Hybrid Closed Loop Therapy and Verapamil for Beta Cell Preservation in New Onset Type 1 Diabetes (CLVer)

A Proof-of-Concept Study

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VERSION HISTORY

The following table lists versions of the protocol:

VERSION NUMBER	AUTHOR	APPROVER	EFFECTIVE DATE	REVISION DESCRIPTION
1.0	Jennifer McVean, Antoinette Moran, Stephanie DuBose	Stephanie DuBose	01Nov2019	Original version
1.1	Stephanie DuBose	Stephanie DuBose	04Nov2019	Expanded age group for quality of life questionnaire 'Problem Areas in Diabetes' in Section 7.3
1.2	Stephanie DuBose	Stephanie DuBose	22Nov2019	JCHR IRB requested the following edits: • Safety visits cannot be completed by local physician • Clarify study drug is dispensed at Randomization–39 weeks • Clarify email/texts should not include PHI • Correct typos
2.0	Stephanie DuBose, Jennifer McVean	Stephanie DuBose	25Nov2019	FDA requested the following edits: • Expand exclusion criteria for Cohort A • Revise study drug titration schedule to be more gradual • Modify timing of safety visits • Specify that cardiologist should review abnormal EKG results throughout study Corrected typos
3.0	Stephanie DuBose	Stephanie DuBose	04Dec2019	○ Clarified details regarding future use of stored samples ○ Updated psychosocial questionnaire details ○ Added possible allergy risk of Boost during MMTT ○ Clarified that non-HCL groups will do ketone testing per usual care ○ FDA requested the following edits: • Change timing of education visit to 7 days post randomization for HCL groups and indicate HCL will be initiated at that time • Modify min low glucose threshold details • Specify how initial insulin profiles will be customized for HCL groups • Add that parents/guardians should be present with participant at night as much as possible • Reference guidance docs that include instructing to check blood glucose when sensor glucose is low or high and how to treat • Add additional stopping criteria for HCL devices related to SH and DKA events • Add that all system requirements must be met before starting HCL
3.1	Stephanie DuBose	Stephanie DuBose	13Dec2019	○ Corrected typos ○ FDA requested the following edits: • Increase frequency of HCL contacts • Add options for remote monitoring of HCL participants • Require overnight fingersticks for first two nights after HCL initiation • Add mechanism to ensure participants know how to adjust pump settings

VERSION NUMBER	AUTHOR	APPROVER	EFFECTIVE DATE	REVISION DESCRIPTION
4.0	Jennifer McVean, Stephanie DuBose, Antoinette Moran	Stephanie DuBose	22Jan2020	○ Corrected typos and added clarifications ○ Updated details regarding blinded CGM wear ○ Updated location for storage of future samples ○ Removed participant questionnaires ○ Noted that pill splitting will be done at home ○ Updated timing of labs ○ FDA requested the following edits: • Clarify acetaminophen eligibility criteria to specify cannot have contraindication to ibuprofen • Add details on setpoint for 670G 4.0 • Add details regarding bolusing prior to meal
4.1	Diana Rojas, Stephanie DuBose,	Stephanie DuBose	06Mar2020	○ Corrected typos and added clarifications ○ Updated timing of labs (including MMTT) ○ Clarified timing of randomization ○ Removed requirement of blinded CGM wear for participants using Medtronic system ○ Revised blood ketone level cutoff for reportable hypoglycemic events ○ Changed description of Tandem pump to reflect Pro software
4.2	Stephanie DuBose	Stephanie DuBose	12May2020	○ Corrected typos ○ Minor updates to procedures to allow flexibility due to COVID-19 • Allow device training and dietitian consult to be completed within 3 days of randomization rather than on day of randomization • Allow 7-day additional HCL training visit to be conducted remotely, per investigator discretion • Allow 6 week visit to be completed remotely for Cohort B, with physical exam not required
4.3	Stephanie DuBose	Jennifer McVean, Antoinette Moran, Stephanie DuBose	27Jul2020	○ Minor updates to procedures to allow flexibility due to COVID-19 • Allow Safety Visits (collection of BP and pulse 1 week after study drug initiation and each dose increase for Cohort A) to be conducted remotely (using study provided BP/pulse machine) • Allow for expanded windows for Screening visit and between Screening and Randomization, as long as participant able to be randomized within 31 days of T1D diagnosis • Allow use of recent Tanner Staging results if available at Screening ○ Updated recommendations for number of grams of carbohydrates to take before blousing, if low ○ Updated setpoint details for 670G 4.0 by age group (per recent Medtronic data and approved by FDA) ○ Updated timing of 6 week visit to be timed from randomization instead of diagnosis
4.4	Stephanie DuBose	Jennifer McVean, Antoinette Moran, Roy Beck	18Nov2020	○ Allow 6 week visit to be conducted remotely for both Cohorts (for flexibility due to COVID-19)
5.0	Jennifer McVean	Stephanie DuBose	26May2021	○ Added new Medtronic 780G HCL system (with option for participants to switch over from 670G 4.0 to new system and option for continued access to system after trial completion) ○ Removed dietitian visit at 52 week visit ○ Removed need to re-consent at age from 14; only re-consent at 18 years old
5.1	Diana Rojas	Stephanie DuBose	01Oct2021	○ Changed Protocol Co-Chair from Jennifer McVean to Gregory Forlenza
5.2	Diana Rojas	Colleen Bauza	01Mar2022	○ Changed Coordinating Center Director from Stephanie Dubose to Colleen Bauza

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AUC	Area Under the Curve
BG	Blood Glucose
CRF	Case Report Form
CGM	Continuous Glucose Monitoring
CI	Confidence Interval
CSII	Continuous Subcutaneous Insulin Infusion
DKA	Diabetic Ketoacidosis
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HCL	Hybrid Closed Loop
ID	Identification
IDE	Investigational Device Exemption
IQR	Interquartile Range
MDI	Multiple daily injections
MMTT	Mixed Meal Tolerance Test
POC	Point-of-Care
PRO	Patient-Reported Outcome
QA	Quality Assurance
QC	Quality Control
RCT	Randomized Controlled/Clinical Trial
RMB	Risk-Based Monitoring
SADE	Serious Adverse Device Event
SAE	Serious Adverse Event
SAP	Sensor-Augmented Pump
SD	Standard Deviation
SH	Severe Hypoglycemia
SMBG	Self-Monitoring of Blood Glucose
UADE	Unanticipated Adverse Device Effect

PROTOCOL SUMMARY

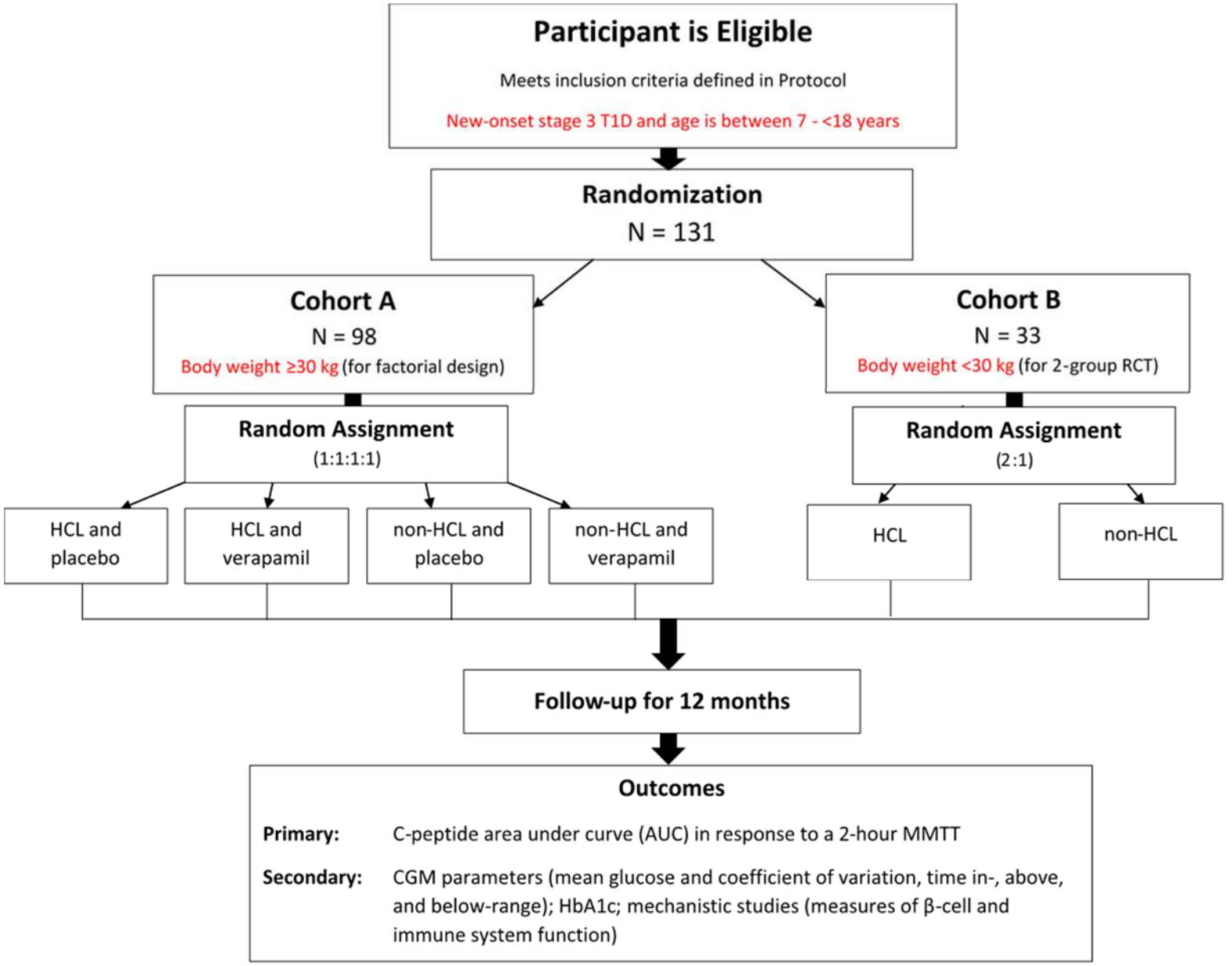
PARTICIPANT AREA	DESCRIPTION
Title	Hybrid Closed Loop Therapy and Verapamil for Beta Cell Preservation in New Onset Type 1 Diabetes: A Proof-of-Concept Study
Précis	Randomized trial of youth aged 7-<18 years with newly diagnosed stage 3 type 1 diabetes to assess the effect of both (1) near-normalization of glucose concentrations achieved through use of a hybrid closed loop (HCL) system and (2) verapamil on preservation of β-cell function 12 months after diagnosis. Participants with body weight ≥30 kg (Cohort A) will be randomly assigned in a factorial design to (1) HCL plus intensive diabetes management or usual care with no HCL and (2) verapamil or placebo. Participants with body weight <30 kg (Cohort B) will be randomly assigned 2:1 in a parallel group design to HCL plus intensive diabetes management or to usual care with no HCL.
Objectives	Primary Objectives 1) To determine if initiation of HCL therapy plus intensive diabetes management soon after diagnosis of stage 3 T1D can achieve near-normalization of glucose concentrations that preserves beta cell function (Cohort A and Cohort B will be combined for the analysis) 2) To determine if oral verapamil started soon after diagnosis of stage 3 T1D preserves beta cell function (Cohort A) Secondary Objectives (comparing HCL vs non-HCL and verapamil vs placebo) 1) To compare CGM parameters of blood glucose control including mean glucose; coefficient of variation; and time in-, above- and below- range (70-180, >180, >250, <70, <54 mg/dL between treatment groups. 2) To compare HbA1c between treatment groups. 3) To compare frequency of episodes of severe hypoglycemia between treatment groups. 4) To compare frequency of episodes of DKA between treatment groups. 5) To conduct mechanistic studies, the exact nature of which will be determined at study end depending on study outcomes.
Study Design	Multi-center randomized 2x2 factorial design controlled trial for participants with body weight ≥30 kg (Cohort A) and 2-group parallel design RCT for participants with body weight <30 kg (Cohort B).
Number of Sites	Six
Sample Size	Cohort A: 98 participants with body weight ≥30 kg (for factorial design) Cohort B: 33 participants with body weight <30 kg (for 2-group RCT)
Endpoint	**Primary Efficacy Outcome:** C-peptide area under curve (AUC) in response to a 2-hour MMTT at 52 weeks **Key Secondary Efficacy Outcomes:** CGM parameters (mean glucose and coefficient of variation, time in-, above, and below-range); HbA1c mechanistic studies (measures of β-cell and immune system function) **Key Safety Outcomes:** Episodes of severe hypoglycemia and DKA
Population	**Key Inclusion Criteria:** • New-onset stage 3 T1D,with ability to be randomized within 31 days of diagnosis • At least one positive type 1 diabetes auto-antibody • Age 7 - <18 years at the time of enrollment

