Study Protocol Title:

Ketone Monitoring Approaches for Diabetic Ketoacidosis Risk Mitigation in People with T1D on Adjunctive SGLT-2 Inhibitors (KARMA)

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List of Abbreviations:

ADA	American Diabetes Association
ASA-24	Automated Self-Administered 24-hour dietary assessment tool
BMI	Body mass index
BOHB	Beta-hydroxybutyrate
CBC	Complete blood count
CGM	Continuous glucose monitor
CKM	Continuous ketone monitor
CMP	Comprehensive metabolic panel
DGK	Dual Glucose / Ketone Monitoring system
DKA	Diabetic ketoacidosis
eGFR	Estimated glomerular filtration rate
FDA	U.S. Food and Drug Administration
HbA1c	Hemoglobin A1c/ Glycated hemoglobin
IPAQ	International Physical Activity Questionnaire
IWT	Insulin Withdrawal Test
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
RFA	Request for applications
SGLT-2i	Sodium-glucose co-transporter-2 inhibitors
T1D	Type 1 diabetes
TSH	Thyroid stimulating hormone
UACR	Urine albumin creatinine ratio

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Introduction

This document is a protocol for a human research study. This study is to be conducted in accordance with AH and FDA institutional research requirements and Good Clinical Practices (GCP) International Conference on Harmonization (ICH) Guidelines (E6) for GCPs standard.

Background Information and Scientific Rationale

SGLT-2 inhibitors were originally approved by the FDA to improve glycemic control in people with type 2 diabetes (T2D), in whom they provide additional clinical benefits – including decreasing risk of hospitalization for heart failure, slowing of the progression of chronic kidney disease, and decreasing the risk of major adverse cardiovascular events (1, 2). Although these additional benefits would provide great value for patients with type 1 diabetes (T1D), the FDA did not approve use of SGLT-2 inhibitors as adjunctive treatments for T1D because of an increased in the risk of diabetic ketoacidosis (DKA) observed in phase 3 clinical trials (3). Published phase 3 clinical trials for SGLT-2 inhibitors in T1D all included self-monitoring of plasma beta-hydroxybutyrate (BOHB), but this type of intermittent monitoring of BOHB levels failed to completely prevent what the FDA viewed as an unacceptable increase in the risk of severe adverse DKA events. Recent technological advances have enabled continuous monitoring of BOHB levels in interstitial fluid – raising the possibility that continuous monitoring of BOHB levels could more effectively mitigate the increased risk of DKA in SGLT-2 inhibitor-treated patients with T1D. NIDDK created an RFA to support pragmatic research to investigate continuous ketone monitoring (CKM) technology with the objective of increasing safety of SGLT-2 inhibitors in patients with T1D. The next step to progress the field is to develop and test pragmatic risk mitigation strategies that clinically integrate continuous Ketone Monitoring (CKM) technology with SGLT-2 inhibitor use. To achieve this objective, we propose addressing three critical questions required to implement an effective risk mitigation strategy based on continuous BOHB monitoring in adults with T1D:

a) What BOHB levels indicate increased risk of developing ketoacidosis?
b) What intervention(s) should be triggered in response to BOHB levels indicating increased risk?
c) Is it possible to design an effective “one-size-fits-all” approach for risk mitigation with SGLT-2 use or is it preferable to individualize the approach to account for variation among individual patients?

Overarching Aim

To develop a risk mitigation strategy employing continuous ketone monitoring that will allow SGLT-2 inhibitors to be safely used in patients with T1D to reduce risk for chronic kidney disease progression and cardiovascular disease.

Overarching Hypothesis: A novel risk mitigation strategy accounting for the physiological effects of SGLT-2 inhibitors on the development and resolution of ketosis will be effective at reducing the number and severity of ketosis events.

We will test this hypothesis by completing two specific aims in a clinical study. The specific aims of the clinical study are:

Primary Objective/Aim/Goal/Hypothesis

Aim 1 of the clinical study is to determine how adjunctive SGLT-2 inhibitor use affects the development and resolution of ketosis and ketoacidosis in adults with T1D by comparing, in a highly controlled, inpatient setting:

1a. The time course of ketosis and ketoacidosis during insulin withdrawal (mimicking insulin pump failure or missed insulin injections) in patients with T1D on insulin therapy to that on insulin + adjunctive therapy with an SGLT-2 inhibitor and

1b. Insulin and carbohydrate requirements to reverse ketosis during these conditions.

Hypothesis: We hypothesize that, compared to insulin alone, adjunctive SGLT-2 inhibitor use will increase the rate of increase and maximal levels of ketones and ketoacidosis during insulin withdrawal in participants with T1D. This will necessitate adapting CKM ketone thresholds for DKA risk mitigation in participants with T1D on adjunctive SGLT-2 inhibitor. It may also suggest a more aggressive recovery protocol is required for those who develop ketosis on SGLT-2 inhibitors as opposed to those not on drug.

Secondary Objective/Aim/Goal/Hypothesis

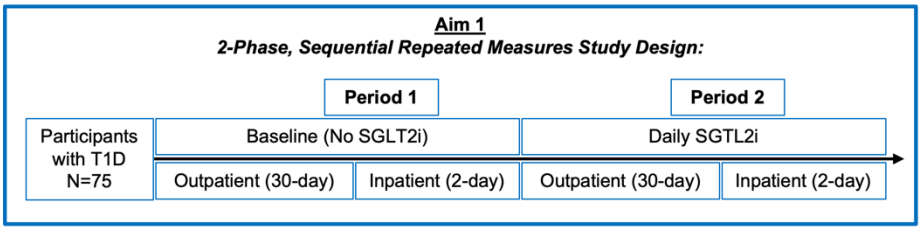
Aim 2 of this clinical study is to test the effectiveness of a CKM-enabled personalized DKA risk mitigation strategy that accounts for the increased risk for ketosis and ketoacidosis with SGLT-2 inhibitors compared to a generalized DKA risk mitigation plan, for reducing ketone events.

Hypothesis: We hypothesize that a personalized strategy (including ketone thresholds, carbohydrate intake, insulin dose, and other physiological factors) accounting for the effects of SGLT-2 inhibitors on the development and resolution of ketosis will be more effective at reducing ketosis events than a generalized one-size-fits-all approach.

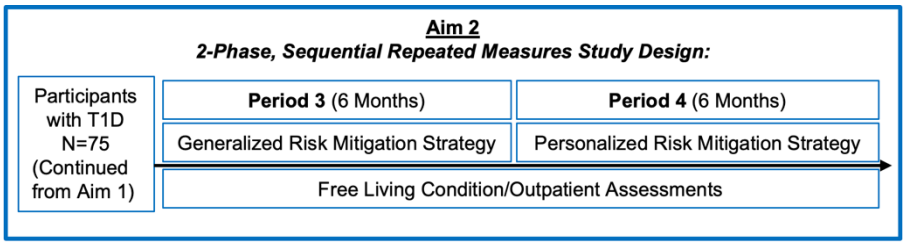
Study Design

Research Design

Aim 1 will be a repeated measures design used to compare changes in ketones during two different settings, which include: 1) outpatient free-living conditions in the presence and absence of an SGLT-2 inhibitor and 2) during a highly controlled inpatient insulin withdrawal test that is expected to increase ketones (and therefore increase DKA risk) in the presence and absence of an SGLT-2 inhibitor. Secondarily, the recovery protocols that reverse elevated ketones during the insulin withdrawal test will be refined. This will be tested during Period 1 and Period 2 of the clinical trial.



Aim 2 will use a sequential, 2-phase study design to compare the number of ketone events during a generalized risk mitigation strategy vs. a personalized risk mitigation strategy. In Phase I/ Period 3 (6 months in duration), we will implement a generalized DKA risk mitigation strategy. In Phase 2/ Period 4 (6 months in duration), we will implement a personalized DKA risk mitigation strategy. We expect that ketone events will be reduced on the personalized risk mitigation plan (Phase 2, Period 4), compared to a generalized risk mitigation plan (Phase 2, Period 3). We will actively update 'decision tree algorithms' for broad risk mitigation advice to incorporate new learnings (including ketone thresholds, carbohydrate intake, insulin dose, and other physiological factors) during the duration of the award period (hence 'adaptive') to better inform clinical advice that is provided for risk mitigation. Factors that may be considered when designing the personalized risk mitigation strategy could include the number, frequency and magnitude of ketone events during SGLT-2 inhibitor use, the rate of development of ketosis during insulin withdrawal, insulin and carbohydrate doses to resolve ketosis during the insulin withdrawal test, demographic factors including age, sex, and BMI and T1D related factors including duration of disease, HbA1c and insulin dose.



The participant cohort that is recruited for Aim 1 is the same cohort that will complete Aim 2. Therefore, the recruitment and retention plan and eligibility criteria for Aim 1 applies to Aim 2.

Research Intervention Description

Aim 1 will use the following interventions: continuous ketone monitor/ continuous glucose monitor (device), sotagliflozin, an SGLT-1 and 2 inhibitors(drug) and generalized DKA risk mitigation strategy. Descriptions of these interventions are below.

Device Description:

The Abbott Sensor Based Dual Glucose / Ketone Monitoring System is intended to monitor interstitial fluid glucose levels and β-hydroxybutyrate (β-ketone) levels in persons aged 2 and older. The System is manufactured by Abbott Diabetes Care and consists of two primary components.

- A disposable sensor application device (Sensor Applicator), that is used to adhere the disposable sensor assembly (Sensor) to the skin. The sensor assembly contains on-body electronics that connect to a subcutaneously implanted electrochemical dual glucose and β-ketone sensor that is inserted just below the surface of the skin. The sensor adheres to the skin of the user.
- A smartphone with a mobile app which activates the sensor and continuously logs glucose and ketone readings via Bluetooth and/or other electronic communication with the sensor. The device's dynamic range for glucose is between 40 and 400 mg/dL. The device’s dynamic range for β-ketone is between 0.0 and 3.0 mmol/L.

Smartphones, sensors, and sensor applicators are uniquely identifiable through individual serial numbers. The Abbott Sensor Based Dual Glucose / Ketone Monitoring (DGK) System is a dual glucose and ketone sensor. To measure two analytes, the investigational device will contain two working electrodes such that one electrode measures glucose and the other measures ketones. These measurements will not be used for treatment adjustment decisions but would rather prompt a confirmatory test of capillary glucose or ketones.

The DGK device is currently under review by the FDA.

