Propranolol as a Treatment for Impaired Awareness of Hypoglycemia in Type 1 Diabetes Mellitus

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Propranolol Use for Treatment of Impaired Awareness of Hypoglycemia

IRB #: 101995

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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
CGM	Continuous Glucose Monitor
CFR	Code of Federal Regulations
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
GFR	Glomerular Filtration Rate
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
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NIH	National Institutes of Health
PI	Principal Investigator
SAE	Serious Adverse Event
T1DM	Type 1 Diabetes Mellitus

VMH	Ventromedial hypothalamus

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.

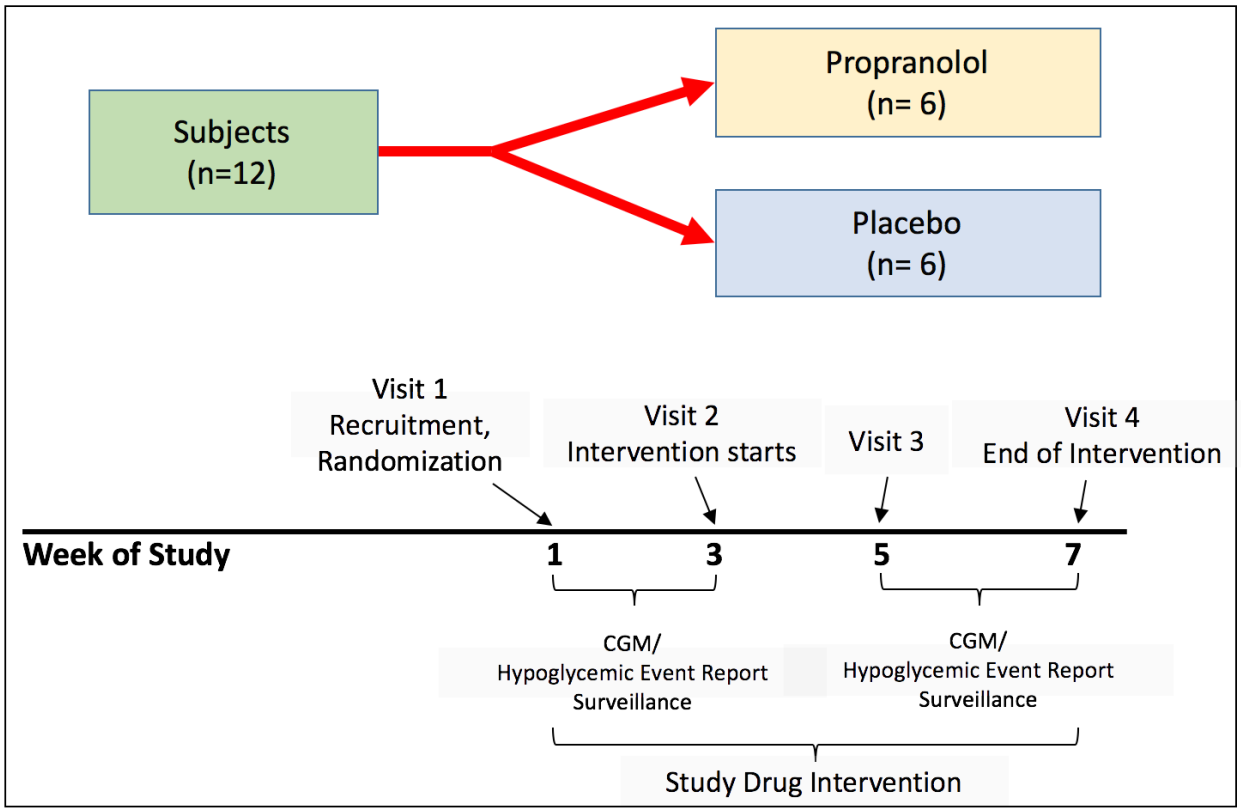
Note: This document is signed electronically through submission and approval by the Principal Investigator in the University of Utah IRB Electronic Research Integrity and Compliance Administration (ERICA) system.