PARTICIPANT AREA	DESCRIPTION
	• Willing to have a parent or legal guardian provide informed consent and child assent • In a female participant with childbearing potential, not currently pregnant and willing to avoid pregnancy and breastfeeding and undergo pregnancy testing throughout the study • English speaking/reading • Able to swallow pills (tested with an inert imitation tablet in clinic prior to randomization) —*Cohort A only* • Willing to not use any non-insulin glucose-lowering agents (such as GLP-1 agonists, Symlin, DPP-4 inhibitors, SGLT-2 inhibitors, biguanides, sulfonylureas) • Willing to use an insulin approved for the pump *(if assigned to HCL)* • Willing to avoid medications containing acetaminophen, and no contraindications for ibuprofen use *(in case assigned to Medtronic HCL system)* **Key Exclusion Criteria:** • Ongoing use of medications known to influence glucose tolerance such as systemic steroids • Other systemic disease which in the opinion of the investigator precludes participation (including psychiatric illness) • Unwilling to abstain from use of HCL therapy for 12 months o Personal pump and CGM use, including systems with a "suspend-before-low" function, will be allowed for participants randomized to non-HCL groups • "Silent" diabetes—i.e., Stage 3 diabetes that is identified by routine OGTT or in the course of surveillance studies but is not accompanied by fasting hyperglycemia or classic symptoms of diabetes • Participation in another research study that involves diabetes care or immune modulation Additional exclusion criteria for Cohort A • Blood pressure (either systolic or diastolic) <5th percentile for age, gender, and height on two out of three measurements • Pulse <2nd percentile for age and gender on two out of three measurements • History of vasovagal syncopal episodes related to hypotension • Abnormal EKG rhythm unless cleared for study participation by a cardiologist • Underlying cardiac disease (ex. left ventricular dysfunction, hypertrophic cardiomyopathy), certain arrhythmias (ex. AV block, accessory pathway such as Wolff-Parkinson-White or Lown-Ganong-Levine syndromes), known liver dysfunction, known renal impairment, Duchenne's muscular dystrophy, active Graves disease or hyperthyroidism, and untreated hypothyroidism • eGFR < 90 • AST and/or ALT greater than 1.5 times the upper limit of normal • Need to use of any of the following medications during the study: beta blocker, seizure medication (carbamazepine, phenobarbital, phenytoin), other antihypertensive medications, HMG-CoA reductase inhibitors, lithium, theophylline, clonidine, or aspirin • Any known hypersensitivity reaction to Verapamil

PARTICIPANT AREA	DESCRIPTION
Study Devices	Random assignment 1:1 of HCL system to participants in HCL groups: • Tandem t:slim X2 with Control-IQ and Dexcom G6 system • Medtronic 670G 4.0 AHCL (prior to protocol version 5.0) or 780G (starting with protocol version 5.0) Dexcom G6 CGM (used by the non-HCL groups in both cohorts)
Investigational Drug	Oral verapamil (extended release)/placebo in dosage of 60-360 mg/day based on weight and tolerance
Treatment Groups	Cohort A: random assignment (1:1:1:1) to HCL and placebo, HCL and verapamil, non-HCL and placebo, or non-HCL and verapamil Cohort B: random assignment (2:1) to HCL or non-HCL (All groups will include use of CGM)
Participant Duration	12 months from time of diagnosis
Protocol Overview/Synopsis	After informed consent is obtained, potential participants will be assessed for eligibility, including eliciting medical history, physical examination, auto-antibody measurement [unless positive auto-antibody results already available], pregnancy test for females with childbearing potential, and if ≥30 kg (Cohort A): EKG, creatinine, AST, and ALT tests. Participants who already have positive auto-antibodies can be randomized immediately once other eligibility criteria are assessed. All other participants will be scheduled for a randomization visit after the auto-antibody results are available. Eligible participants with body weight ≥30 kg at Screening (Cohort A) will be randomly assigned to one of 4 groups: HCL and placebo, HCL and verapamil, non-HCL and placebo or non-HCL and verapamil. Eligible individuals with body weight <30 kg (Cohort B) will be randomly assigned 2:1 to either HCL or non-HCL. Randomization schedules will be separate for Cohort A and Cohort B and will be stratified by site. Participants assigned to HCL will receive intensive diabetes management with frequent contacts by study staff with the goal of near-normalization of glucose concentrations. Participants assigned to non-HCL will receive a Dexcom G6 CGM and diabetes management will follow usual care by their personal diabetes health care provider. Participants will be followed for 12 months from diagnosis, completing a 6 week visit timed from randomization and 13, 26, 39, and 52 week visits timed from diagnosis. Participants will have a MMTT performed, HbA1c measured, and blood drawn for mechanistic studies at Randomization, 13, 26, 39 and 52 weeks. At all follow-up visits, a physical exam will be performed, pregnancy testing performed (if indicated), insulin dose (units/kg/day) recorded, and device data downloaded. Safety assessments will be made throughout the study by querying about episodes of severe hypoglycemia and DKA, and overall health. Participants already enrolled in the study and using the Medtronic 670G 4.0 AHCL may transition to the Medtronic 780G if desired. Contacts will be performed to review CareLink data and check for adverse events and device deficiencies on days 1, 3 and 5 after transition from 670G 4.0 AHCL to 780G. Prior to the 780G system becoming commercially available, study participants using the Medtronic system at 52 weeks will have the opportunity to continue using the 780G system at home until the system is commercially available OR until the CLVer trial is complete (last participant's 52-week visit), whichever comes first.

PARTICIPANT AREA	DESCRIPTION
	Additional Procedures for Cohort A Drug will be double blinded. Drug dose will be weight-dependent and will be escalated at 2-4week intervals, up to a weight-dependent maximum if tolerated. Cohort A will have additional safety visits 1 week after initiation of study drug and after each study drug dose increase, to test blood pressure and pulse. Local lab measurement of AST/ALT will occur, and an EKG will be performed at Screening, 6, 26, and 52 weeks. Creatinine will be assessed at Screening as part of eligibility. Over the course of the trial, study drug dose may be decreased or discontinued if side effects occur.

SCHEMATIC OF STUDY DESIGN*



**Ns are approximate; follow up timed from randomization (6-weeks) and T1D diagnosis (13, 26, 39, 52 weeks)*

SCHEDULE OF STUDY VISITS AND PROCEDURES

The table below shows the visits for all study participants. Participants assigned to HCL in both Cohort A and Cohort B will have an additional visit after 7±2 days for HCL system training and Cohort A will have a safety visit 7±5 days after drug initiation and after each dose increase for drug safety assessments. HCL group will have additional contacts every 1-3 days for the first 2 weeks, at least twice a week for second 2 weeks, and then every 1-2 weeks through end of study. Participants who transition from the Medtronic 670G 4.0 AHCL to the Medtronic 780G will have additional contacts on days 1, 3 and 5 after the transition.

Participants who stop using a CGM or have insufficient CGM data will wear a blinded Dexcom G6 sensor for approximately 10 days at 6, 13, 26, 39 and 52 weeks.

			Follow-up Visits Both Cohorts/All Groups^				
Overview of Study Procedures	**Screening Visit**	**Randomization Visit (within 31d of diagnosis)**	**6 wks* ±3 days**	**13 wks ±3 days**	**26 wks ±7 days**	**39 wks ±7 days**	**52 wks ±7 days**
Informed Consent/Assent	X						
Eligibility	X						
Medical history	X						
Physical Exam[a]	X		X	X	X	X	X
Pregnancy test (as appropriate, done locally)	X	X	X	X	X	X	X
Islet Auto-antibodies (central lab)	X						
Prior/Concomitant Meds	X	X	X	X	X	X	X
Adverse Event Assessments		X	X	X	X	X	X
Daily insulin U/kg[b]		X	X	X	X	X	X
MMTT (glu and cpep, central lab)		X		X	X	X	X
HbA1c (central lab)		X		X	X	X	X
Pro-insulin, Pro-IAPP, unmethylated INS DNA[c] (central lab)		X		X	X	X	X
Micro RNA sequencing[c] (central lab)		X		X	X	X	X
PBMC, serum cytokines[c] (central lab)		X			X		X
Extra plasma samples for future research (central lab)		X			X		X
Device download-as applicable			X	X	X	X	X
Dietitian consult (HCL only)		X	X	X	X	X	
Compliance Assessment			X	X	X	X	X
Randomization		X					
Additional Testing for Cohort A[d]							
EKG	X		X		X		X
AST, ALT (local lab)	X		X		X		X
Creatinine, to calculate eGFR (local lab)	X						

^The 6 week visit is timed from Randomization and the 13, 26, 39, and 52 week visits are timed from date of T1D diagnosis.

*The 6 week visit may be conducted remotely if an in-clinic visit is not feasible, with physical exam not required. Safety testing will still be completed for Cohort A but may be done off-site.

[a]Physical exam includes Tanner staging at Screening and 52 weeks (for participants <Tanner 5 at Screening). Limited, directed physical exam at other visits (pulse, BP, height, weight, examination of injection/insertion sites)

[b]Units/kg/day, by pump download or by patient 3-day records for those on MDI

[c]Samples for some of the time points may or may not be run, depending on final study results.

[d]Cohort A participants also will have a safety visit 7±5 days after drug initiation and after each dose increase to evaluate BP/pulse. (These visits may be conducted remotely, as needed.)

Chapter 1: Introduction

1.1 Background

T1D is a substantial burden for those living with the disease and their families, and is associated with increased morbidity and mortality.

Type 1 diabetes (T1D) affects about 1.25 million people in the United States, with an incidence of approximately 40,000 new cases per year in the US (110 people per day) (JDRF fact sheet: https://www.jdrf.org/about/what-is-t1d/facts/). The worldwide incidence of T1D is increasing, particularly in children; the SEARCH for Diabetes in Youth study found a 21% rise in the prevalence of T1D from 2001-2009 in youth aged 0-19 [1].

Current standard-of-care consists of basal-bolus insulin therapy with either multiple daily injections (MDI) of insulin, or continuous subcutaneous insulin infusion (CSII) by pump [2]. Patients and care-providers make decisions about insulin dosage based on blood glucose measurements obtained from either self-monitoring of blood glucose by multiple daily fingerpricks (self-monitored blood glucose, SMBG), or increasingly, by continuous glucose monitoring (CGM) of interstitial fluid glucose levels. Despite the technologic advances in the management of diabetes, many persons living with the condition struggle to achieve targeted glycemic control. Indeed, data from the T1D Exchange (T1DX) highlight this as <30% of registry participants achieve targets for glycemic control [3]. While sub-optimal control increases the risk of long-term micro- and macrovascular complications, patients may also experience acute life-threatening episodes of severe hypoglycemia or diabetic ketoacidosis (DKA). Such events are not uncommon, with 7% of T1DX registry participants self-reporting an episode of severe hypoglycemia (resulting in seizure or coma) in the past 3 months and 8% experiencing an episode of DKA in the preceding 12 months [4]. Moreover, the poor glycemic control which increased the risk of DKA did not protect against severe hypoglycemia [5].

T1D is caused by autoimmune β-cell destruction; this process is particularly aggressive in the young.

Several factors predict the rate of autoimmune β-cell destruction in patients with T1D, the most important being age [6]. While incident T1D can occur at any age, the natural history and burden of disease is different in those diagnosed as children compared to those diagnosed as adults. T1D diagnosed in adulthood is characterized by a longer asymptomatic period before diagnosis and increased likelihood of preservation of residual β-cell function as compared to the natural course of youth diagnosed with this chronic condition [7]. In a TrialNet consortium's review of 191 T1D patients followed in clinical trials, age was found to be the strongest predictor of the rate of decline in C-peptide secretion with participants less than 21 years of age having a greater rate of decline compared to those older than 21 years of age [6]. The greatest rate of C-peptide decline occurred in children under the age of 12, with progressively less decline in C-peptide over time with older age of onset [8]. This observation has been confirmed by others [9]. Because children and adolescents have the greatest risk for rapid disease progression as measured by loss of residual C-peptide secretion, it is critical that intervention studies target the pediatric population.

Development of safe therapies that preserve residual C-peptide secretion is important to maximally reduce the life-long risk of complications and early death for pediatric T1D patients.

Residual C-peptide secretion has been shown to lower the risk diabetes-related complications. The DCCT showed that rates of both retinopathy and early diabetic nephropathy increased with greater longitudinal loss of β-cell function, regardless of treatment arm (intensive vs. conventional treatment) [9]. Therefore, retention of β-cell function is felt to confer clinical benefit to patients and this may be particularly important for children who will live with diabetes substantially longer than patients diagnosed in adulthood. An additional concern in the pediatric population is evidence that both hyperglycemia and glycemic variation have a negative impact on the developing brain, as they have been shown to be related to neuroanatomical alterations and diminished cognitive ability in children [10]. Thus, there is a clear, unmet need to improve both the natural history of disease progression and glucose variation for everyone with T1D, but especially for youth. It is essential that intervention efficacy is balanced with safety, especially in the children, as the risk associated with the treatment cannot outweigh the potential benefit.

Studies evaluating the impact of near-normalization of blood glucose levels on preservation of residual C-peptide secretion have produced conflicting results.

Promising pre-clinical animal studies led to several small human studies that evaluated the impact of a short-duration of very intensive insulin therapy right after T1D diagnosis, followed by standard intensive therapy for the remainder of the first year, with the aim of preserving β-cell function. These yielded conflicting results. Two weeks of inpatient closed-loop therapy shortly after T1D diagnosis was reported to preserve stimulated C-peptide levels at one year in 12 adolescents compared to 14 controls [11]; however, no difference was observed in a similar study of 9 participants [12]. One to two months of outpatient insulin infusion through a central venous line using a portable infusion pump led to improved short-term C-peptide parameters in 7 adolescents compared to 7 matched controls, but the differences did not persist at 12 months [12]. In contrast to studies evaluating short-term but unsustained intensive insulin therapy very early in the course of T1D, the DCCT compared chronic administration of what was then considered intensive versus conventional insulin therapy. The DCCT provided the strongest evidence to date that lowering blood glucose levels over time may help preserve β-cell function. Compared with conventional therapy, intensive therapy with a resulting reduction in HbA_{1c} reduced the risk of C-peptide loss in participants who had measurable C-peptide at baseline [13].