Study drug (Sotagliflozin):

Sotagliflozin is an oral antihyperglycemic drug that works as a dual inhibitor of the sodium glucose co-transporters 1 and 2, referred to as SGLT-1 and SGLT-2, to lower blood glucose through mechanisms that are insulin-independent. Sotagliflozin is approved for the treatment of heart failure based on the results of two pivotal phase 3 cardiovascular outcomes studies in over 12,000 participants with T2D that demonstrated statistically significant and clinically meaningful efficacy of sotagliflozin in reducing the composite outcome of CV death, hospitalization for heart failure, and urgent visits for heart failure.

Sotagliflozin has also been studied in three randomized controlled phase 3 studies in almost 3000 participants with T1D. Each of these studies showed statistically significant reductions in HbA1C as well as effects on clinically relevant secondary endpoints. However, an increased risk of DKA was noted in these studies and as a result, sotagliflozin has not received FDA approval for glycemic control in T1D.

Rationale for dose selection:

Sotagliflozin has been studied at doses of 200 mg and 400 mg p.o. once daily in phase 3 trials in participants with T2D and T1D. In the SOLOIST and SCORED trials, which demonstrated a significant CV benefit in participants with T2D, participants were to start on 200 mg p.o. once daily then advance the dose to 400 mg p.o. once daily if tolerated. In 2 of the 3 Phase 3 trials in participants with T1D, both the 200 mg and 400 mg once daily doses were tested. In the 3rd trial, only the 400 mg daily dose was tested. While the risk of diabetic ketoacidosis was increased in participants with T1D relative to placebo, it was still uncommon (5% of subjects) and did not appear to be dose-dependent.

In the present study, sotagliflozin will be dosed at 200 mg p.o. once daily for the first two weeks, then the dose will be increased to 400 mg p.o. once daily as tolerated following the strategy for T2D as well that used in the majority of T1D participants in phase 3 studies. The rationale for this strategy is that the 400 mg daily dose was the most efficacious dose for glycemic control and weight reduction in participants with T1D and is aligned with the dose demonstrated to have CV benefits in T2D. Moreover, this dose does not seem to be associated with an increased risk of DKA or other adverse events, relative to the 200 mg daily dose.

Sotagliflozin will be stored between the temperature of +15°C and +30°C (59°F and 86°F). Drug will be dispensed by our study pharmacist for the duration of outpatient assessment period. The participants will take the drug for ~ 13 months.

As sotagliflozin is not currently approved by the FDA as adjunctive to insulin therapy in people with T1D, an investigator-initiated Investigational New Drug (IND) application will be filed for sotagliflozin for the purposes of this study. The principal investigator will ensure that 21 CFR 11, 21 CFR 54, 21 CFR 210, 21 CFR 211, 21 CFR 312, 21 CFR 812, and 21 CFR 820 regulations are understood and met. This includes but is not limited to adhering to consenting requirements, protocol adherence, record keeping, coordinating reports to be submitted directly to the FDA such as serious, unexpected adverse reactions reports, annual reports, amendment submissions, study/project closures.

Aim 2 will use the following interventions: continuous ketone monitor/ continuous glucose monitor (device) and sotagliflozin (drug), which are described above. Aim 2 will additionally use a generalized and a personalized DKA risk mitigation strategy that is described below.

Generalized DKA Risk Mitigation Strategy: We will implement a generalized risk mitigation strategy based upon published protocols in clinical use. This strategy includes two components, which are 1) the clinical integration of CKM devices that provide participants with real time monitoring of interstitial ketones and glucose values potentially alerting participants to an upcoming ketone event and 2) patient education on DKA risks of with SGLT-2 inhibitors as well as resolution protocols. We will use protocols that were previously developed in the **STOP DKA Protocol** {Goldenberg, 2019 #1324}. This protocol includes educating patients on DKA risk mitigation steps: **S**ymptoms, **T**esting ketones and glucose every 2-4 h, **O**ral ingestion of fluid (250-500 mL) and carbohydrates (30-60 carbohydrates) every 2-4 h and follow **P**rotocol instructions for supplemental insulin and carbohydrates. This protocol includes general guidelines for DKA resolution, and various ketone ranges are associated with recommendations for insulin, carbohydrates, and fluid intake instructions.

- **Patient Education**: Participants will be given educational materials covering relevant medication and safety information including an introduction to SGLT-2 inhibitors, diabetic ketoacidosis including euglycemic ketoacidosis, continuous ketone monitoring, and instructions for who to contact if high (>1.0 mmol/L) ketone levels are detected. Patient education materials will be provided via multiple media to respond to individual learning styles and preferences, including web-based blog posts, audio podcasts, and videos.
- **Weekly Telephone Follow-ups**: Participants will communicate with the study team on a weekly basis through electronic means (e.g., phone calls, telehealth, or a secure TEAMS or via EPIC communication) to review any symptoms of DKA or perceived issues with the CKM device and/or the SGLT-2 inhibitor. During these visits, we will also assess whether there are any safety issues related to glycemic control that might warrant adjustment of the insulin dose.

Personalized risk mitigation strategy: The personalized DKA risk mitigation strategy maintains the two components of the generalized risk mitigation strategy described above. We will revise the previously developed **STOP DKA Protocol** {Goldenberg, 2019 #1324} to include personalized ketone ranges based on findings from the outpatient and inpatient testing. Thus, the **central feature** of the personalized risk mitigation strategy is the addition of personalized ketone thresholds and ketosis recovery protocols. While it is difficult to predict with precision, we expect that there will be between-subject heterogeneity in ketone events that is sufficient to warrant participant-specific ketone thresholds associated with risk mitigation strategies, and we aim to account for these differences using personalized advice. We will also take into account external factors including diet and exercise when formulating personalized risk mitigation advice.

- **Adaptive Patient Advice through Education Materials:** Participants will continue to receive education materials on relevant medication and safety information. We will **adapt and disseminate** these materials to reflect new learnings from the outpatient and inpatient testing on a semi-annual basis. Education materials will be re-distributed via multiple mediums including web-

based blog posts, audio podcasts, and videos. We expect that findings related to the heterogeneity of ketone responses and DKA symptoms will be used to develop and disseminate risk mitigation strategies. We will additionally assess patient education materials for effectiveness at 1 month and 6 months after study enrollment using the Patient Education Materials Assessment Tool (PEMAT) Shoemaker, 2014 #1325}. The PEMAT is a validated instrument used to systematically assess the understandability and actionability of both print and audiovisual patient education materials.

Study Site(s)/Location(s) and Number of Subjects

AdventHealth sites (hospital(s), campus, physician offices, etc.): AdventHealth Translational Research Institute, AdventHealth Orlando.

Estimated number of subjects at AdventHealth sites: ~150 screened, 75 enrolled

Name of external site(s) outside of AdventHealth: N/A

Estimated number of subjects at external sites: N/A

Total number of all sites: 1
Estimated number of subjects at all sites combined: 150

Multi-Site Research Logistics/Communication Plan

N/A

Research Conducted in a Foreign Country

N/A

Community-Based Participatory Research

We will leverage our relationships with the T1D stakeholders, associations of patients with T1D, advisory board, and theT1D community for this research. The engagement of stakeholders and the incorporation of multiple, diverse perspectives beyond the traditional research team in the execution of the proposed study will improve research quality and acceptability, as well as the generalizability and translation of the results into clinical practice. In particular, people with T1D will provide a unique perspective into the burden of diabetes and DKA, as well as insight into the feasibility and acceptability of interventions to address these issues.

Subject Selection

Vulnerable Populations (if applicable)

AdventHealth Employees: Recruitment efforts will follow AdventHealth recruitment Standard Operating Procedures (SOPs) for research. AdventHealth employees will not be individually targeted nor excluded from study participation based on employment. AdventHealth employees who engage the AdventHealth Translational Research Institute asking to participate in the study will be processed per standard consent procedures for participants. In addition, during the consent process, the study staff will review standard consent language stating that an employee's participation or lack of participation in the study will not affect their employment status or relationship with AdventHealth.

Students: Students will not be individually targeted nor excluded from study participation based on employment.

Inclusion Criteria

1. Men and nonpregnant women ≥18 years and older
2. Diagnosis of T1D according to American Diabetes Association (ADA) criteria
3. HbA1c < 9 %
4. Participants treated with multiple daily injections of insulin, insulin pump, or advanced insulin delivery systems
5. Has provided written informed consent to participate in the study.
6. Must be willing to wear the investigational device
7. Use of adequate contraception for the duration of the study by women of childbearing potential

Exclusion Criteria

1. Pregnancy, lactation or planning to become pregnant
2. Any form of diabetes other than T1D
3. People with T1D using weekly insulin (when approved)
4. Use of sodium-glucose cotransporter 2 inhibitors within 4 weeks prior to screening
5. Chronic systematic corticosteroids (>4 consecutive weeks) within 6 months before screening
6. History of diabetic ketoacidosis within 6 months of screening
7. History of multiple (≥ 3 infections) genital mycotic infections within 6 months of screening
8. Hypotension at screening is defined as systolic blood pressure < 90 and diastolic blood pressure < 60 with symptoms of low blood pressure (confusion, dizziness, lightheadedness, fainting, heart palpitations)
9. History of a level 3 hypoglycemic event (as defined by ADA criteria) within 3 months of screening

10. Recent myocardial infarction, stroke, hospitalization for unstable angina or heart failure within 3 months prior to screening
11. New York Heart Association Class IV heart failure
12. CKD-EPI estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m²
13. Impairment of systems and organs that may increase their risk of participating in the intervention study or compromise the results (for example: end stage kidney disease, active liver dysfunction, gastroparesis, anemia,), organ transplant.
14. Cancer treatment (excluding non-melanoma skin cancer treated by excision, carcinoma in situ of the cervix or uterus, ductal breast cancer in situ, resected non-metastatic breast or prostate cancer) within one year of screening
15. Active Hepatitis B or C, acquired immunodeficiency syndrome (HIV infection controlled with suppressive medications is allowed) or tuberculosis
16. Abnormal liver function at screening defined as any of the following: aspartate aminotransferase (AST) >2X upper limit of the normal reference range (ULN), ALT >2X ULN, serum total bilirubin (TB) >1.5X ULN
17. Current or past history of decompensated cirrhosis (defined as variceal bleeding, ascites, or hepatic encephalopathy), and/or known diagnosis of cirrhosis
18. Heavy alcohol use (for men, ≥5 drinks on any day or ≥15 drinks per week; for women, ≥4 drinks on any day or ≥8 drinks per week) at screening, history of alcohol use disorder or binge drinking
19. Any condition or factor that would compromise the participant's safety or the scientific integrity of the study (cognitive impairment, bipolar disorder, or history of eating disorder)
20. Inability to perform the study follow up/ unwilling to wear the investigational device
21. People who are unwilling to consume at least 20% of calories from carbohydrates

Female contraception: Females of childbearing potential, must use clinically acceptable and highly effective methods of contraception/birth control during the entire study. Examples of these include an IUD, hormonal implant, or surgical sterilization (tubal ligation or hysterectomy). If they use other methods of birth control, like not having sex, hormonal birth control (pills, patch, or injections), vaginal ring, a condom or barrier methods, they must use TWO of these methods together throughout the course of the study.