STUDY SUMMARY

Title	Propranolol Use for Treatment of Impaired Awareness of Hypoglycemia
Short Title	Propranolol in treating hypoglycemia unawareness
Protocol Number	IRB #: 00101995
IND	Exempted; IND 135258
Phase	II Pilot
Design	Double-blinded, placebo-controlled
Study Duration	Up to 2 years for pilot study
Study Center(s)	University of Utah Health
Objectives	To evaluate whether propranolol will both improve hypoglycemia awareness and also reduce hypoglycemia severity and duration in type 1 diabetes patients with impaired awareness of hypoglycemia
Number of Subjects	Twelve subjects for pilot study
Diagnosis and Main Eligibility Criteria	Type 1 diabetes patients with impaired awareness of hypoglycemia Inclusion: • Type 1 diabetes for more than 5 years • Age between 21 to 59 years old • Hemoglobin A1C ≤ 9% • No beta-blocker use in last 6 months Exclusion: • Coronary, cerebral or peripheral vascular disease or other major cardiovascular diseases • Cardiac conduction abnormality or heart failure history • Advanced kidney/liver disease • Advanced diabetic microvascular complications • Contraindication, including hypersensitivity to beta-blockers
Study Product, Dose, Route, Regimen	Propranolol ER 80 mg oral daily or matching placebo oral daily
Duration of Administration	4 weeks of study drugs (propranolol ER or placebo)
Reference Therapy	Reference: Placebo

Statistical Methodology	The exact Wilcoxon rank sums test 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



CGM, continuous glucose monitoring

1. OBJECTIVES

1.1 Primary Objective

- To determine whether propranolol increases the recognition of hypoglycemic events

1.2 Secondary Objectives

- To determine whether propranolol improves hypoglycemia awareness questionnaire scores;
- To establish if propranolol reduces hypoglycemia severity and duration;
- To assess if propranolol decreases in onset-to-diagnosis/treatment and diagnosis/treatment-to-recovery duration and total hypoglycemia/severe hypoglycemia frequency (total/day/night);
- To establish whether propranolol decreases fear of hypoglycemia; and
- To determine if propranolol decreases overall mean blood glucose value.

2 BACKGROUND

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 with intensive insulin therapy and strict blood glucose control which target hemoglobin A1C to less than 7%. [1] However, tighter glycemic control correlates with a higher incidence of hypoglycemia and severe hypoglycemia. [2] Recurring exposure to hypoglycemia leads to an attenuated sympathoadrenal response to hypoglycemia (which is termed hypoglycemia-associated autonomic failure), and thus a loss or decrease in neurogenic hypoglycemic symptoms (i.e. impaired awareness of hypoglycemia). [3, 4] Impaired awareness of hypoglycemia is associated with a six-fold increased risk of severe hypoglycemia [5] and physician or patient-directed higher glycemic goals. Impaired awareness of hypoglycemia is therefore a major barrier in diabetes management, by precluding optimal glycemic control and realization of its full benefits. [3]

Several therapeutic strategies have been proposed to improve hypoglycemia awareness in T1DM patients. A temporal increase in glycemic goal only sustains hypoglycemia awareness recovery for a short-term. [6, 7] Islet transplantation is invasive, extremely expensive and requires life-long use of immunosuppressants. [8] A widely available and affordable treatment with sustained efficacy for improving hypoglycemia awareness is therefore in urgent need. Pharmaceutical agents targeting potential mechanisms that contribute to the development of impaired hypoglycemia awareness have been proposed, including beta-blockers, opioid receptor antagonists and selective serotonin uptake inhibitors (SSRIs). [4] However, none of these agents has been approved for the treatment of impaired hypoglycemia awareness.

In the current study, we will examine the clinical use of beta-blockers, specifically propranolol, for the treatment of impaired hypoglycemia awareness. Prior rodent studies suggest that norepinephrine levels in the ventromedial hypothalamus (VMH) increase during an *acute* bout of hypoglycemia and that the *acute* activation of the VMH beta-2 adrenergic receptors enhances the