The landscape of diabetes management has drastically changed following completion of these studies, including pharmacologic improvements (insulin analogs) as well as technologic advancements, including the development and wider availability of user-friendly insulin infusion pumps and increased accuracy, affordability and acceptance of CGM. The STAR 3 study in 485 participants, of whom 156 were children, demonstrated that sensor-augmented pump therapy was superior to MDI with regards to HbA1c levels [14]. In the ONSET study [15], all participants received insulin pump therapy and were then randomized to treatment with either CGM or

SMBG. While there was no change in HbA1c, the sensor-treated group had decreased glycemic variability and preserved C-peptide secretion at 12 months.

Most recently, Buckingham and colleagues in the DirectNet consortium conducted a RCT to assess the benefits of intensive treatment following diagnosis as compared to usual therapy, with stimulated C-peptide level one year after diagnosis as the primary outcome measure. The intensively treated group underwent a 3-4 day period of inpatient hybrid closed loop therapy within the first week of diagnosis followed by use of sensor augmented pump therapy [16]. Pump and sensor data were reviewed by clinical staff every 1-2 weeks in the first two months and then monthly with additional data reviews if clinically indicated. Usual-therapy patients were treated by endocrinologists who were not part of the study team. Forty-eight participants were randomized to intensive treatment and compared to 20 participants in the control group who received usual therapy [16]. At the one-year assessment, there was no difference in stimulated C-peptide levels between the groups. Importantly, the level of metabolic control did not greatly differ between groups, with the majority of patients in both groups being treated by insulin pump therapy and a negligible difference in glycemic control achieved one year after diagnosis (intensive treatment group: HbA1c 7.4% vs. usual therapy: 7.3%). Furthermore, after 12 months only 33% of subjects in the intensive group were still using CGM. This study demonstrates it is feasible to recruit participants shortly after diagnosis for a RCT to investigate the impact of technology to achieve targeted control and ameliorate disease course. Yet, it does not prove or disprove the hypothesis that near-normalization of glucose levels preserves β-cell function, as beyond the first few days of inpatient diabetes management and with the tools available at the time, no difference in glycemic control was demonstrated between the groups.

Near-normalization of blood glucose levels has been an elusive goal for most patients with T1D, and especially for children and adolescents.

Although intensive insulin therapy has been the standard-of-care for those with T1D for several decades, most patients have remained sub-optimally controlled despite more advanced treatment modalities. This is particularly true in the pediatric population in whom elevated HbA1c levels continue to be observed in children and adolescents across the world as compared to adults living with this chronic medical condition [17,18]. In the T1DX registry an average HbA1c of 8.2%, which is well above the recommended target of <7.5% for children, has been noted [17]. Indeed, only 21% of T1D adolescents (ages 13-20) had HbA1c levels <7.5%; and less than half of those 6-12 years of age achieved an HbA1c <8% [19]. This increased HbA1c reflects chronic abnormal glucose metabolism, and is associated with diabetes complications and reduced lifespan [20].

Newly available hybrid closed loop (HCL) therapy offers the potential for true chronic near-normalization of metabolic control.

A major problem for previous studies trying to assess the impact of interventions in the first year of T1D diagnosis has been that the vast majority of the new-onset population is in a honeymoon phase, and this combined with improvements in diabetes care have made it difficult to observe differences in metabolic control between the intervention and usual care cohorts [16]. However, our tools have recently been refined with the approval of the first HCL system, the MiniMed 670G,

garnering FDA approval in September 2016. Recently, the labeling has been expanded to include children down to age 7 years. A study including fifty 2-6 year old patients was completed and submitted to the FDA in 2019. HCL insulin delivery is a major leap forward, as it provides more physiologic insulin delivery since basal insulin delivery is based on sensor glucose values. Highlighting the safety of HCL, in the pivotal trial in 124 participants (including 30 adolescents) that allowed for regulatory approval of the system, there were no episodes of either severe hypoglycemia or DKA [14]. Importantly, over a 3-month period, HbA1c levels and the proportion of time in-target range based on sensor glucose values improved. In addition to improving glucose time-in-range, decreased glycemic variability was seen in participants when using HCL therapy compared to a 2-week baseline data collection phase where they were using sensor-augmented pump therapy without automation of insulin delivery [21]. Decreased glycemic variability is associated with C-peptide preservation at 1 and 2 years post diagnosis [15,22], suggesting that technologies that can further normalize glycemic variability may have an even greater impact. Early real-world findings evaluating MiniMed 670G data obtained in the 6-month period following the commercial launch demonstrated that results were similar to those reported in the pivotal trial, and sustained over the time of the observation [23]. Thus, HCL therapy allows a degree of blood glucose normalization and reduction of glucose variability to levels previously unattainable.

Verapamil

Loss of pancreatic beta-cell mass has long been identified as a key factor in the pathogenesis of type 1 diabetes however decades of research in this area have failed to identify viable therapies for human beta-cell preservation.[24] Recent laboratory and animal research has identified thioredoxin-interacting protein (TXNIP), a ubiquitously expressed cellular redox regulator, as an attractive target for beta-cell preservation therapy.[25] TXNIP overexpression has been shown to induce beta-cell apoptosis and its role has been shown to be essential for glucotoxicity-induced beta-cell death.[26] Furthermore, lack of TXNIP has been shown to promote endogenous beta-cell survival and to prevent type 1 diabetes in animal models.[27] Calcium channel blockers, such as verapamil, have been demonstrated to reduce TXNIP expression as well as apoptosis[25,28] through blockade of L-type calcium channels, which results in a decrease in intracellular free calcium leading to inhibition of TXNIP transcription.[25]

Based on promising pre-clinical work, Ovalle conducted a randomized double-blind placebo-controlled phase 2 clinical trial to assess the efficacy and safety of oral verapamil for 12 months in adults with recent-onset T1D.[29] A total of 26 adults 18-44 years old with T1D diagnosed in the previous 3 months were randomized 1:1 to either once daily oral verapamil or placebo. Those treated with verapamil had significantly higher stimulated C-peptide area under the curve in response to a standardized mixed meal tolerance test compared with the placebo group at both 3 and 12 months following initiation of therapy (Figure).[29] Given the preservation of residual beta cell function demonstrated in this cohort of adults with recent onset type 1 diabetes, the oral route of this agent, and its safety profile, we propose to assess this therapy in a pediatric population who are newly diagnosed with type 1 diabetes.

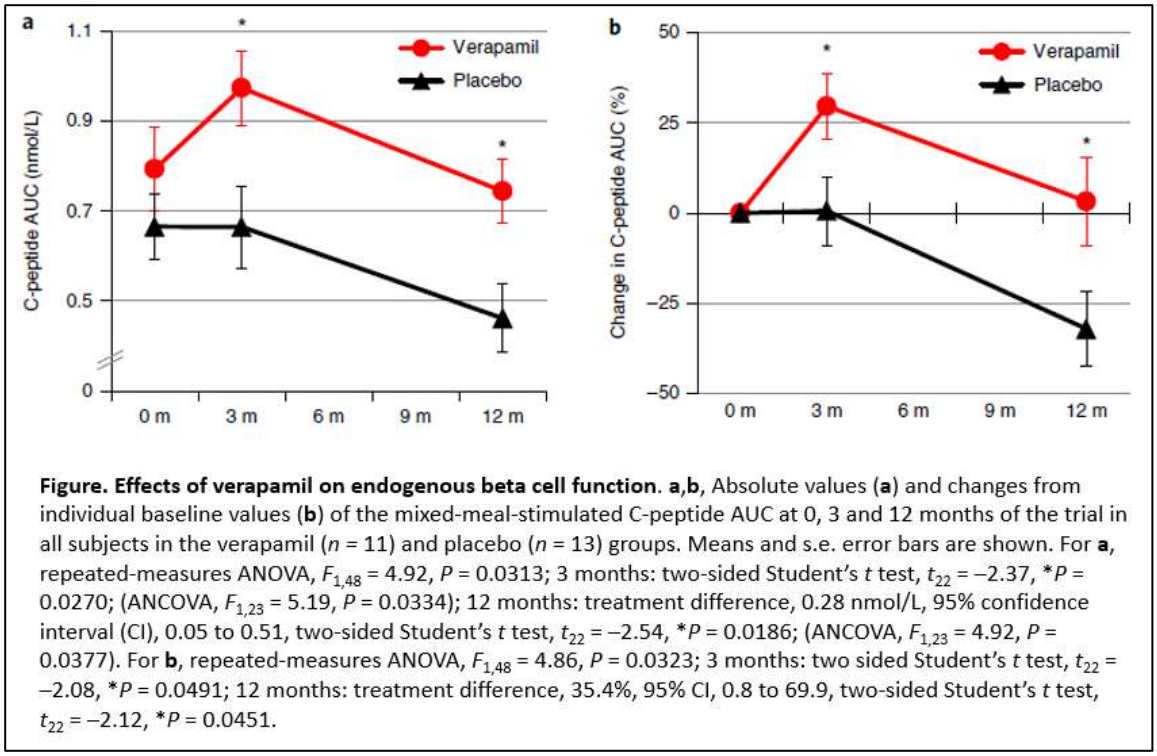


Figure. Effects of verapamil on endogenous beta cell function. **a**,**b**, Absolute values (**a**) and changes from individual baseline values (**b**) of the mixed-meal-stimulated C-peptide AUC at 0, 3 and 12 months of the trial in all subjects in the verapamil (n = 11) and placebo (n = 13) groups. Means and s.e. error bars are shown. For **a**, repeated-measures ANOVA, $F_{1,48}$ = 4.92, P = 0.0313; 3 months: two-sided Student's t test, t_{22} = –2.37, *P = 0.0270; (ANCOVA, $F_{1,23}$ = 5.19, P = 0.0334); 12 months: treatment difference, 0.28 nmol/L, 95% confidence interval (CI), 0.05 to 0.51, two-sided Student's t test, t_{22} = –2.54, *P = 0.0186; (ANCOVA, $F_{1,23}$ = 4.92, P = 0.0377). For **b**, repeated-measures ANOVA, $F_{1,48}$ = 4.86, P = 0.0323; 3 months: two sided Student's t test, t_{22} = –2.08, *P = 0.0491; 12 months: treatment difference, 35.4%, 95% CI, 0.8 to 69.9, two-sided Student's t test, t_{22} = –2.12, *P = 0.0451.

The purpose of this study is to demonstrate proof-of-principle.

As the tools to achieve near-normalization of blood glucose levels have been primitive to-date, the ability to assess whether this approach will preserve β-cell function has been compromised. The current study will be proof-of-principle, as conditions will be optimized beyond those generally achievable in "real life". To ensure success with early generations of HCL systems and to encourage adherence, there will be intensive engagement with the study team, to a level which may or may not be sustainable in clinical practice. The goal for sensor wear and time in HCL therapy is at least 85%. If this proof-of-principle study demonstrates C-peptide preservation, the next step might be a multicenter, intent-to-treat study to determine whether this approach can practically be implemented in routine clinical practice. However, we recognize that the ability to perform this larger study with a control group not on HCL may not be feasible in the future if HCL therapy becomes standard-of-care in the coming years. We anticipate that improved features with future generations of HCL technology will make it more feasible to maintain near-universal automated insulin delivery functionality. Thus, in the future it may no longer be possible to test our hypothesis.

1.2 Potential Risks and Benefits of the Study

The risks of this study are presented in this protocol and in the informed consent form. This study will examine whether near normalization of blood glucose levels beginning early after diagnosis of T1D or Verapamil will preserve beta cell function, but there is no guarantee that this will occur.

1.2.1 Known Potential Risks

Hybrid Closed Loop System

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

- Diabetic ketoacidosis (DKA) resulting from high blood glucose due to suspension of insulin delivery or inadequate insulin delivery (which may result from catheter occlusion, hardware or software malfunction, erroneous CGM readings in closed loop or suspend mode, or inadequate insulin dosing).
- Severe hypoglycemia resulting from over-delivery of insulin (which can result from hardware or software malfunction, erroneous CGM readings in closed loop mode, or erroneous insulin dosing), which may lead to seizure, unconsciousness, and rarely death.

There is a risk of DKA and severe hypoglycemia in anyone with T1D and use of a HCL system is not expected to increase this risk.

Device-related

Potential device related non-serious events at the site of insertion include: skin irritation or redness, infection, pain or discomfort, bruising, edema, rash, bleeding, induration of skin, allergic reaction to adhesives. The risk of skin problems could be greater if a sensor or pump infusion set is used for longer than it is supposed to be used. Therefore, participants (and parents) will be carefully instructed about proper use of the sensor and pump.

On rare occasions, the CGM sensor may break and leave a small portion of the sensor under the skin that may cause redness, swelling or pain at the insertion site. The participant will be instructed to notify the study coordinator immediately if this occurs.