Resources Available

We attest that all AdventHealth Translational Research Institute faculty and staff will be trained, and this training will be documented as described in AdventHealth Translational Research Institute Work Instruction 031.100.015 Documentation of Protocol Training.

We will implement regular, ongoing discussions between the PI, the study team and coordinator as per the AdventHealth Translational Research Institute SOP 030.000.002 Oversight of Research Studies at the Translational Research Institute. The coordinator will review source and communicate with all applicable study team members involved in the study on a regular basis regarding reportable new information, implementing amendments, study progress, and quality assurance/control.

The AdventHealth Translational Research Institute facilities are state-of-the-art, and we have within our building all the required resources and staff to execute the study. We have a medical oversight team, Medical Oversight Committee, and a Quality Committee to appropriately monitor and address adverse events.

Study Procedures

Subject Recruitment and Screening

Recruitment methods utilized may include, but will not be limited to, the following: recruitment from within the AdventHealth TRI patient population, electronic medical records and database searches (including third party recruitment vendors); advertising in multiple media such as print ads, flyers, brochures, posters; radio ads; television spots; and internet/social media advertising. All advertising materials will be submitted to the AdventHealth IRB for review prior to using or publishing them. Recruitment efforts will follow AdventHealth recruitment SOPs for research.

Consent Process

We attest that all study staff delegated the authority to obtain informed consent will follow CW AHC 216, “Informed Consent Process and Written Documentation of Informed Consent”. Upon consent, a research team member will provide the participant with a copy of the signed consent and the original consent form placed in the participant’s chart

Subjects who are not yet adults (infants, children, teenagers)

N/A

Cognitively Impaired Adults

N/A

Adults Unable to Consent

N/A

Documentation of Informed Consent Process

Documentation of the informed consent process is required to establish that the subject was accurately and adequately informed and that no study-related procedures were initiated prior to obtaining informed consent. A research team member will note in the source documentation the consent process, date consent was obtained, and that consent was obtained prior to initiating any research procedures.

Waiver of Written Documentation of Consent or Waiver of Consent

Waiver of Written documentation of Consent (consent will be obtained but signatures will not be required)

N/A

Waiver or Alteration of the Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception)

N/A

Waiver or Alteration of HIPAA Authorization

A partial waiver of HIPAA authorization will be requested.

Non-English-Speaking Subjects

Spanish speaking participants will be enrolled to ensure that the study cohort accurately reflects the racial and ethnic composition of the local population., The consent form along with all the study educational materials will be translated in Spanish by the qualified bilingual team. Additionally, the bilingual qualified staff will conduct weekly telehealth consultation follow-ups in the study. Potential participants who do not speak English or Spanish will not be enrolled at the present time.

Randomization

N/A

Study Visits

The study will enroll 75 participants with T1D. The study will have the following periods:

1. Period 1: Baseline without SGLT-2 inhibitor (~32 days)
2. Period 2: Baseline with SGLT-2 inhibitor (~32 days)

3. Period 3: Risk mitigation strategy- Generalized Risk Mitigation Strategy (~ 6 months: this will include 1 month of Period 2 as participants will be on the SGLT-2 inhibitor during Period 2 and will follow the generalized risk mitigation strategy)
4. Period 4: Personalized Risk Mitigation Strategy (~ 6 months)

The following table summarizes the duration of each period.

Study Periods	Description	Duration	Location
Screening	Screening visit	1 day	AdventHealth Orlando Translational Research Institute (TRI) Outpatient clinic
Period 1	Baseline phase without SGLT-2 inhibitor use	30 consecutive days	Outpatient
		2 consecutive days	TRI Clinical Research Unit – inpatient
Period 2	Baseline phase with SGLT-2 inhibitor use	30 consecutive days	Outpatient
		2 consecutive days	TRI Clinical Research Unit – inpatient
Period 3	Risk mitigation strategy – generalized care	6 months (including 1 month of Period 2)	Outpatient
Period 4	Risk mitigation strategy – personalized	6 months	Outpatient

SCREENING

Screening visit (SV) / (Day –28 – Day –7): Outpatient; ~ 2 – 3 hours

This study visit will take place in AdventHealth Orlando Translational Research Institute (TRI) Outpatient clinic. Participants will arrive for this visit after an 8 hour overnight fast. After obtaining the informed consent, the potential participant will undergo a screening visit to confirm eligibility as per the eligibility criteria. The screening visit will include:

- **Consent Process Checklist** assessing the potential participants' understanding of and willingness to perform all study activities.

- **Demographics and complete medical history** (including, but not limited to, alcohol use, concomitant medications, health conditions, allergies, and exercise habits)
- **Standard physical examination** is performed by a study physician, physician assistant, or nurse practitioner. Standard physical examination includes general status, skin, HEENT, neck, cardiovascular, lungs, abdomen, upper and lower extremities, neurological, musculoskeletal, and psychiatric systems.
- **Vital signs measure**: Heart rate, blood pressure, respiratory rate, and body temperature will be measured.
- **Anthropometrics:** Body weight (calibrated scale) and height will be obtained while the participant is gowned, without shoes. BMI will be calculated. Waist and hip circumference will be measured and waist- hip ratio will be calculated

Screening blood draw to measure the following: (~25 ml)

a. Complete blood count (CBC) white blood count, red blood count, hemoglobin, hematocrit, MCV, MCH, MCHC, RDW, Platelet Count, MPV, Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils, Abs Neutrophil Count, Abs Lymphocyte Count, Abs Monocyte Count, Abs Eosinophil Count, Abs Basophil Count
b. Comprehensive metabolic panel (CMP) (Anion Gap, Albumin, Globulin, A/G Ratio, Alkaline Phosphatase, ALT, AST, Bilirubin Total, BUN, Creatinine, eGFR by CKD-EPI, Calcium, Chloride, CO_2, Creatinine, Glucose, Potassium, Sodium, Total Protein)
c. Lipid panel (Total Cholesterol, HDL, LDL, Chol/HDL ratio, LDL/HDL Ratio, Non-HDL Cholesterol, Triglycerides, VLDL, CHD Risk Assessment)
d. HbA1c
e. Hepatitis B and Hepatitis C antibody tests [Hepatitis B Surface Antigen (HBsAg), Hepatitis B Surface Antibody (HBsAb), Hepatitis C Surface Antibody (HCsAB)]
f. HIV 1 &2 Ag/Ab Screening
g. Blood will also be archived for the biorepository.

- **Urine collection for**:
    a. Urinalysis
    b. Urine albumin/creatinine ratio (UACR)
    c. Urine toxicology screening test (Amphetamine, Barbiturate, Benzodiazepine, Cocaine, Methadone, Opiate, THC, Tricyclics, Oxycodone)
    d. Urine pregnancy test in women of childbearing potential
    e. Urine collection for the biorepository
- **Electrocardiogram (ECG)**
- **Questionnaires**: MOCA, KIMS, Gold score (see details in the Questionnaires section)

Upon review of all clinical and laboratory-based screening endpoints, eligible participants will then be scheduled for Visit 1. Laboratories can be repeated, and participants may be rescreened for the study at the PI or provider's discretion.

PERIOD 1: BASELINE WITHOUT SGLT-2 INHIBITORS
OUTPATIENT PHASE (DAY 1 – DAY 30)

Visit 1 / Day 1: Outpatient visit, ~ 3 – 4 hours

Eligible participants will come to TRI for an outpatient visit (Visit 1) and start the baseline phase of the study. During this period (Day 1 – Day 30) participants will not use any SGLT-2 inhibitor. The following procedures will be performed in non-fasting condition during this visit:

- Vital signs measurement
- Non-fasting blood draw of ~6.5 mL for C-peptide and glucose (which correlates better with the mixed meal test stimulated C-peptide)
- Continuous Dual Glucose Ketone (DGK) Monitoring device placement: All the patients will wear a DGK (Abbott) for the duration of the study. A member of the study team will place the DGK initially, and participants will be instructed on the use, removal and reinsertion of the device as needed every 15 days. The study participants may continue using their personal glucose monitoring devices (CGM) during the study. When using both devices (personal CGM and DGK), the devices will be inserted at an appropriate distance from each other (typically 2 – 3 inches apart or as specified in the DGK manual of procedures). During DGK wear, participants will be instructed to perform standard fingerstick glucose measurements to confirm abnormal glucose values. Additionally, the participants will not use the DGK device for making glucose-based treatment decisions during the first 12 hours of sensor wear. The participants will be instructed to perform fingerstick blood ketone measurements if DGK monitor shows ketones >1.0 mmol/L or if they have symptoms of diabetic ketoacidosis (DKA). (see ketone action plan)
- 24-hour dietary recall collected by The Automated Self-Administered 24-hour (ASA24®) Dietary Assessment Tool: This is a free, extensively validated web-based tool developed by the National Cancer Institute. It enables multiple, automatically coded, self-administered 24-hour diet recalls. The most recent version (2024) will be used. On average, it takes 24 minutes to complete this assessment. Three days of dietary intake will be reported during each of the four measurement periods to enable estimation of means and standard deviations for energy and nutrient intake with sufficient rigor to enable correlations with physiological data. Participants will receive phone and text reminders to complete two of these assessments remotely, with the third recall completed on the first day of each in-person clinic visit. Thus, two of the three recalls will be unscheduled. Study team members will call/ text/ email participants the day of the unscheduled recalls to ask them to fill out the questionnaires for the previous day. The dietary recalls should ideally include two

weekdays and one weekend day, with no consecutive days of reporting. Dietary intake variables will include, but are not limited to, absolute and relative macronutrient intake, total energy intake, and daily fasting duration.

- International Physical Activity Questionnaire (IPAQ): This 27-item questionnaire captures physical activity performed for at least 10 minutes over the past week in 4 different domains: 1) job-related; 2) transportation-related; 3) housework, house maintenance, family caregiving; 4) recreation, sport and leisure time. Computation of the total scores for the long for requires summation of the duration (in minutes) and frequency (days) for all the types of activities in all domains. Domain specific scores or activity specific sub scores may be calculated. Domain specific scores require summation of the scores for walking, moderate-intensity and vigorous-intensity activities within the specific domain, whereas activity-specific scores require summation of the scores for the specific type of activity across domains. The questionnaire also assesses time spent sitting as a proxy for sedentary behavior.
- If available, participants will continue to wear personal devices (smart watches) to collect wearable activity data. Data will be downloaded to the study site via the respective applications (e.g., Apple Health) and incorporated into the trial database for assessment of activity/sleep etc.
- Participants will be instructed to maintain their usual diet and levels of physical activity throughout the duration of the study

Participants will wear the DGK monitor for 30 days during this outpatient period and will return to AdventHealth TRI for Visit 2. Data from the insulin pump, watches/ phones will be collected throughout this study period.