counterregulatory response to hypoglycemia. [9, 10] However, previous studies investigating the effects of *repeated* VMH noradrenergic system activation suggested that recurring hypoglycemia dampened the counterregulatory hormone response to hypoglycemia [11], possibly due to repeated activation of VMH beta2-adrenergic receptors [12]. In addition, carvedilol (a non-specific beta-blocker) prevented the onset of hypoglycemia-associated autonomic failure in rats made recurrently hypoglycemic (Chan O, personal communication). Consistent with these findings, propranolol, which blocks beta-2 adrenergic receptors, has been shown to prevent hypoglycemia-associated autonomic failure in healthy human subjects [13]. These studies suggest that the mechanisms which contribute to the development of hypoglycemia-associated autonomic failure may lie downstream of β2-adrenergic receptor activation and, as previous studies demonstrated, that hypoglycemia avoidance will lead to recovery from impaired hypoglycemia awareness [6, 7]. Therefore, an intervention which can block the propagating mechanism(s) (i.e. repeated activation of beta2-adrenergic receptors) will likely lead to improvements in hypoglycemia awareness. Previous considerations of beta-blocker use in diabetes existed; however, both retrospective and prospective studies have proven its safety [14-22]. In addition, prior insulin clamp study suggested that propranolol increased overall hypoglycemia symptom scores by increasing diaphoresis, without compromising other neurogenic and neuroglycopenic symptoms. [23] We therefore believe that propranolol is a strong testing candidate for potential impaired hypoglycemia awareness treatment.

3 DRUG INFORMATION

Propranolol (investigational drug) has been approved by FDA for indications unrelated to the current study. [24] In the current study, we will use Propranolol extended release (ER). A summary of the FDA label for propranolol has been provided in the following.

Propranolol hydrochloride is a stable, white, crystalline solid which is readily soluble in water and ethanol. Its molecular weight is 295.80. Propranolol hydrochloride extended-release capsules are formulated to provide a sustained release of propranolol hydrochloride.

Propranolol is highly lipophilic and almost completely absorbed after oral administration. However, it undergoes high first pass metabolism by the liver and on average, only about 25% of propranolol reaches the systemic circulation.

Approximately 90% of circulating propranolol is bound to plasma proteins (albumin and alpha-1-acid glycoprotein). The binding is enantiomer-selective. The S(–)-enantiomer is preferentially bound to alpha-1-glycoprotein and the R(+)-enantiomer preferentially bound to albumin. The volume of distribution of propranolol is approximately 4 liters/kg. Propranolol crosses the blood-brain barrier and the placenta, and is distributed into breast milk. Propranolol is extensively metabolized with most metabolites appearing in the urine.

Propranolol is indicated for hypertension, angina pectoris due to coronary atherosclerosis, migraine and hypertrophic subaortic stenosis.

Propranolol is contraindicated in 1) cardiogenic shock; 2) sinus bradycardia and greater than first-degree block; 3) bronchial asthma; and 4) in patients with known hypersensitivity to propranolol hydrochloride.

There have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of propranolol therapy. Therefore, when discontinuance of

propranolol is planned, the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. Since this study will be using the lowest dose of propranolol LA, and the age of the tested population imposes a lower risk of significant atherosclerotic disease, the dose will not be tapered.

Propranolol is Pregnancy Category C based on animal studies. There are no adequate and well-controlled studies in pregnant women. Intrauterine growth retardation, small placentas, and congenital abnormalities have been reported in neonates whose mothers received propranolol during pregnancy. Neonates whose mothers are receiving propranolol at parturition have exhibited bradycardia, hypoglycemia and/or respiratory depression. Adequate facilities for monitoring such infants at birth should be available. Propranolol hydrochloride extended-release capsules should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The following adverse events were observed and have been reported in patients using propranolol.

Cardiovascular: Bradycardia; congestive heart failure; intensification of Atrioventricular node block; hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.
Central Nervous System: Light-headedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; catatonia; visual disturbances; hallucinations; vivid dreams; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. For immediate release formulations, fatigue, lethargy, and vivid dreams appear dose related.
Gastrointestinal: Nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.
Allergic: Hypersensitivity reactions, including anaphylactic/anaphylactoid reactions; pharyngitis and agranulocytosis; erythematous rash; fever combined with aching and sore throat; laryngospasm; respiratory distress.
Respiratory: Bronchospasm.
Hematologic: Agranulocytosis, nonthrombocytopenic purpura, and thrombocytopenic purpura.
Autoimmune: Systemic lupus erythematosus.
Skin and mucous membranes: Stevens-Johnson Syndrome, toxic epidermal necrolysis, dry eyes, exfoliative dermatitis, erythema multiforme, urticaria, alopecia, SLE-like reactions, and psoriasisiform rashes. Oculomucocutaneous syndrome involving the skin, serous membranes, and conjunctivae reported for a beta-blocker (practolol) have not been associated with propranolol.
Genitourinary: Male impotence; Peyronie's disease.

