2012. **20**(3): p. 171-6.
32. Evers, S., et al., *EFNS guideline on the drug treatment of migraine--revised report of an EFNS task force.* Eur J Neurol, 2009. **16**(9): p. 968-81.