PERIOD 1: BASELINE WITHOUT SGLT-2 INHIBITORS
INPATIENT PHASE

Visit 2 / Day 31- Day 32 ± 5 days: Inpatient in CRU for 2 days

At the end of 30 days of DGK use, participants will return to AdventHealth TRI for an in-patient stay of 2 days. Participants will be admitted to the clinical research unit (CRU) for an overnight in-patient stay. During this visit:

1. The study team will download the data from all the wearable monitors (DGK device, insulin pumps, activity from phones/ watches) and
2. Pregnancy test will be performed for the women of childbearing potential before the DEXA scan is performed.
3. Vital signs and anthropometrics will be measured,
4. Adverse events and concomitant meds will be assessed.
5. For participants on multiple daily dose insulin (MDI), the last dose of long-acting insulin will be withheld, depending on the timing and type of insulin. Participants will be advised to adjust insulin dosing with rapid acting insulin to maintain glycemic control.
6. An IV insulin infusion will be started for glycemic management at 20:00.

7. 24-hour dietary recall, IPAQ, System Usability Scale, and Assessments of adverse device effects on day 31
8. Stool sample collection (see details below)
9. DEXA scan on Day 31 (see details below)
10. Participants will be informed about the risk of diabetic ketoacidosis (DKA) with the use of sotagliflozin and they will be given generalized guidance regarding the mitigation strategies of DKA.
11. On day 2 of this in-patient visit (Day 32), participants will undergo an insulin withdrawal test (IWT) after an overnight fast of at least 8 hours. See details of overnight in-patient stay and IWT below
12. Questionnaires: MOCA, KIMS will be done on day 32 of V2 during the insulin withdrawal test when the blood sugar is between 250 –350 mg/dL x 2.
13. At the end of the visit, the SGLT-2 inhibitor (sotagliflozin) will be dispensed to the participants for the outpatient assessment period.

Dual Energy X-Ray Absorptiometry (DEXA): DEXA Scans will be performed to measure body fat and estimate muscle mass using a GE Lunar iDXA whole-body scanner. The participant will remove all metal accessories and may be asked to change into a hospital gown. The participant will lie on the DEXA table while the scanner arm emits low energy X-rays as it passes along the body. The scan takes up to 15 minutes, and the radiation dose is less than 1 mrem, less than half the average daily radiation dose in America. A urine pregnancy test will be completed on all women of childbearing potential (all women except those with prior hysterectomy, tubal ligation, or absence of menses for ≥2 years) prior to the DEXA scan for safety.

Stool sample collection: Participants will be asked to produce a stool sample using a standard kit. A commode hat and container will be provided to collect the sample after receiving instructions from a member of the study team. The container will be sealed immediately after sample is produced. Samples will be processed within 60 minutes of collection with our existing protocols. Briefly, 1-2 g of the fecal specimen will be aliquoted into two empty 2 mL cryovials. Aliquots will be snap frozen and archived at -80° C for future use, including whole shotgun metagenomic sequencing for measurement of microbiome composition, and function, and fecal metabolomics.

Overnight in-patient stay: Participants will be admitted to the clinical research unit at ~ 6:00 p.m. the evening before the insulin withdrawal test. They will be fed a standard, weight-maintaining meal and allowed to cover the meal with insulin according to their carb ratio/correction factor. At ~8:00 pm, their insulin pump (if worn) will be disconnected and an IV placed. Regular human insulin will be administered by intravenous infusion to maintain glucose levels at a target of 100-120 mg/dL using a computerized program (Glucomander). For participants on MDI, they will be instructed to discontinue long-acting insulins at least 2 half-lives before admission but will be allowed to manage glucose excursions with short acting insulins up until dinner as above. People with T1D using

weekly insulin administration (when approved) will not be included in the study. At ~8:00 p.m. an insulin infusion will be initiated to manage glucose as above.

Insulin withdrawal test (IWT)

On day 2 of the in-patient stay, participants will undergo IWT after an overnight fast of at least 8 hours. A peripheral intravenous cannula will be inserted into an antecubital vein for blood sampling for a total of approximately 221.0 mL of blood drawn. To induce insulinopenia and ketogenesis, the insulin infusion will be suspended at ~6:00 am. Participants in Period 1 will not take any sotagliflozin during IWT. Participants in Period 2 will take sotagliflozin 400 mg orally at the time of insulin suspension. During the IWT, glucose, BOHB, lactate, bicarbonate and venous pH will be measured in real time at 30 min intervals. Glucose and BOHB will be measured using a bedside Glucose/Ketone meter (StatStrip glucose/ketone monitor, Nova Biomedical) and pH, lactate and bicarbonate will be measured by iSTAT analyzer (i-STAT CG4+ Abbott). Participants will consume 200 mL water hourly. Fluid intake and urine output will be monitored. The IWT will conclude after 6 hours or sooner if participants meet the early termination criteria (bedside ketone ≥3.0 mmol/L, bedside glucose >399 mg/dL or persistent bothersome symptoms including but not limited to nausea, vomiting). From 6 a.m. to 2 p.m. blood samples will be collected every 30 minutes for biorepository. Furthermore, urine voids occurring between 6:00 AM and 2:00 PM will be individually collected for volume assessment and will be stored in biorepository. After the test, participants will receive intravenous and oral fluids, a subcutaneous insulin bolus, and a meal. Basal insulin via insulin pump or subcutaneous injectable insulin will resume. Participants will be discharged from clinical research unit (CRU) when symptoms are improved, BOHB <1.0 mmol/L, and glucose trends downwards.

PERIOD 2: BASELINE WITH SGLT-2 INHIBITORS OUTPATIENT PHASE (DAY 33 – DAY 63)

Participants will start Period 2 of the study from Day 33 (±5 days) in which they will take SGLT-2 inhibitors for approximately 30 days. During the first 2 weeks, participants will take 200 mg of sotagliflozin, orally, once daily before the first meal of the day. If tolerated, they will increase to 400 mg of sotagliflozin, orally, once daily for the duration of their participation in the study. Participants will wear the DGK monitor for ~30 days during this outpatient period and will return to AdventHealth TRI for Visit 3.

Female participants will be instructed to use appropriate contraception methods.

Participants will be instructed to maintain their usual diet and levels of physical activity throughout the duration of the study

Weekly Telephone Follow-ups

Week 1 – 4 (Day 40 – Day 61 ±2 days): remote, ~30minutes

A study team member will have weekly telephone or telehealth follow-up visits to assess adverse events and to answer their questions during this study period.

PERIOD 2: WITH SGLT-2 INHIBITORS

INPATIENT PHASE

<u>Visit 3 / Day 64 – Day 65 (± 5 day)</u>: Inpatient in CRU for 2 days,

At the end of 30 consecutive days of sotagliflozin and DGK use, participants will return to AdventHealth TRI for an in-patient stay of 2 days.

1. Participants will be admitted to the clinical research unit (CRU) for an overnight stay.
2. The study team will download the data from all the wearable monitors (DGK device, insulin pumps, activity from phones/ watches)
3. Pregnancy test will be performed for the childbearing females
4. Vital signs and anthropometrics will be measured
5. Adverse events and conmeds will be assessed.
6. 24-hour dietary recall and IPAQ
7. Stool sample collection

For those participants on MDI, long-acting insulin will be stopped a day before the IWT.

8. An IV insulin infusion will be started for glycemic management at 20:00 hr.
9. On day 2 of this in-patient visit, participants will take the study drug before the start of IWT.
10. Participants will undergo an IWT after an overnight fast of at least 8 hours. See details of IWT above.
11. At the end of the visit, the SGLT-2 inhibitor (Sotagliflozin) will be dispensed to the participants.
12. Questionnaires: MOCA, KIMS will be done on day 65 of V3 during the insulin withdrawal test when the blood sugar is between 250 –350 mg/dL x 2.
13. Blood draw of approximately 3.0 mL and urine collection for the biorepository.

PERIOD 3: GENERALIZED RISK MITIGATION STRATEGY (DAY 33 – DAY 216)

Participants will continue to take sotagliflozin during Period 3 of the study. Simultaneously, they will have a DGK monitor during this period of the study.

Weekly Telephone Follow-up

Week 5 – 12 (Day 71 – Day 120 ±2 days): remote, ~30minutes

A study team member will have weekly telephone follow-ups to assess adverse events and to answer their questions during this study period. Any change in the insulin dose will be made with consultation of the medical team.

Visit 4 / Day 124 ± 5 days: Outpatient at TRI for ~2 – 3 hours

- CGM/CKM device distribution/ insertion
- Study drug distribution
- Data download from all the available wearable monitors (DGK device, insulin pumps, activity from phones/ watches)
- Adverse events and conmeds will be assessed.
- Vital signs and anthropometrics will be measured
- HbA1c blood draw of approximately 3.0 mL
- Urine pregnancy test will be performed for the childbearing females
- Blood collection of approximately 10.0 mL and urine collection for biorepository

Weekly Telephone Follow-up

Week 13 – 25 (Day 127 – Day 211 ±2 days): remote, ~30minutes

A study team member will have weekly telephone follow-ups to assess adverse events and to answer their questions during this study period.

Period 3 of the study will continue until V5. Therefore, participants will follow the general risk mitigation strategy for 6 months.

Visit 5 / Day 216 ± 5 days: Outpatient at TRI for ~2 – 3 hours

- Participants will transition from the generalized DKA risk mitigation strategy to a personalized DKA risk mitigation strategy at this visit.
- DGK device distribution/ insertion
- Study drug distribution
- Data download from all the available wearable monitors (DGK device, insulin pumps, activity from phones/ watches)
- Adverse events and concomitant meds will be assessed.
- Vital signs and anthropometrics will be measured
- Blood collection of approximately 17.5 mL for labs (CMP, CBC, HbA1c, biorepository)
- Urine collection for urine analysis, UACR, and biorepository
- Pregnancy test will be performed for women of childbearing potential
- 24-hour dietary recall and IPAQ
- Participants will be educated about the personalized risk mitigation strategies of DKA. These personalized strategies will be inferred from their in-patient and outpatient experience including data from the DKA during the study.
- Questionnaires: MOCA, KIMS, IPAQ, System Usability Scale, Assessments of adverse device effects will be done

PERIOD 4: PERSONALIZED RISK MITIGATION STRATEGY (DAY 217 – DAY 400)

The personalized risk mitigation strategy will continue for 6 months following the generalized risk mitigation strategy. Participants will continue to take SGLT-2 inhibitor during this period 4. Simultaneously, they will have a DGK monitor. Participants will be informed about the risks of DKA with the use of SGLT-2 inhibitors.