4 STUDY DESIGN

4.1 Description

The current investigation is a phase II pilot clinical trial with randomization and double-blinding design. After recruitment, the subjects will be randomized into two arms (Group 1 or Group 2), and under go a two-week assessment with Hypoglycemia Event Report and continuous glucose monitoring (CGM) with a Dexcom Professional CGM system. The subjects will then to be placed on either propranolol (Group 1) or placebo (Group 2) for a 4-week Intervention. Two weeks after the intervention is initiated, subjects will again be asked to undergo Hypoglycemic Event Report and CGM assessments for another two weeks.

4.2 Dose Limiting Toxicity

Propranolol ER will be administered at a dose of 80 mg daily during the Interventional Phase. This dose of propranolol is within the range of other indications that have been approved by FDA previously. If study subjects experience serious adverse events or intolerable toxicities determined by the PI to be related to treatment with propranolol, subjects will be discontinued from the trial, or treatment may be held for one week and resumed if adverse events resolve to a tolerable level as determined by the investigator.

4.3 Number of Subjects

Twelve patients will be enrolled and treated on this pilot study. We will use the collected information to conduct a power analysis to determine the number of subjects needed for the definitive trial.

4.4 Number of Study Centers

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

4.5 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 three months.

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 Type 1 diabetes for more than 5 years

2. _____ Age between 21 to 59 years old
3. _____ Hemoglobin A1C ≤ 9%; most recent value within 3 months
4. _____ No beta-blocker use history in the last 6 months
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. _____ History of coronary, cerebral, peripheral vascular or other major cardiovascular diseases
2. _____ History of cardiac conduction abnormality or heart failure
3. _____ History of advanced kidney disease
4. _____ History of advanced liver disease
5. _____ Active malignancy
6. _____Major Central or Peripheral Nervous System disease
7. _____ History of human immunodeficiency virus infection
8. _____ Contraindication to beta-blockers, including hypersensitivity to beta-blocker and bronchial asthma
9. _____ Female in pregnancy or not able to practice effective contraception during the study period
10. _____ Concomitant acetaminophen use
11. _____ Current use of unblinded real-time continuous glucose monitoring
12. _____ Advanced diabetic microvascular complications including retinopathy, neuropathy and nephropathy
13. _____ Inability to understand or cooperate with study procedure, including performing glucometer glucose assessment a minimum of four times a day, carrying glucose tablets and following standardized hypoglycemia treatment, completing hypoglycemia diary, wearing continuous glucose monitoring, and using a single glucometer
14. _____ Recent or current use or involvement in clinical studies of other therapies (e.g. opioid antagonist, behavioral modification, relaxation of glycemic control) that may improve hypoglycemia awareness or prevent impaired hypoglycemia awareness development

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 Group 1

After randomization and the initial two-week CGM assessment, subjects randomized to Group 1 will be initiated on propranolol ER 80 mg daily (before bedtime) for four weeks, and will then stop the intervention.

6.1.2 Group 2

After randomization randomization and the initial two-week CGM assessment, subjects randomized to Group 2 will be initiated on placebo: one capsule daily (before bedtime) for four weeks, and will then stop the intervention.

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

6.2.1 How Supplied, Stored, Packaged and Labeled

Propranolol ER 80 mg capsules: Over-encapsulated for blinding.
Matching placebo capsules: Capsules identical to the ones used to encapsulate propranolol ER 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] Protect from light, moisture, freezing, and excessive heat. Dispense in a tight, light-resistant container as defined in the USP.

6.2.2 Preparation and Administration

Subjects will be given a 4-week supply of blinded study medication at treatment visit 2. Subjects will be asked to return this supply with any unused capsules at the end of the intervention period.

6.2.3 Accountability and Compliance

Subjects will be asked to medication bottles and any unused capsules for reconciliation at the end of the intervention period.

6.3 Duration of Therapy

The standard treatment period for the interventional period (propranolol or placebo) will last 4 weeks (28 days).