Verapamil

Verapamil is a calcium channel blocker. The most common side effect of verapamil is constipation. Patients taking verapamil should also be monitored for severe hypoglycemic episodes, hypotension, decreased heart rate, changes in electrocardiogram (EKG) including abnormalities in QTc and PR intervals, changes in liver function (AST and ALT), and reports of dizziness, nausea or headaches. Use of verapamil during pregnancy may cause adverse effects towards the fetus (e.g., bradycardia, heart block, hypotension).

Venipuncture and MMTT Risks

Blood draws can cause some common reactions like pain, bruising, or redness at the sampling site. Less common reactions include bleeding from the sampling site, formation of a small blood clot or swelling of the vein and surrounding tissues, and fainting.

The Boost drink required for the MMTT contains milk and soy ingredients. People with severe allergies to these could have a reaction.

Fingerstick Risks

About 1 drop of blood will be removed by fingerstick for measuring blood glucose, as needed, and sometimes other tests. Pain is common at the time of lancing. In about 1 in 10 cases, a small amount of bleeding under the skin will produce a bruise. A small scar may persist for several

weeks. The risk of local infection is less than 1 in 1000. This should not be a significant contributor to risks in this study as fingersticks are part of the usual care for people with diabetes.

Other Risks

Data downloaded from diabetes devices will be collected for the study. Some people may be uncomfortable with the researchers' having such detailed information about their daily diabetes habits.

1.2.2 Known Potential Benefits

There are recognized benefits to simply being in a clinical study, including close clinical monitoring.

The use of HCL therapy offers the prospect of direct benefit. As described above in this protocol, HCL therapy is a Food and Drug Administration (FDA)-approved therapy for T1D in people 7-75 years of age. It is now being used in pediatric clinical practice and has been shown to be safe and effective in children[30]. However, its efficacy in treating newly diagnosed cases of T1D is not established, and although HCL may be prescribed at the time of T1D diagnosis, at this time it is not the standard approach of many endocrinologists. Therefore, there is strong equipoise among the investigators with respect to the trial's randomization.

1.2.3 Risk Assessment

The risks for events such as DKA and severe hypoglycemia are no greater and possibly less likely with use of HCL therapy compared with usual care not using a HCL system.

For patients in the HCL arm, the study offers the prospect of direct benefit, including closer monitoring than is generally clinically available, as well as the potential, if the study hypothesis is correct, for preservation of C-peptide. Likewise, the verapamil arm offers the prospect of direct benefit if it is demonstrated to preserve C-peptide. Participants not receiving HCL therapy will be provided with CGM, which offers the prospect of direct benefit.

Therefore, this protocol is consistent with the United States Department of Health and Human Services, Protection of Human Subjects, Subpart D, section 46.405 (research involving greater than minimal risk but presenting the prospect of direct benefit to the individual child subjects involved in the research).

1.3 General Considerations

The study is being conducted in compliance with the policies described in the study policies document, with the ethical principles that have their origin in the Declaration of Helsinki, with the protocol described herein, and with the standards of Good Clinical Practice (GCP).

The study will involve the use of an investigational device and an investigational drug (verapamil will be used off-label). The U.S. Food and Drug Administration (FDA) has determined that an investigational device exemption (IDE) will be required to conduct the study, but not a separate investigational new drug (IND) application.

Chapter 2: Study Enrollment and Screening

2.1 Participant Recruitment and Enrollment

The study will recruit two cohorts—Cohort A will include participants who weigh ≥30 kg at Screening and Cohort B will include participants who weigh <30 kg at Screening.

Enrollment will proceed with the goal of at least 98 participants in Cohort A and 33 in Cohort B being randomized and at least 88 in Cohort A and 30 in Cohort B completing the trial. Participants who have signed consent and started the screening process may be permitted to continue into the trial, if eligible, even if the randomization goal has been reached.

Potential study participants will be identified clinically from the general pediatric diabetes new-onset population and recruited from ~6 clinical centers in the United States. All eligible participants will be included without regard to gender, race, or ethnicity. There is no restriction on the number of participants to be enrolled by each site toward the overall recruitment goal. The maximum number to be enrolled for screening for the study (meaning that informed consent is signed) is 200.

2.1.1 Informed Consent and Authorization Procedures

Potential eligibility initially may be assessed as part of a routine-care examination. Before completing any procedures or collecting any data that are not part of usual care, written informed consent will be obtained.

Since all potential participants will be under 18 years of age at Screening, a parent/legal guardian (referred to subsequently as "parent") will be provided with the Informed Consent Form to read and will be given the opportunity to ask questions. Potential participants will be given a Child Assent Form (for children ages 7 to 17 years old) to read and discuss with his/her parents and study personnel. If the parent and child agree to participate, the Informed Consent Form (and Child Assent Form) will be signed. A copy of the consent form will be provided to the participant and his/her parent and another copy will be added to the participant's study record.

As part of the informed consent process, each participant will be asked to sign an authorization for release of personal information. The investigator will review the study-specific information that will be collected and to whom that information will be disclosed. After speaking with the participant, questions will be answered about the details regarding authorization.

A participant is considered enrolled when the informed consent form has been signed.

Participants who turn 18 during the course of the study will need to re-consent with the Informed Consent Form.

2.2 Participant Eligibility Criteria

2.2.1 Participant Inclusion Criteria

Individuals must meet all of the following inclusion criteria in order to be eligible to participate in the study.

1. New-onset stage 3 T1D, with a history of unequivocal symptoms of T1D (e.g., persistent/severe polyuria/polydipsia and/or weight loss) and HbA1c ≥6.5%, within 21 days of diagnosis and with ability to be randomized within 31 days of diagnosis (time from diagnosis to screening can be longer provided that investigator is confident that all screening testing can be completed in order to randomize the participant within 31 days of diagnosis)
    - Date of diagnosis is defined as the date that insulin therapy was started.
    - If informed consent is to be signed >21 days from diagnosis, the Coordinating Center must be contacted for confirmation of timelines prior to enrollment
2. At least one positive T1D auto-antibody
    - If clearly positive result (≥20% above lab's upper limit of normal) available at Screening, repeat antibody testing for central lab not required
    - Insulin auto-antibodies only considered if insulin use <10 days when blood drawn
3. Age 7-<18 years at the time of signing informed consent
4. Willing to provide informed consent and child assent
5. In a female participant with childbearing potential, not currently pregnant and willing to avoid pregnancy and breastfeeding and undergo pregnancy testing prior to MMTTs for the duration of the study.

   Women of childbearing potential must use an acceptable form of birth control. Acceptable forms include oral/injection contraceptives, transdermal contraceptives, diaphragm, intrauterine devices, condoms with spermicide, documented surgical sterilization of either the participant or their partner, or abstinence.
6. English speaking/reading (because of the intense interaction required with the study team)
7. Able to swallow pills (tested with an inert imitation tablet in clinic prior to randomization)—*Cohort A only*
8. Willing to not use any non-insulin glucose-lowering agents (such as GLP-1 agonists, Symlin, DPP-4 inhibitors, SGLT-2 inhibitors, biguanides, sulfonylureas)
9. Willing to use an insulin approved for the pump *(if assigned to HCL)*
10. Willing to avoid medications containing acetaminophen, and no contraindications for ibuprofen use *(in case assigned to Medtronic HCL system)*

2.2.2 Participant Exclusion Criteria

Individuals meeting any of the following exclusion criteria at Screening will be excluded from study participation.

1. Ongoing use of medications known to influence glucose tolerance such as systemic steroids.
2. Other systemic disease, which in the opinion of the investigator precludes participation (including psychiatric illness).
3. Unwilling to abstain from use of HCL therapy for 12 months.
    - Personal pump and CGM use, including systems with a "suspend-before-low" function, will be allowed for participants randomized to a non-HCL group.

4. "Silent" diabetes—i.e., Stage 3 diabetes that is identified by routine OGTT in the course of a surveillance study but is not accompanied by fasting hyperglycemia or classic symptoms of diabetes.
5. Participation in another research study that involves diabetes care or immune modulation

Additional Exclusion Criteria for Cohort A

6. Blood pressure (either systolic or diastolic) <5th percentile for age, gender, and height on two out of three measurements
7. Pulse <2nd percentile for age and gender on two out of three measurements
8. History of vasovagal syncopal episodes related to hypotension
9. Abnormal EKG rhythm, unless cleared for study participation by a cardiologist
10. Underlying cardiac disease (ex. left ventricular dysfunction, hypertrophic cardiomyopathy), certain arrhythmias (ex. AV block, accessory pathway such as Wolff-Parkinson-White or Lown-Ganong-Levine syndromes), known liver dysfunction, known renal impairment, Duchenne's muscular dystrophy, active Graves disease or hyperthyroidism, and untreated hypothyroidism
11. eGFR < 90
12. AST and/or ALT greater than 1.5 times the upper limit of normal *(if results available from usual care within 4 weeks of Screening, testing does not have to be repeated at Screening)*
13. Need to use of any of the following medications during the study: beta blocker, seizure medication (carbamazepine, phenobarbital, phenytoin), other antihypertensive medications, HMG-CoA reductase inhibitors, lithium, theophylline, clonidine, or aspirin
14. Any known hypersensitivity reaction to Verapamil

2.3 Screening Procedures

After written informed consent and assent have been obtained, a potential participant will be evaluated for study eligibility through the elicitation of a medical history, performance of a physical examination by study personnel, and laboratory testing. The visit and procedures may be performed on one or over multiple days.

Screen Failures

Individuals who do not initially meet study eligibility requirements may be rescreened at a later date per investigator discretion, provided that they still fall in the eligibility time window from time of diagnosis.

2.3.1 Data Collection and Testing

The following procedures will be performed/data collected/eligibility criteria checked and documented:

- Inclusion and exclusion criteria assessed
- Demographics *(date of birth, sex, race and ethnicity)*
- Contact information *(retained at the site and not entered into study database)*

- Medical history
- Concomitant medications
- Physical examination, including Tanner Staging *(Tanner Staging does not have to be repeated if results available from the previous 4 weeks)*
- Blood draw for Islet autoantibodies *(not needed if positive autoantibodies already available and ≥20% above lab's upper limit of normal)*
- Local urine or serum pregnancy test for all females who have reached menarche

Additional procedures for Cohort A:

- EKG *(The screening EKG must be read by a pediatric cardiologist to ensure there is no underlying abnormality that precludes study participation.)*
- Blood draw for AST, ALT, creatinine *(local lab; does not have to be repeated if results available from the previous 4 weeks)*

2.4 Randomization

After participants and parents/legal guardians sign the assent/consent forms and eligibility is determined, the randomization process will occur on the study website. Randomization should occur as soon as possible but ≤31 days from diagnosis.

- Cohort A will be randomly assigned 1:1:1:1 to receive (a) HCL and placebo, (b) HCL and verapamil, (c) non-HCL and placebo, or (d) non-HCL and verapamil.
- Cohort B will be randomly assigned 2:1 to HCL or non-HCL.

Both randomization schedules will be stratified by clinical site using a permuted block design. *(Due to small sample size in each cohort at each site, no other factors are being used for stratification—instead, imbalances in key variables such as age and time since diagnosis will be adjusted for in analysis.)*

Participants assigned to a HCL group will have the HCL system assignment made through 1:1 randomization, stratified by site.

Once a study participant is randomized, that participant will be included in the data analysis regardless of whether the assigned treatment is received. Thus, the investigator must not proceed to randomize an individual until he/she is convinced that the individual is eligible and will accept whichever treatment group is assigned through randomization.

2.4.1 Randomization Visit Procedures

The following procedures should be completed at the Randomization visit:

- Concomitant medications
- Adverse event assessment
- Recording of daily insulin dose
- Urine or serum pregnancy test for all females who have reached menarche—*must be negative before the MMTT can be started*
- MMTT

- Blood draw for the following central labs:
    - HbA1c
    - Proinsulin – *collected during MMTT at 0 and 90 minutes time points*
    - Pro-IAPP – *collected during MMTT at 0 and 90 minutes time points*
    - Unmethylated INS DNA
    - PBMCs
    - Cytokines
    - mRNAseq
    - Extra plasma for storage
- Receipt of study devices/drug and training, as applicable *(see Chapters 3 and 4)*
- HCL groups will receive a dietitian consult *(may be remote)*

**The pregnancy test, MMTT, and labs should be completed at randomization ±3 days. Device training and dietitian consult (as applicable) should be completed within 3 days of randomization.*

Chapter 3: Study Devices

3.1 Description of the Study Devices

3.1.1 Hybrid Closed Loop Systems

Participants assigned to a HCL group will initially be randomly assigned 1:1 to use either the Tandem t:slim X2 with Control-IQ technology or a Medtronic HCL system (Medtronic 670G 4.0 AHCL (prior to protocol version 5.0) or Medtronic 780G (starting with protocol version 5.0)).

> *Randomization is being used for the assignment solely for feasibility reasons, in order to have an approximate equal balance between the two companies' systems and because there are no criteria for the investigator to determine that one company's system or the other would be better for a given participant. There is no intent to compare the systems.*

If the participant has significant issues with the system (such as an allergy to the adhesive or need for waterproof feature), the participant could be switched to a different HCL system, after consultation with one of the Protocol Chairs.

3.1.1.1 Tandem t:slim X2 with Control-IQ Technology

The system will include the Tandem t:slim X2 pump with the Control-IQ Pro software imbedded, communicating with the Dexcom G6 CGM. The system is investigational in children aged <6 years and the Pro software is currently only available for research.