Visit 6 / Day 308 ± 5 days: Outpatient at TRI for ~2 – 3 hours

- DGK device distribution/ insertion
- Study drug distribution
- Data download from all the available wearable monitors (DGK device, insulin pumps, activity from phones/ watches)
- Adverse events and conmeds will be assessed.
- Vital signs and anthropometrics will be measured
- HbA1c blood draw of approximately 3.0 mL
- Urine pregnancy test will be performed for the childbearing females
- Blood collection of approximately 10.0 mL and urine collection for biorepository
- Pregnancy test will be performed for the childbearing females

Weekly Telephone Follow-up

Week 40 – 53 (Day 316 – Day 393 ±2 days): remote, ~30minutes

A study team member will have weekly telephone follow-ups to assess adverse events and to answer their questions during this study period.

Visit 7/Day 400 ± 5 days: Outpatient at TRI for ~2 – 3 hours

- DGK device distribution/ insertion
- Data download from all the available wearable monitors (DGK device, insulin pumps, activity from phones/ watches)
- Adverse events and conmeds will be assessed.
- Vital signs and anthropometrics will be measured
- Blood collection of approximately 17.5 mL for labs like CMP, CBC, HbA1c, biorepository
- Urine collection for urine analysis and UACR, biorepository
- Pregnancy test will be performed for the childbearing females before the DEXA scan is performed
- 24-hour dietary recall and IPAQ
- Stool sample collection
- DEXA scan
- Removal of DGK device.
- Questionnaires: MOCA, KIMS, Gold score, IPAQ, System Usability Scale, Assessments of adverse device effects, device issues will be done

The personalized risk mitigation strategy for DKA will end at V7.

Weekly Telephone Follow-ups

Week 53 – 57 (Day 407 – Day 421 ±2 days): remote, ~30minutes

A study team member will have weekly telephone follow-ups to assess adverse events and to answer their questions during this study period.

Visit 8: End of study safety follow up / Day 430 ± 5 days: Outpatient at TRI for ~2 – 3 hours

Approximately one month after visit 7, participants will have an end of study safety follow up visit. The participants will undergo the following procedures during this visit:

- Medical history, physical exam,
- Vital signs measurement,
- Anthropometrics measurement,
- Blood draw of approximately 7.5 mL for safety labs (CBC, CMP, HbA1c),
- Urine analysis, UACR
- Assessment of adverse events and conmeds.

Questionnaires:

KIMS: The Kentucky Inventory of Mindfulness Skills (KIMS) is a 39-item self-report questionnaire designed to assess four core mindfulness skills: Observing, Describing, Acting with Awareness, and Accepting without Judgment. Each skill is measured through a dedicated subscale, and responses are scored on a Likert scale, with some items reverse-scored. The KIMS is widely used in both clinical and research settings to evaluate mindfulness as a teachable and measurable trait. (6)

MOCA: The Montreal Cognitive Assessment; Performance-based assessment of general mental status consisting of several short tasks (executive function, visual spatial skills, naming, attention, language, verbal, memory and orientation). Total score = 30. (7)

Gold Score: The Gold score is a questionnaire used to assess hypoglycemia awareness. It consists of a single question. Responses are scored from 1 to 7. (8)

System Usability Scale: A 10-item questionnaire that measures the overall usability of a system. It is a valid and reliable measure of the perceived usability of a system and is technology-agnostic. (9)

Schedule of Activities for Period 1 and Period 2							
Study Period	**Screening**	**Period 1/Baseline (No SGLT-2 inhibitor)**			**Period 2 (Daily SGLT-2 inhibitor)**		
Visit number	**SV**	**V1**	**V2**			**V3**	
Day number		**1**	**31**	**32**	**33**	**64**	**65**
Informed Consent, review of eligibility criteria, history, and medical exam	**x**						
Vital signs, anthropometrics (height, weight, BMI, waist-hip ratio)	**x**		**x**			**x**	
Stool sample collection*			**x**			**x**	
Screening labs (CMP, CBC, lipid profile, TSH, Hep B and Hep C, HIV screening, urine analysis, UACR, ECG, toxicology screen)	**x**						
HbA1c	**x**					**x**	
Pregnancy test	**x**		**x**			**x**	
Assess adverse events, conmeds	**x**	**x**	**x**			**x**	
Non-fasting C-peptide and glucose		**x**					
DGK Wear		**x**	**x**	**x**		**x**	**x**
Activity Monitor Wear, if available	**x**	**x**	**x**	**x**		**x**	**x**
24-hour dietary recall (ASA-24) ▲		**x (3)**	**x (3)**			**x (3)**	
International Physical Activity Questionnaire (IPAQ)		**x**	**x**			**x**	
Questionnaires (KIMS, MOCA)	**x**			**x**			**x**
Questionnaires (Gold score)	**x**						
Questionnaires (System Usability Scale, Assessments of adverse device effects, device issues)				**x**			
Blood and urine collection for Biorepository	**x**						
Drug distribution				**x**			
Data Download (DGK/ insulin/ activity monitor)				**x**			**x**

Patient Education for Generalized Risk Mitigation			**x**				
Telehealth consults/text messages to assess AEs and con-meds (Frequency: Weekly)			**x(4)**			**x(4)**	
Inpatient Testing in CRU							
Admit in CRU			**x**			**x**	
DEXA scan			**x**				
Test: Insulin Withdrawal Test (IWT)				**x**			**x**
Standard Meal			**x**	**x**		**x**	**x**
For 10h time series: Assess ketones, glucose, lactate, bicarbonate, and venous pH				**x**			**x**
6 AM to 2PM blood samples collected every 30 minutes for biorepository				**x**			**x**
6 AM to 2PM urine voids collected for biorepository samples, assess volume				**x**			**x**
*Stool sample can be collected on either day of V2 (day 31 or 32) and V3 (day 64 or day 65). DGK: continuous ketone/glucose monitor, ▲Two unscheduled dietary recalls will be collected by the study team before this visit.							

Schedule of Activities for Period 3 and Period 4					
Study Period	**Period 3:‡ Generalized Risk Mitigation Strategy**		**Period 4: Personalized Risk Mitigation Strategy**		**EOS Safety Follow Up**
Visit number	**V4**	**V5¶**	**V6**	**V7**	**V8**
Month number/ (Day number)	**3 (124)**	**6 (216)**	**9 (308)**	**12 (400)**	**13 (430)**
DGK Wear	**x**	**x**	**x**	**x**	**x**
Activity Monitor Wear (optional)	**x**	**x**	**x**	**x**	**x**
Assess adverse events, conmeds	**x**	**x**	**x**	**x**	**x**

Vital signs and anthropometric measurement	**x**	**x**	**x**	**x**	**x**
HbA1c	**x**	**x**	**x**	**x**	**x**
Safety labs (CMP/CBC, urine analysis, UACR)		**x**		**x**	**x**
Questionnaires (KIMS, MOCA)		**x**		**x**	
Questionnaires (Gold score)				**x**	
Questionnaires (System Usability Scale, Assessments of adverse device effects, device issues)		**x**		**x**	
Stool sample collection				**x**	
DEXA scan				**x**	
24-hour dietary recall (ASA-24)		**x (3)**		**x (3)**	
International Physical Activity Questionnaire (IPAQ)		**x**		**x**	
Blood and Urine Collection for Biorepository	**x**	**x**	**x**	**x**	
Pregnancy test (urine)	**x**	**x**	**x**	**x**	
Data Download (DGK/insulin/activity monitor)	**x**	**x**	**x**	**x**	
Drug distribution	**x**	**x**	**x**		
Patient Education for Generalized Risk Mitigation					
Patient Education for Personalized Risk Mitigation		**x**			
Tele-consults/ text messages to assess AEs and con-meds (Frequency: Weekly)	**x (13)**	**x (13)**	**x(13)**	**x(13)**	**x (4)**
‡Period 3 will start from Day 33 and will overlap with Period 2 for the first month. ¶V5 is the transition visit between Period 3 and Period 4. Period 3 will end at V5, and Period 4 will start from V5					

Study Duration

Projected start date of study: December 2025

Estimated duration to enroll all study subjects: 15 months

Total length of time participants will remain in the study: approximately 15 months which includes 14 months of intervention and 1 month of follow-up

Estimated date for investigators to complete the study (including analysis): December 2028 (3 years)

Materials of Human Origin: Collection, Preparation, Handling and Shipping

Materials of human origin will be collected as described in the specific study visits section of this protocol.

Biospecimen samples will be stored in ultra-low temperature freezers and liquid nitrogen drawers, or other storage units located at each facility. The TRI facility is secured via key card and equipped with a back-up generator system. Laboratory personnel in the facility have 24/7 key-controlled access to the laboratory. Chain of custody of biospecimen samples is maintained through requisition forms and in the StarLIMS database. All biospecimen tubes are coded and labeled appropriately, and biospecimen requests and distribution are documented.

The TRI facility will be the main repository for biospecimen samples

Study Outcome Measures (Endpoints)

Outcomes	Description
Primary Outcomes	
Ketone events with Beta-hydroxybutyrate (BOHB) >1.5 mmol/L	Number of ketone events with BOHB > 1.5 mmol/L for 15 consecutive minutes, as measured by the DGK. The event will end when BOHB is < 1.5 for 15 consecutive minutes. These events will be measured during the risk mitigation phase (Period 3 and Period 4) of the study.
Ketone events with Beta-hydroxybutyrate (BOHB) >1.0mmol/L	Number of ketone events with BOHB >1.0mmol/L for 15 consecutive minutes, as measured by the DGK. The event will end when BOHB is <1.0 mmol/L respectively for 15 consecutive minutes. These events will be measured during the risk mitigation phase (Period 3 and Period 4) of the study.
% time spent in ketosis of > 1.5 mmol/L	Average percentage of time spent in ketosis (>1.5 mmol/L) in 24 hours, measured by the DGK, during the risk mitigation Period 3 and Period 4 of the study.