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. 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.
- Development of severe hypoglycemia for which subject was required to visit emergency room or to be hospitalized

Discontinued or withdrawn subjects may be replaced on study to ensure completion of five study subjects in each treatment arm.

7 TOXICITIES AND DOSE MODIFICATION

Toxicities will be monitored in each study subject according to the study calendar and Section 9.9, 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, or treatment may be held for one week and resumed if adverse events resolve to a tolerable level as determined by the investigator.

8 STUDY CALENDAR

Period	**Screening**[1]	**Study**[2]			
			Intervention Phase		
Visit No.		1	2	3	4
Week	-4 to 1	1	3	5	7
Assessments					
Informed consent	X				
Inclusion/Exclusion criteria	X				
Demographics	X				
Vital signs	X		X		X
Physical Examination	X		X[3]	X[3]	X[3]
Hemoglobin A1C	X				
Pregnancy Test	X		X		
ECG	X				
AE Assessment			X	X	X
Concomitant Medications			X		X
Investigational Drug Treatment			X		
Primary Objective Assessment		X[4]		X[4]	
Secondary Objective Assessment		X	X		X

ECG, electrocardiogram; AE, adverse event

1. All screening procedures should be completed within 4 weeks of study enrollment, except that an ECG completed within 3 months will be considered as valid. Screening visit and Study Visit 1 may occur on the same day.
2. All visits within the Intervention Phase should occur within ± 3 days of the target dates. Pregnancy test which must be completed within 48 hours before investigational drug treatment starts.
3. Physical exam to be conducted at the discretion of PI/Sub-investigator based on reported adverse events.
4. Two-week assessment with Hypoglycemia Event Reports and continuous glucose monitoring.

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 Pre-screening

The principal investigator (PI) will work with the University of Utah Enterprise Data Warehouse (EDW) and generate a list of potential candidates with based on the elements of inclusion/exclusion criteria (e.g. type 1 diabetes, age, recent hemoglobin A1C, etc) on the Human Subject Recruitment tool. Human Subject Recruitment tool is a computer software managed by EDW for subject recruitment with a constantly updating database, and this tool has been utilized by clinical investigators at the University of Utah. PI will review of these candidates' medical charts for further candidate selection.
The list of potential candidates will then be used to recruit subjects in the following routes:

1) The primary care physicians or Endocrinologists with established clinical relationship 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 offered to the potential candidates by the medical assistants of physicians with established clinical relationship with these candidates, with permissions of the physicians.

3) A recruitment letter sent via mail or myChart message to the potential candidates, and if no response is received in at least 7 days, a phone call may be generated to discuss the study.

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 interested candidates, we will proceed with further eligibility pre-screening through telephone discussions and mailing paper surveillance of Personal Medical History and Hypoglycemia Awareness Questionnaires. A copy of the consent form will also be mailed to the candidates to look over for at least 1 day before obtaining consent.

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

Social Networking Sites: We may share recruitment materials on social network sites such as Facebook or Instagram that provide a brief announcement and description about the study, along with study contact information directing interested individuals to the University of Utah study coordinator(s). Current required IRB disclaimer language will be attached to all online recruitment materials utilized.* Recruitment language options are being attached as a word document to this study application. This recruitment language may be utilized in any of the above methods at various times throughout the recruitment period of the study. If the study team determines that IRB approved recruitment language requires a substantive change, we will submit that language to the IRB prior to use.

*IRB Disclaimer Language (required for all social media recruitment)
The information posted on this site is consistent with the research reviewed and approved by the University of Utah Institutional Review Board (IRB). However, the IRB has not reviewed all material posted on this site. Contact the IRB if you have questions regarding your rights as a research participant. Also contact the IRB if you have questions, complaints, or concerns which you do not feel you can discuss with the investigator. The University of Utah IRB may be reached by phone at 801-581-3655 or by email at irb@hsc.utah.edu.

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 study compensation being an undue influence, we will not share compensation information during pre-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 Screening and 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. 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 T1DM, and other relevant past medical history will be collected during the screening period and recorded in the appropriate CRF.