If the CGM signal becomes unavailable for more than 20 minutes consecutively, Control-IQ or closed loop will not operate to automatically adjust insulin. If the CGM is not connected, the system will revert to usual function of the pump and deliver insulin with the insulin dosing parameters programmed in the system for that individual. Resumption of closed loop will occur automatically once CGM signal is available again.

If the study system is unable to activate Control-IQ for any reason, the pump will automatically revert to preprogrammed basal insulin delivery without any need for instruction from the user. The user should assess the pump for error messages and take the necessary steps to restart closed loop.

If the t:slim X2 detects a system error that does not allow the pump to operate, a Malfunction Alarm will display. Participants will follow guidance documents to resolve the issue.

3.1.1.2 Medtronic 670G 4.0 AHCL and Medtronic 780G

The Medtronic system will be either the Medtronic 670G 4.0 AHCL insulin pump communicating with the Medtronic Guardian 3 CGM (for participants that enrolled prior to protocol version 5.0) or, for participants that enrolled after the implementation of protocol version 5.0, the Medtronic 780G insulin pump communicating with the Medtronic Guardian 4 CGM. Both systems are investigational.

Participants already enrolled in the study and using the Medtronic 670G 4.0 AHCL may transition to the Medtronic 780G if desired. Contacts will be performed to review CareLink data

and check for adverse events and device deficiencies on days 1, 3 and 5 after transition from 670G 4.0 AHCL to 780G.

New study participants aged 7-13 years using the Medtronic 670G 4.0 AHCL system or Medtronic 780G system will start at the 120 mg/dL setpoint for 2 weeks. The setpoint will then be adjusted to 100 mg/dL. New study participants aged 14 years and older will use a setpoint of 100 mg/dL from the beginning.

If the study system exits from HCL mode for any reason, the pump will automatically revert to preprogrammed basal insulin delivery. The suspend before low feature will be automatically enabled for participants using the Medtronic 780G system. The user should assess the pump for error messages and take the necessary steps to restart Auto Mode/SmartGuard.

If the Medtronic 670G 4.0 AHCL or Medtronic 780G detect a system error that does not allow the pump to operate, the Malfunction Alarm will display. Participants will follow guidance documents to resolve the issue.

Participants will be instructed to calibrate the Medtronic 670G 4.0 AHCL system CGM in accordance with manufacturer labelling. With the Medtronic 780G system and the Guardian 4 Transmitter, calibration is not required. However, a calibration is optional and will occur if a BG is entered. Occasionally, participants may receive a notification if the pump needs a BG to enter or stay in Auto Mode/SmartGuard.

Medtronic 780G Continued Access Period:
Prior to the 780G system becoming commercially available, study participants using the Medtronic system at 52 weeks will have the opportunity to continue using the 780G system at home until the system is commercially available OR until the CLVer trial is complete (last participant's 52-week visit), whichever comes first. During the continued access period, participants will be asked to use the system as intended. At usual care visits (post-RCT, approximately every 3 months), adverse events and device issues will be captured.

3.1.2 Dexcom G6 Continuous Glucose Monitoring System

Participants assigned to a non-HCL group will be provided a commercially available Dexcom G6 CGM and will be instructed to use it according to the user manual.

Any participants who stop using a CGM or have insufficient CGM data will wear a blinded Dexcom sensor for approximately 10 days at 6, 13, 26, 39 and 52 weeks. The blinded sensor will be placed at or before the clinic visit and then the participant will mail the receiver back to the clinic or Coordinating Center (or could return it to the clinic in person) for download after blinded wear unless there is a mechanism for data transfer to occur from home. Participants with insufficient data may be asked to wear a blinded sensor for another 10 days at certain time points.

3.1.3 Blood Glucose Meter and Strips

Participants using the Medtronic HCL system will be provided with a meter and test strips for sensor calibration for the duration of the study.

All other participants will use a blood glucose meter and test strips that they obtain through their insurance.

Participants without insurance may be provided with a meter and test strips.

3.1.4 Ketone Meter and Strips

For participants using a study HCL system, blood ketone levels will be measured using the Abbott Precision Xtra meter and blood ketone strips in accordance with the manufacturer's labeling, which will be provided to participants in HCL groups. The blood glucose meter component of the Precision Xtra device will not be used.

- Participants will be instructed on how to perform blood ketone testing per manufacturer guidelines.
- Participants will be given guidelines for treatment of elevated blood ketones.

Participants in the non-HCL group will perform ketone monitoring per usual care.

3.2 Study Device Accountability Procedures

Device accountability procedures will be detailed in the site procedures manual.

Participant may keep the study ketone meter, blood glucose meter, and CGM if these devices are not marked for investigational use only and there is not a requirement from the company providing the devices to return them. Participants will need to return all investigational study-provided devices at study end.

3.3 Safety Measures

Any time glucose alerts and CGM readings do not match symptoms or expectations or CGM is failing, a blood glucose meter should be used to make diabetes treatment decisions.

3.3.1 Hypoglycemia Threshold Alert and Safety Protocol

During the course of the study, participants will be permitted to change the CGM low glucose threshold alert setting on their device or mobile app. If the participant's total daily insulin dose is < 0.5 units/kg and he/she is having <3% of sensor glucose readings <70 mg/dL, then the threshold alarm can be lowered to 65 mg/dL. Otherwise, study participants will be advised to choose a value no less than 70 mg/dL.

If a participant receives a CGM hypoglycemia threshold or predictive alarm or notes that the CGM glucose is below the hypoglycemia threshold alarm value, confirmatory fingerstick testing will be performed if required by CGM labeling and the participant will be instructed to use the appropriate treatment of hypoglycemia.

3.3.2 Hyperglycemia Threshold Alert and Safety Protocol

During the course of the study, participants will be permitted to change the CGM high glucose threshold alert setting on their device or mobile app, but will be instructed to choose a value no greater than 300 mg/dL. If a participant receives a CGM hyperglycemia threshold alarm or notes that the CGM glucose is above the hyperglycemia threshold alarm value, confirmatory fingerstick testing will be performed if required by CGM labeling. If a participant's CGM reading is >300 mg/dL for over 1 hour or ≥400 mg/dL at any point, the participant will be instructed to take the following steps:

- Perform a blood glucose meter check.
- If the blood glucose is >300 mg/dL, check for blood ketones with the study ketone meter.
- If the ketone level is ≥1.0 mmol/L, take correction insulin via syringe/pen, change insulin (pump) infusion site and contact study staff.
- If a participant administers correction insulin via insulin syringe/pen, participants will be instructed to turn hybrid closed loop mode off for approximately four hours.

Chapter 4: Study Drug

4.1 Study Agent(s) and Control Description

4.1.1 Acquisition

The Central Pharmacy will obtain commercially available verapamil extended release 120 mg tablets and will make a placebo to match the drug (referred to collectively as Study Drug). The placebo will be comprised of GRAS excipients and where possible, excipients included in the commercial verapamil 120 mg XR tablet.

The Study Drug will be bottled and labeled by the pharmacy as 100 tablets per bottle. Each bottle label will contain a drug number provided by the Coordinating Center and both study participants and investigators will be blinded to the drug assignment.

4.1.2 Dosing and Administration

Study Drug will be taken orally once per day. The following dosing scheme, using 120 mg tablets or 60 mg half tablets as guided by the dosing scheme below, will be used by Cohort A:

<30 kg: none

30-34 kg:
60 mg/day x 4 weeks, then 120 mg/day x 48 weeks
Max Dose 3.5-4 mg/kg/day

35-49 kg:
60 mg/day x 2 weeks, then 120 mg/day x 2 weeks, then 180 mg/day x 2 weeks, then 240 mg/day x 46 weeks
Max dose 4.9-6.9 mg/kg/day

50+kg:
120 mg/day 2 weeks, then 180 mg/day x 2 weeks, then 240 mg/day x 2 weeks, then 300 mg/day x 2 weeks, then 360 mg/day x 44 weeks
Max dose 7.2 mg/kg/day

Participants will be provided with a pill splitter and will cut the tablets at home, while half tablets are needed during the titration.

If a participant in Cohort B reaches body weight of ≥30 kg, he/she will not receive study drug.

4.1.3 Dose Adjustments/Modifications/Delays

The dose of Study Drug can be reduced/discontinued at investigator discretion if side effects develop or abnormality is found on clinical exam, EKG, or blood testing.

The dose also may be adjusted if the participant's weight changes during the study, per above dosing scheme. The participant's weight will be assessed for possible dose changes at scheduled study visits.

4.1.1 Dispensing Study Drug

At each visit (Randomization –39 week), participants in Cohort A will be provided a sufficient number of bottles of drug to last until the next visit (beyond the end of the window of the next visit).

4.1.2 Assessing Participant Adherence

Participants will be asked to bring all bottles of Study Drug dispensed to them to each visit where any remaining pills will be counted. Sites are to keep all used and unused inventory for monitoring.

4.2 Study Agent Accountability Procedures

Drug accountability procedures will be detailed in the site procedures manual.

Chapter 5: Diabetes Management

5.1 Participants Using Hybrid Closed Loop

Participants will be trained and will start the pump and CGM in open-loop mode with the suspend-before-low feature activated (on Medtronic systems) within 3 days of randomization. HCL therapy will be started at the day 7 training visit. Participants/parents will be instructed to perform overnight fingersticks for two nights after initiation of HCL, as well as for two nights after a decrease in setpoint.

Participants will meet with a dietitian for education regarding carbohydrate counting. They will be given age appropriate carb targets for meals and snacks. They will be encouraged to eat at least 3 meals per day and add protein and fat to breakfast every day. They will also be instructed to give insulin 15 minutes before eating, unless glucose <70 mg/dL. If glucose is <70 mg/dL before a meal, patient will be instructed to consume 8-15 grams of carbohydrate, depending on glucose concentration, prior to giving insulin for the meal.

The participant's parent/legal guardian will be required to attend the training procedures and will be trained in all aspects aforementioned. All training will be conducted considering age of participant and parent involvement in his/her diabetes treatment.

Upon completion of HCL training, study staff will document using a checklist that the participant is familiar with the function/feature and/or capable of performing each of the tasks specified.

Participants will be provided hypoglycemia, hyperglycemia, and ketone guidelines (see Section 3.3) for when their glucose levels are >300 mg/dL for more than 1 hour or >400 mg/dL at any time or <70 mg/dL or ketones ≥1.0 mmol/L.

5.1.1 Home Use of HCL

The specific approach to HCL therapy will be outlined in the site procedures manual and will be individualized to the participant's needs. General principles include:

- Participants will be instructed to bolus 15 minutes before meals or snacks, unless glucose is <70 mg/dL.
    - If glucose is 54-<70 mg/dL, participants will be instructed to consume 8-10 grams of carbohydrate before delivering the meal or snack bolus.
    - If glucose is <54 mg/dL, participants will be instructed to consume 15 grams of carbohydrate before delivering the meal or snack bolus.
- Participants will be instructed to calibrate the sensor as recommended by the manufacturer (if needed).
- Participants will be asked to upload their pump/CGM data prior to each contact (unless this occurs automatically). Participants may be provided with a laptop to use during the study if necessary. The study team will be in contact with the participants to make adjustments to settings and recommendations to change behaviors will be made as needed.

- Guidelines for time in HCL, insulin delivery, target range, and sensor wear as well as management of diet, exercise and hypoglycemia can be found in the site procedures manual and/or participant guidance documents.

The participant will be instructed to use the system in closed-loop mode except 1) when no calibrated CGM sensor is available, 2) if insulin is delivered by any means other than the study pump (e.g., injection of subcutaneous insulin via syringe/pen in the event of infusion site failure), or 3) if participant is hospitalized. If insulin is delivered by any means other than the study pump, participant will be instructed to turn off HCL for approximately four hours. If participant is hospitalized, participant must be in open loop (but can use suspend before low feature).

The participant will also be instructed to contact study staff during periods of illness with an elevated temperature >101.5 degrees Fahrenheit (38.6 degrees Celsius), periods of significant illness, or during periods of use of medications such as epinephrine for the emergency treatment of a severe allergic reaction or asthma attack in addition to use of oral or injectable glucocorticoids to determine if closed-loop use should be temporarily discontinued.

Parents/guardians who have been trained on the study devices will be instructed to be present at night with the participants, as much as possible. If remote monitoring is not available, baby monitors will be provided so the parent can hear alarms.

Participants will be provided with guidance documents with instructions for how to handle any health-related issues and technical issues with the HCL system. The guidance will also include instructions on checking blood glucose when sensor glucose is high or low and how to treat based on the fingerstick blood glucose value. Participants may use the study pump without the AID algorithm activated and study CGM during periods of component disconnections or technical difficulties. Participants can contact study staff to ask any questions they may have during the study.

Study staff will discuss with the participant that routine contact is required and will make arrangements with the participant for the contacts. If the participant cannot be reached, the participant's other contact methods will be utilized, including the emergency contact. Participants who are not compliant with the arranged contacts on two separate occasions may be discontinued at the discretion of the investigator.

5.1.2 Discontinuation of HCL

Participants in an HCL group who discontinue HCL will continue to receive diabetes management from the study team. They will be encouraged to continue to use the study pump and CGM in open-loop mode. Efforts will be made to help them return to HCL, including a possible switch to another HCL system. Participants discontinuing pump use will be asked to keep a log of insulin dose for 3 days prior to each study visit.