% time spent in ketosis of >1.0 mmol/L	Average percentage of time spent in ketosis (> 1.0 mmol/L) in 24 hours, measured by the DGK, during Period 3 and Period 4 of the study.
Mean BOHB levels	Mean BOHB levels (mmol/L) across period 3 and period 4, as measured by the DGK.
%CV of BOHB	Mean percentage of coefficient of variation of ketones across period 3 and period 4, as measured by the DGK.
Symptomatic ketone events	Number of symptomatic ketone events; defined as BOHB >1.0 mmol/L along with symptoms (including weakness, nausea, vomiting, confusion, fruity-breath, polyuria, and/or polydipsia) across Period 3 and Period 4 of the study
Severe ketone events	Number of severe ketone events requiring hospital admissions/ emergency room visits/ or third-party intervention across Period 3 and Period 4 of the study
BOHB responses during Insulin withdrawal test (IWT)	Measured by Ketogenesis index; calculated by dividing the max BOHB level by the termination time of the IWC (max BOHB/Time min); maximum BOHB during IWC; time to BOHB max during IWC; difference in BOHB (max-min) during IWC
Secondary Outcomes	
Venous pH responses during IWT	Measured by change in pH over time during IWT, minimum level of pH, time to minimum pH, pH delta (max-min).
Lactate and glucose responses during IWT	Measured by change in lactate and glucose over time during IWT, • maximum lactate and glucose, • time to maximum lactate and glucose, • lactate and glucose delta (max-min)
Glycemic outcomes measured by continuous glucose monitoring (CGM)	Glycemic outcomes will be measured by mean glucose and standard deviation, % time below range < 70 mg/dL, % time below range < 54 mg/dL, % time in range 70-180 mg/dL, %time above range >180 mg/dL, % time above range >250 mg/dL, coefficient of variation across period 3 and period 4
Insulin requirements	Average units of insulin delivered daily as basal insulin, bolus insulin, total daily dose of insulin (TDD), TDD/kg body weight across period 3 and period 4
Body weight, blood pressure, HbA1c, kidney functions	Body weight in kg, mean systolic and diastolic blood pressure (mmHg), HbA1c, eGFR will be measured across period 3 and period 4.

Bicarbonate response during IWT	Measured by change in bicarbonate over time during IWT, minimum bicarbonate, time to minimum bicarbonate, bicarbonate delta (max-min)
Other Outcomes	
BOHB response to changes in glucose during IWT	Measured during IWT as change over time (slopes) in BOHB and glucose; differences in BOHB and glucose across time points.
BOHB response to changes in lactate during IWT	Measured during IWT as change over time (slopes) in BOHB and lactate; differences in BOHB and lactate across time points.
BOHB response to changes in pH during IWT	Measured during IWT as change over time (slopes) in BOHB and pH; differences in BOHB and pH across time points.

Data Management and Quality Plan

Clinical trial monitoring will be conducted by AdventHealth Office of Research Integrity and Compliance (ORIC) monitoring team to ensure compliance with all applicable federal and state regulations, ICH GCP E6 (R2) standards and approved protocol. This study will be monitored using a risk-based approach. A monitoring plan will be created to ensure patient safety; data quality and integrity is ongoing throughout the life of the study. The frequency and elements of monitoring will be outlined in the monitoring plan. The monitor will ensure the study is conducted, recorded, and reported as required by federal regulations and IRB of record. Monitoring will be conducted on-site and/or remotely. After completion of the site monitoring, a report will be provided to PI and study team. The PI and study team are required to review the report and work on significant findings or discrepancies to resolution. If any findings are required to be reported to the IRB, the PI will be made aware and prompted to self-report. All serious and continuing non-compliance is shared with the Research Oversight Committee who may require appropriate actions.

Data De-identification

Participants will be enrolled and assigned a participant identification number (PID) at TRI. This PID is a code consisting of a combination of numerals and letters, which serves as the identifier for this participant for this research study and links them back to their hospital medical record and/or their protected health information (PHI). Access to the “link” between the PIDs, the PHI, and to the clinical data are only granted to the clinical research team as assigned on the Delegation of Authority Log. All the clinical research and survey data is recorded in a de-identified fashion onto our paper source documents and/or electronic case report forms (CRF). Data will be entered into REDCap, a HIPAA-compliant, web-based forms and survey platform approved for use by AdventHealth. REDCap will be used for storage and to facilitate analysis. All data not entered into REDCap (e.g., data collected from individual activity monitors, insulin

pumps, wearables) will be stored on a shared OneDrive folder only accessible to the assigned study-specific research team at AH TRI.

Clinical data generated by research devices also uses the PID, and once the data has been transformed into interpretable results it is stored into the clinical research database (either REDCap or OneDrive). Both storage locations are password-protected, secured and only assessable to the assigned clinical research team from AH TRI. The "link" will not be used to re-identify participants except in the event of a serious adverse event (SAE) requiring "unblinding" to treat the participant. The "link" will be stored in the Patient Protocol Manager and in the OneDrive folder, where only the research team has access.

Data Confidentiality, Storage, and Retention

The identity and personal health information of study participants will be kept confidential to the extent permitted by the applicable laws and/or regulations and will not be made publicly available. If the results of this study are published or presented, the identities will not be revealed. Confidentiality will be maintained during and after the study. This information is also included in the informed consent, which is discussed with participants prior to enrollment.

Study documentation and paperwork will be stored in our locked medical records room at AH TRI. The data records will also be stored as electronic records in REDCap and OneDrive. This data will be safeguarded so that only those on the research team have access to any of the clinical data (both source documentation and data warehouse storage). The electronic data is maintained by Adventist Information Technology (AIT) security controls.

AdventHealth Translational Research Institute retention policy is maintained in the Records Management Policy. Electronic de-identified data will be kept indefinitely in our data warehouse. Per the institutional policy, investigator records must be kept for a minimum of 7 years after completion of discontinuation of the study, or for longer if required by applicable local regulations, or what is applicable per the Sponsor.

Data Quality

Data quality control will occur according to our SOPs on Data Entry, Quality Control Procedures and Query Management. All data will be entered into an electronic data capture (EDC) system (REDCap) and checked against the paper source for accuracy by a second party (Data Entry SOP) and errors resolved through the Query Management SOP. Ten percent of the data points will be routinely checked at the beginning, middle, and close of a study for quality control (Quality Control SOP). Finally, all critical endpoints (as determined by the PI or Sub-I) will be assessed using quality control analyses. The data will be loaded into the clinical research database. Data in the warehouse will also be routinely monitored over time.

Data Sharing

Some of the endpoint testing might be conducted at outside institutions. To perform these analyses/testing/etc. and to interpret results, certain data elements will need to be shared along with the biospecimen samples. Data Use Agreements will be obtained, which will identify the specific data elements to be shared and will govern the sharing of data related to this study. Data will be de-identified, but a link/code is managed within an electronic research management system and maintained by a study coordinator

Sample Size Determination

The primary endpoint to address the overarching aim is the number of ketone events with BOHB >1.5 mmol/L during generalized vs. personalized risk mitigation strategies. We therefore estimated a standardized effect size of 0.29 calculated from the mean and standard deviation of fasting BOHB in a randomized crossover placebo-controlled study testing the effects of SGLT-2 inhibitor therapy with or without concomitant glucagon receptor antagonist therapy in 12 adults with type 1 diabetes. A sample size of 75 participants provides 80% power to detect an effect size of 0.29 using a one-sided paired t-test at an alpha level <0.05. We assume an equivalent or larger effect size in our study given the longer follow-up duration.

Statistical Analysis Plan

Primary Objective Analysis

The primary objective is to compare the ketosis and ketoacidosis (beta-hydroxybutyrate, pH, lactate, bicarbonate, glucose) response during the insulin withdrawal challenge in participants with T1D with and without SGLT-2 inhibitor. To analyze this, within-subjects repeated measures linear mixed model will be used to compare these outcomes assessed during IWT with and without SGLT-2 inhibitor.

Secondary Objective Analysis

The secondary objective is to compare the number of ketone events (DGK assessed BOHB levels) with 6-months personalized DKA risk mitigation strategy compared to 6-months generalized DKA risk mitigation plan in participants with T1D on SGLT-2 inhibitors use. A stratified Cox proportional hazards model using the intervention assignment (generalized vs. personalized risk mitigation strategy) as fixed factors will be used. Subgroup analyses will be performed by adding the interaction term between subgroup at intervention assignment

Potential Risks and Benefits

Potential Benefits

Potential benefit for the participants could be:

- Access to SGLT-2 inhibitors may improve their glycemic control and body weight.
- SGLT-2 inhibitors have been shown to reduce progression of chronic kidney disease and cardiovascular disease including heart failure in other populations. It is unknown whether these benefits will be evident in persons with T1D
- Access to advanced education and support provided by highly qualified personnel.
- Participants could benefit from a better understanding of diabetic ketoacidosis and its management.
- Results from clinical blood work will be shared with the participants.

Potential Risks

Described below are all the known risks of being in this study

- Intravenous lines/blood draws (lab samples, e.g.): there is a risk of pain, vasovagal syncope, hematomas, and/or infection at IV insertion/blood draw site (low risk of SAEs). The total amount of blood collected is about 542.5 mL over 430 days.
- Surveys: There are no risks involved beyond what would reasonably be encountered in everyday life. It is possible that participants may experience the following during completion of surveys:
    1. Loss of privacy as a result of a breach of confidentiality
    2. Undue stress related to content on the survey instruments
- Dual Glucose and Ketone monitoring: There is a low risk of developing a local skin infection at the site of the sensor needle placement. Itchiness, redness, bleeding, and bruising at the insertion site, and local tape allergies may occur. Individuals who develop severe reactions may be withdrawn from the study.
- Insulin delivery methods: Participants will continue to use their preferred insulin delivery methods for the duration of the study. They could use hybrid closed loop systems (HCL), continuous subcutaneous insulin infusion, or multiple daily injections of insulin. Hypoglycemia is a potential risk of insulin use. All insulin delivery methods are standard of care for persons with T1D.
- Insulin withdrawal test: During this test, participants might have symptoms of weakness, fatigue, nausea, vomiting, excessive thirst, frequent urination, abdominal pain, confusion.

SGLT-2 inhibitor (sotagliflozin) use: Use of sotagliflozin in people with T1D lowers blood glucose in a manner not dependent upon insulin. There is a risk of developing atypical

or euglycemic DKA. Additionally, sotagliflozin use may increase the risk of genital and urinary tract infections, necrotizing fasciitis, dehydration, and death. SGLT-2 inhibitors are associated with osmotic diuresis and volume depletion, which may lead to dizziness or hypotension, especially in the elderly. The risk of hypoglycemia was not increased with sotagliflozin in clinical trials. However, insulin is known to cause hypoglycemia. The dose of insulin may need to be adjusted to minimize the risk of hypoglycemia when these agents are used in combination with sotagliflozin in patients with T1D. Overall, the risks associated with sotagliflozin use are mild to moderate, and the risk of serious DKA mitigated by continuous monitoring with the DKG device.