9.5 Laboratory Variables

Hemoglobin A1C and pregnancy test will be performed as indicated on the Study Calendar. Hemoglobin A1C Analysis 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 Hemoglobin A1C

Hemoglobin A1C: Hemoglobin A1C, blood

9.5.2 Pregnancy Testing

Urinary pregnancy test: Qualitative Beta-human chorionic gonadotropin, urine

9.5.3 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, and heart rate are to be conducted.

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 the studied medications (propranolol/placebo) through the last study visit will be documented and recorded in the CRF.

9.9.1 Prohibited Concurrent Medications

The following medications are prohibited during the study:

- Beta-blockers other than propranolol
- Naltrexone and other medications that have been proposed to have the potential in improving hypoglycemia awareness or preventing the development of impaired awareness of hypoglycemia

9.9.2 Prohibited Procedure

The use of un-blinded continuous glucose monitoring is prohibited during the study. Behavioral modifications or relaxation of glycemic control aiming to improve hypoglycemia awareness are prohibited.

9.10 Efficacy Measurements

9.10.1 Primary Objective Assessment

The primary objective assessment will be done through the determining the total and self-reported hypoglycemic events based on CGM data and hypoglycemia diary, respectively.

A single CGM hypoglycemic episode will be defined by any CGM readings < 70 mg/dL, followed by at least one reading ≥ 70 mg/dL from the Dexcom Professional Mobile CGM system. A subject's self-reported hypoglycemic episode will be defined by a hypoglycemic symptom record on the hypoglycemia diary with a confirmatory glucose value (glucometer value < 70 mg/dL, or CGM glucose value < 70 mg/dL if glucometer value is not available), or an incidental glucometer value < 70 mg/dL if no hypoglycemia symptom develops.

The Hypoglycemia Event Report includes the initial glucometer value and time and treatment time; the first and the most prominent symptom during the hypoglycemia episode; whether the episode requires outside help (severe hypoglycemia).

At the end of each hypoglycemia event report/CGM assessment (i.e., visits 2 and 4), CGM data will be downloaded into a secure system and exported into an Excel format, and Hypoglycemic Event Reports will be collected for analysis.

The primary objective to determine whether propranolol increases the recognition of hypoglycemic events will be determined by an increase in the ratio of self-reported hypoglycemic events over total (i.e. CGM) hypoglycemic events while subjects are in the intervention period treated with propranolol compared to placebo.

9.10.2 Secondary Objective Assessment

Data for the secondary objective assessments will be collected through hypoglycemia awareness questionnaires (Gold, Clark and Pedersen-Bjergaard) [25-27], CGM data, and Fear of Hypoglycemia Questionnaire [28]. The questionnaires will be completed by study subjects at the first, second and the last visit of the study.

The questionnaires and CGM data will be used to determine changes in hypoglycemia awareness, severity and duration of hypoglycemia, onset-to-diagnosis/treatment and diagnosis/treatment-to-recovery durations, fear of hypoglycemia, and overall mean blood glucose values in subjects during the intervention period treated with propranolol compared to placebo.

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 Safety Monitoring

Vital signs, including heart rate and blood pressure, and adverse events will be assessed during the screening and at the beginning and the end of the interventional phase. Physical examination will be conducted and instruction for further medical assessment will be provided if needed. A pregnancy test will be conducted during the screening and before the study drug intervention. The subjects will be provided contact information for questions and needs related to the study.

9.11.2 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 propranolol and placebo and continue through the last treatment 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 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.
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. 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.

9.11.3 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.

9.11.4 Serious Adverse Event Reporting Requirements

An event determined to be an SAE must be reported to the IRB 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

9.11.5 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. 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 cross-over trial as 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 [S1, S2] to compare the primary outcome defined by the ratio self-reported hypoglycemic events over total (i.e. CGM) hypoglycemic events between the propranolol and placebo treatments under the assumption of no-carry over effects. Hodges-Lehman estimates [S3] 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, period, and carryover [S4].

S1. Tudor, G., & Koch, G. G. (1994). Review of nonparametric methods for the analysis of crossover studies. *Statistical Methods in Medical Research*, 3(4), 345-381.
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S3. Hettmansperger, T. (1991). Statistical Inference Based on Ranks. Krieger, Malabar, FL
S4. Jones, Byron, and Michael G. Kenward. Design and Analysis of Cross-Over Trials. CRC Press, 2014.

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 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 University of Utah 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 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

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