5.1.3 Transition to Usual Care at End of Study

At the end of the study, the participants will be required to return the study Tandem HCL system to the site. The investigator will determine with the participant whether the participant will switch to a personal HCL system, use multiple daily injections or an insulin pump. As noted in section 3.1.1.2, participants initially assigned to and using the Medtronic 780G HCL system will

be able to continue use until the HCL system is commercially available OR until the CLVer trial is complete (last participant's 52 week visit).

- Participants that initially started the study using the 670G, and who have opted to switch to the 780G, will also have the option to continue using the HCL system.

5.2 Participants Assigned to Groups Not Using Hybrid Closed Loop

Participants will receive standard diabetes care and be managed by their primary diabetes team or a designated control-arm management team. Study investigators assigned to the intensive management group will not provide routine diabetes care for these participants.

Since the CGM is being prescribed from the time of diagnosis of T1D with high frequency and rapidly becoming standard care, the study will provide a commercially available Dexcom G6 CGM device and sensors for all participants. CGM initiation will be performed by the study team but further training and management of the CGM will be provided by the participant's primary diabetes care team or a designated control-arm management team, not study staff assigned to the intensive management group.

Insulin therapy will include either MDI or insulin pump therapy per patient and provider preference. Participants may use sensor augmented pump therapy with a suspend-before-low feature; however, use of automated HCL insulin delivery will be prohibited. Insulin dosing decisions and instructions will be handled by the participant's primary diabetes team.

Participants using MDI will be asked to keep a log of insulin dose for 3 days prior to each study visit.

For Cohort A, verapamil/placebo use will be managed by the study team.

Chapter 6: Follow-up Visit Schedule

6.1 Study Visits and Phone Contacts

Follow-up visits for all groups in both cohorts will occur 6 weeks from randomization and 13, 26, 39, and 52 weeks from the date of T1D diagnosis.

The HCL groups also will have an education visit about 7 days after randomization (i.e., 'day 7 visit'), to cover additional training and initiate HCL. This education visit may be conducted remotely, per investigator discretion. All system requirements for initiating HCL will be met prior to starting HCL.

Phone or email/text contacts will be completed by certified study staff every 1-3 days for the first two weeks, at least twice a week for the second two weeks and then every 1-2 weeks for the duration of the 12 months. The email/text contacts must not include any unnecessary identifying information (e.g., cannot include protected health information (PHI) other than first names in the greeting). Participants in the HCL groups can have unlimited contact with the study team throughout the study. Participants enrolled in the study who desire to transition from the Medtronic 670G 4.0 AHCL to the Medtronic 780G will have additional contacts to review CareLink data and check for adverse events and device deficiencies on days 1, 3 and 5 after the transition.

Additionally, Cohort A participants will have a safety visit 7 ±5 days after drug initiation and after each dose increase to assess blood pressure and pulse. This visit may occur in clinic with certified study staff or remotely, via a telehealth visit, using a study-provided blood pressure and pulse machine at home.

Participants will remain in the study and continue use of study interventions until the final study visit is completed, even if the final visit is delayed.

6.1.1 Study Visits and Windows

Target dates and windows for each study follow-up visit (6 week timed from randomization and all others timed from date of diagnosis) for all treatment groups in both cohorts are shown below:

Target Day/Week	Target Window (around Target Day/Week)	Allowable Window (around Target Day/Week)
Week 6*	+/- 3 days	+/- 7 days
Week 13 (3 mo)	+/- 3 days	+/- 7 days
Week 26 (6 mo)	+/- 7 days	+/- 14 days
Week 39 (9 mo)	+/- 7 days	+/- 14 days
Week 52 (12 mo)	+/- 7 days	+/- 14 days

*The 6 week visit may be conducted remotely

6.1.2 Procedures at Study Follow-up Visits

The following procedures will be performed at each visit listed in the table above, unless otherwise specified:

- Adverse event assessment
- Concomitant medications review
- Recording of total daily insulin dose
- Compliance assessment *(pill count and self-report)*
- Device downloads *(pump, CGM, and ketone meter)*
- Physical examination: Limited, targeted physical exam at visits prior to 52 week visit with complete physical exam, including Tanner staging, performed at the 52 week visit.
    - *The 52 week Tanner staging is not necessary for those who were Tanner Stage 5 at Screening*
    - *The limited physical exam may be skipped at 6 week visit, when visit is conducted remotely*
- Urine or serum pregnancy test for all females who have reached menarche—*must be negative before the MMTT can be started (13, 26, 39, and 52 week visits)*
- MMTT (*13, 26, 39, and 52 week visits)*
- Blood draw for central labs:
    - HbA1c *(13, 26, 39, and 52 week visits)*
    - Proinsulin – collected during MMTT at 0 and 90 minutes time points *(13, 26, 39, and 52 week visits)*
    - Pro-IAPP – collected during MMTT at 0 and 90 minutes time points *(13, 26, 39, and 52 week visits)*
    - Unmethylated INS DNA *(13, 26, 39, and 52 week visits)*
    - mRNAseq *(13, 26, 39, and 52 week visits)*
    - PBMC *(26, and 52 week visits only)*
    - Serum cytokines *(26, and 52 week visits only)*
    - Extra plasma for storage *(26 and 52 week visits only)*
- Blinded CGM placement for participants not using CGM* *(except at 52 week visit, see note below)*
- Additional testing for the Cohort A participants will include:
    - EKG *(6, 26, and 52 week visits)*
        - Any automated EKG readings suggesting abnormalities in QTc and/or PR intervals will be referred to a pediatric cardiologist for interpretation
    - Blood draw for AST/ALT *(6, 26, and 52 week visits)*
- HCL groups will receive a dietitian consult *(may be remote and is not required at 52 week visit)*

**A blinded CGM for participants not using CGM will be placed prior to, rather than at, the 52 week visit. The participant will either return to the clinic prior to the 52 week visit to have the sensor placed or the participant will be provided with a sensor inserter kit at the 39 week visit for the participant to place at home, wear, and return prior to the 52 week visit. Details are described in the site procedures manual.*

6.1.3 Participant Contact outside of Study Visits

During the study, participants in the HCL therapy groups will have HCL downloads regularly reviewed and adjustments made as indicated by the investigators. The study team will contact the participant every 1-3 days for the first two weeks, at least twice a week for the second two weeks, and every 1-2 weeks for the remainder of the study. The first two times pump settings are changed by the participant, the device will be reuploaded so the site can confirm it was done correctly.

Participants in the non-HCL standard therapy group will have their diabetes managed by their primary diabetes team (which will not include members of the study team assigned to the intensive management group) according to standard clinical practice. These clinical contacts will be standard care and not considered study contacts.

6.1.4 Unscheduled Visits

An unscheduled visit may be performed at investigator discretion.

Chapter 7: Testing Procedures

7.1 Physical Examination

A standard physical exam will be performed by the study investigator or designee (a physician, fellow, nurse practitioner or a physician assistant) at Screening and each visit except the day 7 visit (no exam) and study drug safety visits (collection of blood pressure and pulse only). The standard physical exam will include vital signs (including measurement of blood pressure, pulse, height and weight) and examination of injection/insertion sites. A complete physical exam, including Tanner staging, will be obtained at Screening and at the 52 week visit (no repeat Tanner staging for those who are Tanner 5 at Screening).

The physical exam is not required at the 6 week visit when visit is conducted remotely.

For Cohort A, at Screening, blood pressure and pulse will be tested three times to assess eligibility. At follow up visits, blood pressure and pulse are only tested one time, unless any result has been abnormal. If abnormal, 3 readings will be obtained each time and the blood pressure should be tested manually.

7.2 Laboratory Testing

1. Diabetes auto-antibody panel:
   Blood for IAA, IA-2, GAD65, and ZnT8 measurement will be obtained at Screening visit and sent to a central laboratory (unless auto-antibody results are already available and ≥20% above lab's upper limit of normal).
2. EKG
   For Cohort A, an EKG will be performed at Screening and at the 6, 26, and 52 week visits. The screening EKG must be read by a pediatric cardiologist to ensure there is no underlying abnormality that precludes study participation. The automated reading will be acceptable if normal for subsequent EKGs. Any automated EKG readings suggesting abnormalities in QTc and/or PR intervals will be referred to a pediatric cardiologist for interpretation.
3. Liver function tests
   For Cohort A, AST/ALT will be measured locally at Screening and at the 6, 26, and 52 week visits
4. Kidney tests
   For Cohort A, creatinine will be measured locally at Screening and used to calculate eGFR
5. Urine or serum pregnancy:
   Performed locally for females with childbearing potential at Screening and each follow up visit, and also anytime pregnancy is suspected. Must be negative to perform the MMTT.
6. MMTT:
   2-hour MMTT for stimulated glucose and C-peptide will be done at Randomization, 13, 26, 39, and 52 week visits, with samples collected at 0, 15, 30, 60, 90 and 120 minutes. Criteria will be detailed in the site procedures manual.

7. HbA1c:
   Collected for central lab analysis at Randomization, 13, 26, 39, and 52 week visits
8. Measures of beta cell health and immune function:

   Blood/serum/plasma will be drawn and sent to the appropriate lab, to assess several measures detailed below. Samples at some of the time points may or may not be run depending on final study results.

   i. Pro-insulin and Pro-IAPP and their ratios to C-peptide during the MMTT at 0 and 90 minutes, collected at Randomization, 13, 26, 39, and 52 week visits
   ii. Circulating unmethylated INS DNA, collected at Randomization, 13, 26, 39, and 52 week visits
   iii. Circulating plasma miRNA sequencing, collected at Randomization, 13, 26, 39, and 52 week visits
   iv. T-cell characteristics by PBMC and peripheral cytokine levels, collected at Randomization, 26 and 52 week visits only.
   v. Collection and storage of extra samples of plasma as blood volume limitations for size allow and/or storage of any remaining samples for future research, collected at Randomization, 26, and 52 week visits only, as approved by the participants.

Local laboratory testing will be performed if needed to screen for exclusionary medical conditions.

Chapter 8: Unanticipated Problems, Adverse Events, Device Issues, and Stopping Rules

8.1 Unanticipated Problems

Site investigators will promptly report to the Coordinating Center on a CRF all unanticipated problems meeting the criteria below. Sites overseen by the JCHR IRB must report Unanticipated Problems to the IRB within seven calendar days of recognition. For this protocol, an unanticipated problem is an incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places participants or others at a greater risk of harm than was previously known or recognized (including physical, psychological, economic, or social harm)

The Coordinating Center also will report to the IRB all unanticipated problems not directly involving a specific site such as unanticipated problems that occur at the Coordinating Center or at another participating entity such as the central laboratory. These instances must be reported to the JCHR IRB within seven calendar days of recognition. The Director of the Human Research Protection Program will report to the appropriate regulatory authorities if the IRB determines that the event indeed meets the criteria of an Unanticipated Problem requiring additional reporting.

8.2 Adverse Events

8.2.1 Definitions

Adverse Event (AE): Any untoward medical occurrence in a study participant, irrespective of the relationship between the adverse event and the drug/device(s) under investigation (see Section 8.2.2 for reportable adverse events for this protocol).

Serious Adverse Event (SAE): Any untoward medical occurrence that:

- Results in death.
- Is life-threatening; (a non-life-threatening event which, had it been more severe, might have become life-threatening, is not necessarily considered a serious adverse event).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions (sight threatening).
- Is a congenital anomaly or birth defect.

- Is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the participant or may require medical/surgical intervention to prevent one of the outcomes listed above).

Unanticipated Adverse Device Effect (UADE): Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the package insert, this protocol, or the informed consent document, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants (21 CFR 812.3(s)).

Adverse Device Effect (ADE): Any untoward medical occurrence in a study participant which the device may have caused or to which the device may have contributed (Note that an Adverse Event Form is to be completed in addition to a Device Deficiency or Issue Form, unless excluded from reporting as defined in Sections 8.2.2-8.2.4). *An event that occurs solely due to participant (i.e., user) error in which the device functions properly generally will not be considered an ADE unless it is determined that the instructions on the screen of the device or user manual (or similar training materials) may have contributed to the event (note: the event may still meet criteria for reporting as an adverse event).*

Device Complaints and Malfunctions: A device complication or complaint is something that happens to a device or related to device performance, whereas an adverse event happens to a participant. A device complaint may occur independently from an AE, or along with an AE. An AE may occur without a device complaint or there may be an AE related to a device complaint. A device malfunction is any failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed. (21 CFR 803.3). Note: for reporting purposes, sites will not be asked to distinguish between device complaints and malfunctions.

8.2.2 Reportable Adverse Events

A reportable adverse event includes all events meeting the definition of an adverse event, except as noted below.

Hypoglycemia and hyperglycemia not meeting the criteria below will not be recorded as adverse events unless associated with an Adverse Device Effect. Skin reactions from sensor placement are only reportable if severe and/or required treatment.

All reportable AEs—whether volunteered by the participant, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means—will be reported on an AE form online. Each AE form is reviewed by the Medical Monitor to assess safety and to verify the coding and the reporting that is required.