- DEXA scan – there is a very small risk of cancer with excessive exposure to any radiation. There are also risks for unborn children associated with radiation exposure. The radiation dose from the scan is less than a chest x-ray, or less than half the average amount a person would receive in a day in America

Mitigation of Risks

The following risk minimization procedures will be in place.

Privacy and Confidentiality

The information gathered during this study will be kept confidential to the extent permitted by law. To ensure the privacy of interests of participants, conversations or other communications about individual information will be conducted privately and the information held in confidence. All study data will be collected by the research team, reviewed by the PI, and stored in secure, locked files and/or password-protected electronic databases to protect from inadvertent loss or improper access. All laboratory specimens, evaluation forms, reports, and other records that are processed in laboratories, used in analyses, or shared with laboratory staff will be identified only by coded number to maintain subject confidentiality. Blood samples will be stored in alarmed -80ºC freezers in the TRI's locked laboratory. All specimen containers will be labeled by subject code and date. There will be no direct link to participant identifying information without access to protected files containing the identifying information linking the specimens to a given subject. Access to linked identifiers will be limited to research personnel directly involved with the project. Information gained from this study that can be linked to the subject's identity will generally not be released to anyone other than the PI, Research Coordinator, other key personnel, the participant, or the subject's physician. However, representatives of the coordinating center (monitors), sponsor (National Institutes of Health), the Data Safety Monitoring Board, the U.S. Food and Drug Administration (FDA), and AdventHealth's Institutional Review Board (IRB) - will be able to inspect data records and have access to confidential information that identifies the subject by name. The results of these studies will be the subject of scientific presentations or published in scientific journals without identifying individual subjects.

Laboratory tests

Qualified staff will conduct all venipuncture and infusion procedures using aseptic techniques to avoid extravasation or excessive discomfort.

DEXA Scan: A urine pregnancy test will be done prior to scans of all women of childbearing potential (all women except those with prior hysterectomy, tubal ligation, or absence of menses for >2 years).

Insulin withdrawal test (IWT)

The following will be done to protect against the risk of DKA:

- In-house supervision by a qualified physician or mid-level provider at all times during the procedure
- Frequent monitoring of blood glucose, ketones, lactate, bicarbonate, and pH during the procedure (every 30 minutes)
- Establishing early termination criteria for the IWT: bedside ketone ≥3.0 mmol/L, bedside glucose >399 mg/dL or persistent bothersome symptoms including but not limited to nausea and vomiting.
- Immediate availability of corrective measures (insulin, glucose, hydration)

Dual glucose and ketone monitoring

The site of sensor insertion will be periodically monitored, and strategies to prevent local skin reactions will be suggested, such as site rotation, liquid adhesive, or changing the type of tape in contact with the skin. Individuals who develop severe skin reactions to the device may need to be discontinued from the study.

Insulin use with sotagliflozin:

In people with T1D, concomitant use of sotagliflozin with insulin may lead to hypoglycemia, hyperglycemia, and/or DKA. The DGK will be used to trigger capillary blood ketone measurements to assess and treat DKA. The DGK device provided by Abbott provides alarms when ketone levels are above a certain threshold. For ketones, there will be two available alarms – an optional alarm at 0.6 mmol/dL and a mandatory alarm at 1.5 mmol/dL. For ketones, there will be 3 trend arrows indicating rapidly rising, rapidly falling, and steady ketone levels.

Similarly, the device provides alarms when glucose is above or below a certain threshold and will trigger capillary blood testing. For glucose, there will be 5 trend arrows indicating rapidly rising, rising, falling, rapidly falling, and steady glucose levels. To prevent medically relevant hyperglycemia during the intervention, cut-offs have been set up to modify insulin treatment. Participants will be expected to cover meals with prandial insulin and correct for hyperglycemia. If the blood glucose is persistently > 250 mg/dl, the study team will notify the TRI provider immediately to review glucose values and initiate treatment. To prevent severe hypoglycemia, participants will be instructed to consume carbohydrate according to the “rule of 15” for glucose values ≤70 mg/dl as prescribed in clinical practice i.e., consume 15 grams of carbohydrate, wait about 15 minutes, then recheck blood glucose levels.

The CGM glucose level should be checked anytime a patient has symptoms of hypoglycemia or hyperglycemia and verified with a fingerstick glucose meter.

Participants will be monitored weekly by telephone/video/ text messages consultation by the study team. Periodic DGK profile downloads, insulin pump downloads, study smartphone app downloads, adverse events, and concomitant medication collection will take place throughout the study.

Risk of DKA with sotagliflozin in T1D

There is an increased risk of diabetic ketoacidosis with the use of sotagliflozin in people with T1D. Proposed mitigation strategies of DKA are attached. Please refer to the generalized DKA risk mitigation strategies which will leverage on the evidence from previous studies of sotagliflozin and other SGLT-2 inhibitors in people with T1D.(4, 5)

The risk of DKA increases if the reduction of total daily dose of insulin is approximately 20% or more from baseline. Participants will be instructed to closely monitor their ketone levels when taking the SGLT-2 inhibitor. The importance of monitoring ketone levels, irrespective of glucose levels will be emphasized as DKA can occur with low, normal, or high blood sugars in patients with T1D taking SGLT-2 inhibitors. Ketones should also be monitored regardless of blood glucose levels when a patient is not eating, is more physically active, drinking alcohol, or experiencing symptoms like general malaise and abdominal pain.

Temporary stopping criteria for SGLT-2 inhibitors:

- If participants have symptoms of DKA (as outlined in patient education handout), they will stop the drug as per the STOPDKA protocol.
- Participants will be advised to stop sotagliflozin 3-4 days before an elective surgery or procedure associated with prolonged fasting and resume post-operatively when tolerating oral intake.
- If the DGK monitor shows blood ketone ≥ 1.0 mmol/L without any symptoms of DKA, confirm the ketone levels with fingerstick blood ketone monitor, and withhold the next sotagliflozin dose if ketones of ≥ 1.0 mmol/L are confirmed on the blood ketone monitor. Participants will be instructed to reach out to the clinical site in case the blood ketone is ≥ 1.0 mmol/L

If blood ketones ≥ 1.0 mmol/L, participants will be instructed to

- Hold the SGLT-2 inhibitor
- Continue insulin, consider increasing basal insulin.
- Consume 15 – 30 grams of carbs each hour (glucose containing sports drinks/ oral rehydration fluid)
- Give bolus insulin for the carbs even if blood glucose is normal
- Take anti-emetics if necessary
- Sotagliflozin will be restarted if ketones remain <0.6mmol/L for 48 hours

Participants may experience an episode of DKA while participating in the study. If this occurs, the study team will investigate the circumstances of the episode. In the event that there was a clear precipitating factor (pump failure, occlusion, intercurrent illness, etc.), participants will be given the choice of restarting the SGLT-2 inhibitor. If they elect not to,

they will be able to remain in the study and continue to participate in DGK monitoring and scheduled visits.

Mandatory discontinuation of drug

The reasons for **permanent** discontinuation of the study drug are as follows:

1. A serious adverse event (SAE) related to the study drug or an intolerable AE such as a persistent allergy or rash
2. Diabetic Ketoacidosis (DKA)
    a. One episode of DKA requiring hospitalization, an Emergency Room visit, and/or intensive therapy (e.g., intravenous fluids)
    2. Severe (Grade 3) hypoglycemia as per the definition of ADA
    Two episodes of severe hypoglycemia associated with significant impairment of mental function such that the person requires assistance from another person to recover
4. Unexplained clinically significant persistent changes from baseline based on laboratory safety assessment which do not respond to temporary 2-week discontinuation of study drug and/or recurs upon re-institution of drug
5. Non-compliance
6. Pregnancy
7. Possible evidence of drug-induced liver injury that meets one (or more) of the following criteria:
    a. Alanine Aminotransferase (ALT) or aspartate aminotransferase (AST) > 3x upper limit of normal (ULN) with the appearance of fatigue, nausea, vomiting, right upper quadrant pain/tenderness, fever, rash, and/or eosinophilia (>5%);
    b. ALT or AST > 3x ULN and total bilirubin > 2x ULN or INR > 1.5;
    c. ALT or AST > 5x ULN for more than 2 weeks;
    d. ALT or AST > 8x ULN

Volume depletion with Sotagliflozin:

SGLT-2 inhibitors are associated with osmotic diuresis and volume depletion, which may lead to dizziness or hypotension, especially in the elderly. All patients will be advised to maintain proper fluid intake (200 mL/hour) and to consider increasing it if they sense greater thirst, increased urination, or if they feel dizzy or faint.

In cases of clinically significant volume depletion, study drug may be temporarily discontinued until the event has resolved.

Note: If serum creatinine increases by ≥30% above the baseline value during the study, the following assessments will be considered: volume status, diuretic dosage, discontinuing nonsteroidal anti-inflammatory drugs (NSAIDs), and other relevant testing including renal imaging techniques, as appropriate.

Patient Education: Participants will be given educational materials covering relevant medication and safety information including an introduction to SGLT-2 inhibitors, diabetic ketoacidosis, continuous ketone monitoring, and instructions for who to contact if high (>1.0 mmol/L) ketone levels are detected. Patient education materials will be provided via multiple mediums to respond to individual learning styles and preferences, including web-based blog posts, audio podcasts, and videos.

Emergency Card: Participants will be provided an emergency card stating that they are participating in a clinical trial and taking the drug sotagliflozin. The card will state that sotagliflozin may cause euglycemic ketoacidosis and provide the lead coordinator's mobile phone number and email address. Participants will be instructed to show during an event and other interactions with health providers.

Provisions to Protect the Privacy Interest of Subjects

Participants will be assigned unique identifiers for study-related records. All precautions will be taken to ensure only authorized individuals access participant research records. The collection of sensitive information about participants will be limited to the minimum necessary to achieve the aims of the research, so that no unneeded sensitive information will be collected

Early Withdrawal of Subjects

Investigator Withdrawal of Subjects

Participation in this study may be stopped at any time by the study PI without the participant's consent because:

- The study medical investigator thinks it is necessary for the subject's health or safety.
- Participants have not followed study instructions (non-compliance).
- The AdventHealth Translational Research Institute has stopped the study.
- Administrative reasons require the participants' withdrawal.
- After one event of Diabetic Ketoacidosis (DKA).
- ADA defined Level 3 Hypoglycemic Event. A severe hypoglycemic event characterized by altered mental or physical status requiring the assistance for treatment of hypoglycemia, irrespective of glucose level.
- Possible evidence of drug-induced liver injury that meets one (or more) of the following criteria:
    - Alanine Aminotransferase (ALT) or aspartate aminotransferase (AST) > 3x upper limit of normal (ULN) with the appearance of fatigue, nausea, vomiting, right upper quadrant pain/tenderness, fever, rash, and/or eosinophilia (>5%)
    - ALT or AST > 3x ULN and total bilirubin > 2x ULN or INR > 1.5
    - ALT or AST > 5x ULN for more than 2 weeks

    - ALT or AST > 8x ULN
- Pregnancy.