8.2.3 Hypoglycemic Events

Hypoglycemia not associated with an Adverse Device Effect is only reportable as an adverse event when the following definition for severe hypoglycemia is met: the event required

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

When a hypoglycemic event meets the above reporting requirements, a Hypoglycemia Form should be completed in addition to the Adverse Event Form. Severe hypoglycemia events should be considered to be serious adverse events with respect to reporting requirements.

8.2.4 Hyperglycemic/Ketotic Events

Hyperglycemia not associated with an Adverse Device Effect is only reportable as an adverse event when one of the following 3 criteria is met:

- the event involved DKA, as defined by the Diabetes Control and Complications Trial (DCCT) and described below
- evaluation or treatment was obtained at a health care provider facility for an acute event involving hyperglycemia or ketosis, or the participant contacted the site and received guidance on how to manage the hyperglycemia/ketosis
- blood ketone level >1.5 mmol/L, even if there was no communication with a health care provider at the time of the event

<u>Hyperglycemic events are classified as DKA if the following are present:</u>

- Symptoms such as polyuria, polydipsia, nausea, or vomiting;
- Serum ketones >1.5 mmol/L or large/moderate urine ketones;
- Either arterial blood pH <7.30 or venous pH <7.24 or serum bicarbonate <15; and
- Treatment provided in a health care facility

When a hyperglycemia/ketotic event meets the above reporting requirements, a Hyperglycemia/DKA Form should be completed in addition to the Adverse Event Form. Events meeting DKA criteria should be considered to be serious adverse events with respect to reporting requirements. Hyperglycemia events not meeting criteria for DKA generally will not be considered as serious adverse events unless one of the SAE criteria in Section 8.2.1 is met.

8.2.5 Relationship of Adverse Event to Study Device, Drug, or Procedure

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

To ensure consistency of adverse event causality assessments, investigators should apply the following general guideline when determining whether an adverse event is related:

Yes

There is a plausible temporal relationship between the onset of the adverse event and the study device, drug or procedure, and the adverse event cannot be readily explained by the participant's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study device, drug or procedure; and/or the adverse event abates or resolves upon discontinuation of the study device, drug or procedure or dose reduction and, if applicable, reappears upon re-challenge.

No

Evidence exists that the adverse event has an etiology other than the study device, drug or procedure (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to study device, drug or procedure.

8.2.6 Severity (Intensity) of Adverse Events

The severity (intensity) of an adverse event will be rated on a three point scale: (1) mild, (2) moderate, or (3) severe. A severity assessment is a clinical determination of the intensity of an event. Thus, a severe adverse event is not necessarily serious. For example, itching for several days may be rated as severe, but may not be clinically serious.

- MILD: Usually transient, requires no special treatment, and does not interfere with the participant's daily activities.
- MODERATE: Usually causes a low level of inconvenience, discomfort or concern to the participant and may interfere with daily activities, but is usually ameliorated by simple therapeutic measures and participant is able to continue in study.
- SEVERE: Interrupts a participant's usual daily activities, causes severe discomfort, may cause discontinuation of study device, and generally requires systemic drug therapy or other treatment.

8.2.7 Expectedness

For a serious adverse event that is considered possibly related to study device or drug, the Medical Monitor will classify the event as unexpected if the nature, severity, or frequency of the event is not consistent with the known risk information.

8.2.8 Coding of Adverse Events

Adverse events will be coded using the MedDRA dictionary. To facilitate coding, the site will enter a preliminary MedDRA code which the Medical Monitor may accept or change (the Medical Monitor's MedDRA coding will be used for all reporting). The Medical Monitor will review the investigator's assessment of causality and may agree or disagree. Both the investigator's and Medical Monitor's assessments will be recorded. The Medical Monitor will have the final say in determining the, expectedness and causality as well as whether an event is classified as a serious adverse event and/or an unanticipated adverse device effect.

8.2.9 Outcome of Adverse Events

The outcome of each reportable adverse event will be classified by the investigator as follows:

- RECOVERED/RESOLVED – The participant recovered from the AE/SAE without sequelae. Record the AE/SAE stop date.
- RECOVERED/RESOLVED WITH SEQUELAE – The event persisted and had stabilized without change in the event anticipated. Record the AE/SAE stop date.
- FATAL – A fatal outcome is defined as the SAE that resulted in death. Only the event that was the cause of death should be reported as fatal. AEs/SAEs that were ongoing at the time of death; however, were not the cause of death, will be recorded as "resolved" at the time of death.
- NOT RECOVERED/NOT RESOLVED (ONGOING) – An ongoing AE/SAE is defined as the event was ongoing with an undetermined outcome.
    - An ongoing outcome will require follow-up by the site in order to determine the final outcome of the AE/SAE.
    - The outcome of an ongoing event at the time of death that was not the cause of death, will be updated and recorded as "resolved" with the date of death recorded as the stop date.
- UNKNOWN – An unknown outcome is defined as an inability to access the participant or the participant's records to determine the outcome (for example, a participant that was lost to follow-up).

If any reported adverse events are ongoing when a participant completes the study (or withdraws), adverse events classified UADEs will be followed until they are either resolved, or have no prospect of improvement or change, even after the participant has completed all applicable study visits/contacts. For all other adverse events, data collection will end at the time the participant completes the study. Note: participants should continue to receive appropriate medical care for an adverse event after their participation in the study ends.

8.3 Reportable Device Issues

All UADEs and ADEs as defined in Section 8.2.1 will be reported on both a device issue form and AE form, except for skin reactions from CGM sensor placement or pump infusion set placement that do not require pharmacologic treatment. As noted in Section 8.2.1, events that occur due to participant (user) error generally will not require completion of a device issue form.

Device complaints and device malfunctions will be reported except in the following circumstances. These occurrences are expected and will not be reported on a Device Issue Form assuming criteria for a UADE or ADE have not been met:

- CGM sensor lasting fewer days than expected per manufacturer
- CGM tape adherence issues
- Battery lifespan deficiency due to inadequate charging or extensive wireless communication
- Intermittent device component disconnections/communication failures not requiring system replacement or workaround/resolution not specified in user guide/manual.

- Device issues clearly addressed in the user guide manual that do not require additional troubleshooting
- Device issues in the non-HCL groups using commercially available Dexcom G6 CGMs if not associated with an adverse event.

8.4 Timing of Event Reporting

Serious AEs that are possibly related to a study device, drug or study participation must be reported to the Coordinating Center within 24 hours of the site becoming aware of the event. This can occur via phone or email, or by completion of the online serious adverse event form and device issue form if applicable. If the form is not initially completed, it should be competed as soon as possible after there is sufficient information to evaluate the event.

All other reportable ADEs and other reportable AEs should be submitted by completion of an electronic case report form within 7 days of the site becoming aware of the event.

The Coordinating Center will notify all participating investigators and the IRB of any adverse event that is serious, related, and unexpected. Notification will be made within 10 working days after the Coordinating Center becomes aware of the event and no later than seven calendar days where the event is fatal or life threatening.

Upon receipt of a qualifying event, the Coordinating Center/Medical Monitor will investigate the event to determine if a UADE is confirmed, and if indicated, report the results of the investigation to the all overseeing IRBs and the FDA, within 10 working days of the Coordinating Center becoming aware of the UADE per 21CFR 812.46(b) (2). The Medical Monitor must determine if the UADE presents an unreasonable risk to participants. If so, the Coordinating Center must ensure that device use presenting that risk is terminated as soon as possible but no later than 5 working days after the Medical Monitor makes this determination and no later than 15 working days after first receipt notice of the UADE.

Device malfunctions will be handled by the Coordinating Center as described below. In the case of a device malfunction related to a device that is donated to the study by the manufacturer, information may be forwarded to the manufacturer by the site personnel or the Coordinating Center.

Each principal investigator is responsible for reporting serious study-related adverse events and abiding by any other reporting requirements specific to his/her Institutional Review Board or Ethics Committee. When the JCHR IRB is the overseeing IRB, sites must report all serious, related adverse events regardless of whether they are expected/anticipated and regardless of whether they are fatal or life threatening within 7 calendar days. The Coordinating Center will be responsible for notifying the FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than seven calendar days after initial receipt of the information. In addition, the Coordinating Center will notify FDA and all participating investigators of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the Sponsor determines that the information qualifies for reporting.

8.5 Independent Safety Oversight

A Data and Safety Monitoring Board (DSMB) will review compiled safety data at periodic intervals (approximately every 6 months). SAEs, UADES, and any adverse events leading to study discontinuation will be reviewed immediately by the DSMB. The DSMB also will be informed of any ADEs not meeting criteria for a UADE if the Medical Monitor requests the DSMB review. The DSMB can request modifications to the study protocol or suspension or outright stoppage of the study if deemed necessary based on the totality of safety data available. Details regarding DSMB review will be documented in a separate DSMB document.

8.6 Stopping Criteria Related to Study Devices or Drug

8.6.1 Participant Discontinuation of Study Device

In the case of an unanticipated system malfunction resulting in a severe hypoglycemia or DKA event (or a malfunction that could have led to severe hypoglycemia or DKA), use of the HCL system will be suspended for all participants while the problem is diagnosed. The UADE will be reported to the IRB, DSMB, and FDA. After assessment of the problem and any correction, use of the system will not be restarted until approval is received from the IRB, DSMB, and FDA.

In the absence of a device malfunction, use of the HCL system by a participant will be discontinued if any of the following occur:

- The investigator believes it is unsafe for the participant to continue on the study device *This could be due to the development of a new medical condition or worsening of an existing condition; or participant behavior contrary to the indications for use of the device that imposes on the participant's safety*
- The participant requests that the treatment be stopped
- Participant has two distinct severe hypoglycemia events as defined in Section 8.2.3
- Participant has two distinct episodes of DKA as defined in Section 8.2.4 (not related to insulin set failure)
- Participant pregnancy
    - Upon discovery of pregnancy, the use of closed loop will be stopped; however, the participant may continue use of the study pump and CGM in open loop until an alternative method for insulin delivery and glucose monitoring is in place. This is to ensure safety of the participant and unborn child.

Each DKA or severe hypoglycemia event will be reviewed by the Medical Monitor and the DSMB with respect to determination of cause and whether the occurrence of the event can be attributed to use of the HCL system.

An additional requirement for continued system use following a single DKA or severe hypoglycemia event will be that (1) the site investigator believes that the event is explainable, unlikely to recur, and that it is safe for the participant to continue to use the system and (2) the Medical Monitor and DSMB concur. If either the Medical Monitor or DSMB determines that the occurrence of the event indicates that it is not safe for the participant to continue to use the HCL system, use will be discontinued.

Participants who discontinue a study HCL system will remain in the study (unless the participant is pregnant, in which case the participant will be dropped from the study). Participants who discontinue a study HCL system and are not pregnant will remain in the study and be encouraged to use CGM and an insulin pump, which may be provided by the study.

8.6.2 Participant Discontinuation of Study Drug

Rules for discontinuing study drug use are described below.

- The investigator believes it is unsafe for the participant to continue to receive the drug. This could be due to the development of a potential side effect of the drug, a new medical condition or worsening of an existing condition; or participant behavior contrary to the indications for use of the drug that imposes on the participant's safety
- The participant requests that the treatment be stopped
- Participant pregnancy

Even if the study drug is discontinued, the participant will be encouraged to remain in the study through the final study visit (unless the participant is pregnant, in which case the participant will be dropped from the study).

8.6.3 Criteria for Suspending or Stopping Overall Study

If any UADE occurs, the use of that study device may be suspended or stopped completely, pending Medical Monitor and DSMB review. If the study device in question is deemed to be unsafe, any participants currently using that device will be switched to a different HCL system, if possible. If there is not another FDA approved system, enrollment of the trial as a whole may be stopped until the issue is resolved.

In addition, study activities could be suspended if the manufacturer of any constituent study device requires stoppage of device use for safety reasons (e.g., product recall). The affected study activities may continue if participants can switch to a different FDA approved HCL system or the underlying problem can be corrected by a protocol or system modification that will not invalidate the results obtained prior to suspension.

If any death occurs in the study which is assessed as related to study treatment regimen by the study site investigator and Medical Monitor (but not limited to a specific study device that can be switched), enrollment in the trial will be halted, pending DSMB review.

As part of their ongoing safety review, the DSMB will make independent judgments regarding other adverse events that may warrant trial interruption.

The study Medical Monitor will review all adverse events and adverse device events that are reported during the study typically on a weekly basis and will review compiled safety data at periodic intervals (generally timed to the review of compiled safety data by the DSMB). The Medical Monitor may request suspension of study activities or stoppage of the study if deemed necessary based on the totality of safety data available.

8.7 Unmasking of Study Drug Due to Adverse Event

Emergency unmasking criteria for an individual participant:

- For the purpose of management of pregnancy as per the documentation and request of a treating physician, with PI approval.
- For the occurrence of an adverse event that is assessed as serious, related and unexpected (SUSAR) by the Medical Monitor
- A medical condition or surgery that is deemed necessary to unmask by the study PI and Medical Monitor

The Investigator and Coordinating Center will document the unmasking, the reason for unmasking and the date and time of unmasking. The Investigator will be instructed to call the Medical Monitor prior to asking the Coordinating Center to break the blind. All instances of unmasking will be reported to the IRB, the Sponsor, the DSMB and the Protocol Chairs.

Emergency unmasking criteria for the study:

- A safety trend/pattern is detected during the conduct of a study that is deemed by the Medical Monitor and DSMB to be a safety concern for the continuation of the study.