Subject Request for Withdrawal from Study

Participation in this study is voluntary. Participants may decide not to participate in this study or may withdraw from this study at any time without penalty or loss of benefits. If a participant leaves the study before the final regularly scheduled visit, she/he may be asked by the study doctor to make a final visit for some 'end-of–study' procedures. This is to make sure that there are no safety concerns.

Data Collection and Follow-up for Withdrawn Subjects

Participants who request withdrawal or who are withdrawn by the PI from the study will have their data maintained in the research database up to the point of withdrawal. The available data will be included in subsequent analysis because keeping these participants in the analysis is essential for study validity.

Adverse Events - Recording and Reporting

Each participant will be evaluated for adverse events at every study visit and weekly via phone calls and/or text message consultations. Any event that is reported to the study staff will be documented as such and graded as to its attribution (unrelated to protocol, or, probably, or definitely related to protocol) and severity (mild, moderate, or severe). Any severe and/or unanticipated adverse event will be immediately reported to the IRB according to AdventHealth IRB guidelines.

At each contact with the subject, the study team will seek information on adverse events by specific questioning and, as appropriate, by the Provider through examination. Information on all adverse events will be recorded immediately in the source document, also in the appropriate adverse event module of the case report form CRF. All clearly related signs, symptoms, and abnormal diagnostic procedures results will be recorded in the source document. All adverse and unexpected events will be reported according to AdventHealth IRB guidelines.

Safety Monitoring Plan

Safety Monitoring

Adverse events (AEs) will be documented periodically during the study. AEs will be collected during study visits. Additionally, participants will be contacted weekly to inquire about AEs. AEs will be reported by the study coordinator, medical investigator, or other TRI staff. Research and safety data will be reviewed by the PI. This review will take place at regular meetings with the research coordinator and principal investigator. Other

items discussed will include progress or adverse events occurring in the following: participant confidentiality, participant recruitment, and consent process. TRI has a standing committee that meets monthly to review all adverse events in the clinical trials and will additionally be charged with review of the study.

All adverse events (AEs) will have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (de-challenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory re-challenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another

etiology. There must be an alternative, definitive etiology documented by the clinician.

The study may be stopped for any of the following:

- Grade 5 (death) in a subject likely related to the study intervention
- At the discretion of the Medical Monitor/ Safety Committee after review of SAEs

The Study may be paused (will be placed on enrollment hold; we will continue to f/u with enrolled patients) for any of the following:

- Any death irrespective of attribution
- A grade 4 SAE that is not unrelated to the study procedures
- A grade 3 or above SAE in the first 3 subjects that is not unrelated to the study procedures
- 3 grade 3 SAEs that are for the same SAE that are not unrelated to the study procedures
- 2 grade 3 SAEs that are related or likely related to the procedure

The DSMB will re-evaluate the study design to determine potential explanations for SAEs. Further decisions related to the trial will depend on the outcome of such investigations.
If for any of the above reasons the study is paused or stopped (terminated), the IRB will be notified of these actions, and if the study resumes, they will be alerted prior.
No interim statistical analysis is planned to assess the safety data during the study. However, regular monitoring of the study will be performed as mentioned in the 'Study monitoring' section below.

Study monitoring:

Study monitor(s) will be appointed to provide routine monitoring of study beginning of the review of the first subject enrolled and then periodically (for example approximately every 6 to 10 weeks during the recruitment period), schedule will be adjusted based on recruitment volume. The monitoring schedule after the end of recruitment period will be extended to 8 to 12 weeks for review of data elements until close out, if applicable. Some elements are monitored at 100% and others at a lower percentage based on criteria, such as total number of subjects enrolled, or screen failed. During the course of the study, if Serious and Non-Compliance is observed, the monitoring frequency will be adjusted to ensure compliance with approved protocol and applicable requirements. The monitor will meet with principal investigator and/or delegate at each of the monitoring visits to discuss study progress and any issues that might be observed. The Biostatistics Research Center will be in charge of monitoring the study.

Monitoring will focus on evaluating the following processes to ensure patient safety, data quality and integrity are occurring throughout the life of the study until study close out. The first 1-2 subjects enrolled will be reviewed shortly after their first in-patient visit.

Access to EMR (electronic medical record), source documents (paper), EDC (Electronic Data Capture) system and regulatory documents are required to perform the following monitoring activities:

- Informed consent process
- Study Eligibility Criteria is met. .
- Accurate abstraction of data from paper source information to EDC system
  - Source will be reviewed against data entered into the EDC system
- Reporting of serious adverse events and protocol violations according to IRB policies and procedures
- Procedures Assessment Review
  - Insulin withdrawal challenge, imaging study, device usage and other protocol required procedures will be reviewed to ensure they were conducted as required per protocol and AE reported promptly if applicable.
- Training Process
  - Documentation of protocol training documents
  - Research personnel and Delegation of Responsibility log review.
- Regulatory Documentation
  - Review and verification of completed preparatory to research forms for all members which are involved in screening subjects.
  - IRB approvals are obtained, renewed and on file
  - IRB correspondence is filed
  - Deviations reported to the IRB and filed
  - All other applicable regulatory documentation will be reviewed as detailed in the table above
- PI Oversight
  - Confirm PI/Sub-I and designee are reviewing Inclusion/Exclusion Criteria, SAEs and present and/or signing PI oversight study status meetings.

Each time on site or remote monitoring is conducted, the monitor will sign the monitoring site visit log, and a report will be generated by the monitor within approximately 10 days of site visit.

- Monitoring Report
  - The monitoring report will consist of a summary of study observations along with significant findings, action items, subsequent requirements, and recommendations that are needed to ensure study is compliant with all rules and regulations as described in this report.
- Monitor Responsibility
  - The monitor is tasked to ensure study is conducted, recorded, and reported as required by protocol, institutional policies and procedures and applicable regulatory bodies. Monitor is to communicate any concerns or issues at the time of the visit that might arise to the attention of the PI and/or designee, IRB, and any applicable regulatory bodies.
  - In the event a high error rate is noted, the monitor will escalate the incidence to the monitor's leadership for consideration of monitoring additional subjects over what is outlined in this monitoring plan.
  - Any Serious and Continuing non-compliance will be reported to the Research Oversight Committee/DSMB and additional requirements may be required by PI and/or study team.

- Report will be completed within approximately 10 business Days of the visit. If it's determined there would be a delay in the report completion the monitor will communicate any pressing issues via phone or email until the report is delivered.

- Dissemination of report
  - The monitoring report will be sent via email to the following parties:
    - Principal Investigators
    - Sub-Investigators
    - Study Coordinator
    - Regulatory Manager
    - Team Manager/Director
- Site Responsibilities
  - The site is expected to promptly review monitoring reports, work on significant findings or discrepancies till resolution.
  - Action items must be completed by the specified due date on the monitoring report.
  - If any findings require IRB reporting, it's expected that site will report these findings in an "Promptly Reportable Information" form to the IRB promptly as required by the IRB of record and any applicable regulatory bodies.
  - Promptly notify Regulatory team and the monitor of any reportable new information, deviations, enrollment activities and all inspections.
  - Submit all monitoring reports to the IRB.

Data and Safety Monitoring Board (DSMB) or Equivalent

Since the project has more than minimal risk and plans to enroll participants with a wide age range including the elderly, the NIDDK Program Official(s) will appoint an independent Data and Safety Monitoring Board (DSMB) according to NIDDK requirements. The board will review compiled safety data, study progress, and interim results at periodic intervals. The DSMB will be comprised of conflict-free independent experts. The NIDDK Program Official will serve as the Executive Secretary and/or NIDDK program representative on the DSMB.

The DSMB will consist of members with the following range of qualifications:

1. A physician with particular expertise in type 1 diabetes
2. A physician who can lead the effort in monitoring the overall event rate of various adverse events (AE) and serious adverse events (SAE), as well as balance between intervention groups
3. A physician who can lead the effort in monitoring the safety of insulin withdrawal test
4. A person with T1D with a medical background (nurse, nutritionist, diabetes educator, etc.)
5. An external statistician who can monitor data collection, critique analysis plans, request additional data analysis, and provide an interpretation of results the DSMB

This DSMB will meet quarterly, unless enrollment numbers do not warrant a meeting. The study team will provide semiannual data and safety monitoring reports to the NIH for electronic review.

Ethical Considerations

Participation in this study is voluntary. Subjects may decide not to participate in this study or may withdraw from this study at any time without penalty or loss of benefits. No vulnerable populations will be studied in this protocol.
Sharing of Results with Subjects:

Participants will be offered the opportunity to meet with the Principal Investigator or designated medical staff to review the results of their lab assessments or other standard clinical data. Copies of their testing results will be made available to the participants upon request. In addition, the Principal Investigator or designated study staff will provide an overview of the study's outcome to the participant if he or she requests the information.

Funding Source

This study is supported by the National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases 1U01DK143384 - 01.

Subject Stipends or Payments

Participants may receive up to $1850.00 for completion of all procedures.

Participant compensation will occur as follows:

- A reloadable Payment Card will be provided to receive payments for the study. The terms and Conditions for this card will be provided to the participant for review.
- Payment will be requested within 3 business days from completion of the following study visit(s) or task completion; Screening visit, Period 1 (Visit 1 & Visit 2), Period 2 (Visit 3), Education (Visits 4 – Visit 7), and completing all ASA 24 forms.
- If participant is unable to complete all study visits or it is determined by the study doctor or sponsor that you should stop the study early, the stipends will be prorated to the following:

Visit	Prorated amount
Screening visit	$ 50.00
Period 1 (Visit 1 & Visit 2)	$ 250.00
Period 2 (Visit 3)	$ 250.00
Visit 4 – Visit 7 (Education)	$1200.00
Completing all ASA 24 forms	$ 100.00

Total for all completed visits	$1850.00

Publication Plan

We attest that the AH-TRI faculty and staff will adhere to POLICY-TRI-ADM-005 (Access to Clinical Trial Data for Publication Purposes). Assignment of authorship and the contributions of each author will be determined by the International Committee of Medical Journal Editors (ICMJE) policy to guide authorship.

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