Chapter 9: Miscellaneous Considerations

9.1 Drugs Used as Part of the Protocol

Participants in a HCL group will use an insulin approved for the pump. When transitioning from MDI to SAP therapy, total daily basal insulin dose will be decreased by 20%, divided by 24, and one basal rate will be set. When transitioning from SAP to HCL, CGM data will be used to guide device setting changes. If time spent < 70 is > 4%, carb ratios will be weakened by 10%.

Participants in a non-HCL group will be prescribed insulin as part of usual diabetes management by their personal diabetes care provider. The study will not be providing insulin to participants in any group, unless the participant has no means of obtaining insulin.

9.2 Collection of Medical Conditions and Medications

Pre-Existing Condition: Any medical condition that is either present at Screening, a chronic disease, or a prior condition that could impact the participant's health during the course of the study (e.g., prior myocardial infarction or stroke).

Medications: All medications that the participant is currently taking at Screening and during the course of the study will be recorded. Nutraceuticals and preventative treatment also will be recorded. This will include the treatment of chronic pre-existing conditions, medical conditions that occur during the study, and/or adverse events. Medications only taken as needed either can be recorded when prescribed or only recorded if used during the study. Glucagon for treatment of severe hypoglycemia will only be recorded if used during the study.

9.3 Prohibited Medications, Devices, Treatments, and Procedures

Participants will be asked to consult with their study team, if possible, before starting any new prescription therapy unless it is medically urgent. If treatment with a beta blocker, seizure medication, other antihypertensive medications, HMG-CoA reductase inhibitors, lithium, theophylline, clonidine, or aspirin is required, participants in Cohort A may have study drug (verapamil/placebo) discontinued.

Participants will be instructed, if possible, not to use systemic prednisone, other immunosuppressive agents, or chronic inhaled or nasal corticosteroids during this trial as these agents may accelerate ß-cell decline.

Treatment with any non-insulin glucose-lowering agent (such as GLP-1 agonists, Symlin, DPP-4 inhibitors, SGLT-2 inhibitors, biguanides, sulfonylureas) will not be permitted.

Participants are not permitted to use diabetes management devices that are not FDA approved, outside of study devices (such as do-it-yourself closed-loop systems).

Study devices (insulin pump, study CGM systems) must be removed before Magnetic Resonance Imaging (MRI), Computed Tomography (CT) or diathermy treatment.

For Medtronic HCL users, acetaminophen should be avoided.

9.4 Rescue Medications, Treatments, and Procedures

All participants will be required to have a commercially available glucagon (or glucagon analog) preparation for treatment as needed of severe hypoglycemia. The study will not be providing glucagon to participants in any group, unless the participant has no means of obtaining it.

9.5 Pregnancy Reporting

If pregnancy occurs, the participant will be dropped from the study, but information about the outcome of the pregnancy will be collected. Use of study devices and study drug will be stopped as detailed in Sections 8.6.1 and 8.6.2. The occurrence of pregnancy will be reported to the Coordinating Center and to the JCHR IRB as an Unanticipated Problem, both within seven calendar days.

9.6 Participant Compensation

Participant compensation will be specified in the informed consent form.

9.7 Participant Withdrawal

Participation in the study is voluntary, and a participant may withdraw at any time. For participants who withdraw, their data will be used up until the time of withdrawal.

Participants who discontinue study treatment will be requested to remain in the study to at least return for the 52 week visit even if the participant is unwilling to return for all visits.

9.8 Confidentiality

For security and confidentiality purposes, participants will be assigned an identifier that will be used instead of their name. Protected health information gathered for this study will be shared with the Coordinating Center, the Jaeb Center for Health Research in Tampa, FL. De-identified participant information may also be provided to research sites involved in the study.

Chapter 10: Statistical Considerations

10.1 Statistical and Analytical Plans

The approach to sample size and statistical analyses are summarized below and will be further detailed in the Statistical Analysis Plan.

10.2 Statistical Hypotheses

The primary outcome is the C-peptide area under the curve (AUC) in response to a 2-hour MMTT at 52 weeks.

The study hypotheses can be stated as follows:

HCL vs. non-HCL comparison:

- *Null Hypothesis:* There is no difference in the C-peptide AUC in response to a 2-hour MMTT at 52 weeks between HCL with intensive care and non-HCL with standard care for the combined Cohort A and B population.
- *Alternative Hypothesis:* There is a nonzero difference in the C-peptide AUC in response to a 2-hour MMTT at 52 weeks between HCL with intensive care and non-HCL with standard care for the combined Cohort A and Cohort B population.

Verapamil vs. Placebo comparison:

- *Null Hypothesis:* There is no difference in the C-peptide AUC in response to a 2-hour MMTT at 52 weeks between verapamil and placebo for the Cohort A population.
- *Alternative Hypothesis:* There is a nonzero difference in the C-peptide AUC in response to a 2-hour MMTT at 52 weeks between verapamil and placebo for the Cohort A population.

10.3 Sample Size

The sample size calculation is detailed in a separate document and is summarized below. Sample size was driven by the verapamil vs. placebo comparison as the test only includes participants in Cohort A. The mean of the transformed C-peptide (log(AUC + 1)) and the root mean square error in the placebo group were assumed to be 0.315 and 0.18, respectively, based on 90% CIs from prior studies[31]. The corresponding geometric-like mean C-peptide value of 0.370 pmol/mL was calculated using the inverse transformation: $\exp(0.315) - 1$. A recent randomized trial [29] found a 62% increase in mean C-peptide in verapamil compared with placebo, although the total sample size was small (N=24) and confidence intervals were wide. Therefore, this study assumed a smaller, 50% increase in mean C-peptide using verapamil. The expected geometric-like mean C-peptide value in the verapamil arm was $0.370 \cdot 1.50 = 0.555$ pmol/mL. After a log(x+1) transformation, the mean values in the control and treatment groups are 0.315 and 0.441, respectively, giving a treatment effect of 0.441-0.315=0.126.

With these estimates, a sample size of 88 participants in Cohort A was calculated to provide 90% power with a 5% two-sided type 1 error rate and a 1:1 treatment group allocation to detect a

verapamil vs. placebo treatment group difference assuming the true relative difference between groups was 50%. To account for a 10% dropout rate, the sample size in Cohort A will be 98 participants.

A sample size of 33 participants for Cohort B was selected based on convenience. Participants in Cohort B will be allocated to either HCL or non-HCL in a 2:1 treatment group allocation. Thus, we expect 131 participants in be enrolled in either Cohort A or Cohort B with approximately 71 participants in HCL/intensive care and 60 participants in non-HCL/standard care arm. Assuming around a 10% dropout rate, an HCL/intensive care treatment effect of 50%, and an upper confidence limit estimate of 0.18 for the standard deviation (same presumed estimates for verapamil vs. placebo comparison), this study has 96% power to detect a significant HCL/intensive care vs. non-HCL/standard care treatment group difference with a type 1 error rate of 5%.

10.4 Outcome Measures

C-peptide

The primary outcome is the C-peptide in response to a 2-hour MMTT at 52 weeks. This is measured as the area under the stimulated C-peptide curve (AUC). AUC is computed using a trapezoidal rule, which is a weighted sum of the C-peptide values over the 120 min.

A variety of secondary C-peptide outcomes is planned, with randomization (±3 days) AUC as baseline, including the following:

- C-peptide AUC 13, 26, and 39 weeks (52 weeks is primary outcome)
- Peak C-peptide during a 2-hour MMTT at 13, 26, 39, and 52 weeks

CGM Metrics

CGM metrics from the Dexcom G6 and Medtronic Guardian Sensor 3 will be used to assess the level of glycemic control over the course of the study with respect to the study hypothesis that requires achieving near-normal glycemia in the intervention group and a separation between treatment groups in glycemic control. CGM metrics also will be used as secondary outcomes.

CGM-derived indices will be computed over the study period for 24 hours, daytime (6AM to midnight) and nighttime (midnight to 6AM), and at 6, 13, 26, 39, and 52 weeks.

- Mean glucose
- Percentage of sensor glucose from 70 to 180 mg/dL
- Percentage of sensor glucose >180 and >250 mg/dL
- Percentage of sensor glucose <54 and <70 mg/dL
- Coefficient of variation

The Statistical Analysis Plan (SAP) will describe how CGM derived indices will be calculated.

HbA1c

HbA1c levels will be used as a measure of hyperglycemia.

HbA1c outcomes at 13, 26, 39, and 52 weeks will include the following:

- Mean HbA1c
- Percentage of patients with an HbA1c <7.0% and <6.5%

10.5 Analysis Datasets

The primary analysis will follow the intention-to-treat principle. It will include all randomized participants, and data will be analyzed based on the treatment assigned from randomization regardless of the actual treatment received.

A per-protocol analysis that includes participants adhering to the protocol will be performed and detailed in the SAP. Sensitivity analyses on the primary outcome will be described in the SAP.

All participants will be included in safety analyses.

10.6 Analysis of the Primary Efficacy Endpoint

Both primary analyses will follow the intention-to-treat principle.

10.6.1 HCL vs. non-HCL Analysis

The HCL/intensive care versus non-HCL/standard care comparison will combine participants from Cohort A and B. A constrained longitudinal analysis will be performed by fitting the baseline (randomization) and 52 week log(AUC+1) as the outcome and testing for device use indicator (randomized to HCL/intensive therapy or randomized to no HCL/standard therapy) controlling for age, time from diagnosis to randomization, and drug use indicator (verapamil, placebo, or no drug [Cohort B]). The log(AUC+1) transform is expected to make the residuals approximately normally distributed, but regression diagnostics will be performed to check the residuals and an appropriate alternative transformation or a nonparametric analysis based on ranks will be performed if the residuals have a skewed distribution. The primary analysis test assumes there is no interaction between device use and drug use; an analysis described below will assess possible treatment interactions.

10.6.2 Verapamil vs. Placebo Analysis

The verapamil vs. placebo comparison will only include participants in Cohort A. A similar constrained longitudinal analysis will be performed except testing for the drug use indicator (randomized to verapamil or randomized to placebo) and controlling for device use (HCL or no HCL).

10.7 Analysis of the Secondary Endpoint

Secondary analyses for HCL/intensive care vs. non-HCL/standard care and verapamil vs. placebo will be performed and described in the SAP.

10.8 Safety Analyses

All adverse events will be listed by cohort. Events also will be listed separately for the HCL/intensive and non-HCL/standard care arms since differential reporting may occur due to the many additional study contacts occurring in HCL participants.

In all safety analyses comparing the HCL/intensive to the non-HCL/standard care group, Cohorts A and B will be combined.

For SH events, DKA events, and hospitalizations, the following outcomes will be compared between treatment groups if there are at least 5 events that occur during the study:

- Number of events per participant
- Number of participants with at least one event
- Incidence rate per 100 person-years

For the count outcomes and the incidence rates, a Poisson regression model will be used. All models will adjust for site as a random effect. Additionally, the models for the DKA outcomes will adjust for the presence or absence of a DKA event at diagnosis.

For SH events, separate analyses also will be done for the outcomes listed above that will only include events that resulted in seizure or a loss of consciousness.

10.9 Intervention Adherence

HCL system use, verapamil, and placebo adherence will be tabulated at each time point and reported in a table.

10.10 Protocol Adherence and Retention

Tabulations and figures by treatment group to assess protocol adherence will include:

- Flowchart accounting for all participants according to treatment group for all visits
- Visit completion rates for each follow up visit
- Protocol deviations
- Numbers and reasons for unscheduled visits and phone calls

10.11 Baseline Descriptive Statistics

Baseline demographic and clinical characteristics will be tabulated overall, by cohort, and by treatment group.

10.12 Device Issues

All reportable device issues occurring during the study will be tabulated and reported in a table.

10.13 Planned Interim Analyses

No formal interim analyses or stopping guidelines are planned for this study.

The DSMB will review data for safety per the DSMB Standard Operating Procedures approximately every six months. The data to be reviewed will include information regarding adverse events, device issues, and protocol adherence/deviations as they may relate to participant safety.

10.14 Interaction Analyses

The primary outcome will also test for a possible device by drug interaction. The same model described above for the primary analysis will fit with the inclusion of a device by drug interaction. If the interaction is significant, a subgroup analysis of the effectiveness of HCL/intensive care will be assessed by drug use indicator (verapamil, placebo, or no drug [Cohort B]). Additionally, if the interaction is significant, a subgroup analysis of the effectiveness of verapamil will be assessed by device use indicator (HCL or no HCL).

10.15 Subgroup Analyses

Subgroup analyses of effect modification (interaction) will be performed separately for the HCL/intensive care vs. non-HCL/standard care and verapamil vs. placebo primary analyses. Subgroup analyses will assess the effectiveness of HCL/intensive care and the effectiveness of verapamil by various patient characteristics as described in the SAP. Interpretation of the analyses will be made with caution and tests only performed if the overall treatment effect is significant.

10.16 Multiple Comparisons

For the primary analysis, no adjustments for multiplicity will be made because two different interventions are being tested separately.

For secondary analyses, Benjamini-Hochberg false discovery rate adjusted p-values will be calculated within several subcategories. The subcategories will be separate for each of the two interventions.

10.17 Additional Analyses

The relationship between C-peptide and glycemic outcomes (e.g., % time in range), pooled across all treatment groups, will be assessed and detailed in the SAP. Mechanistic studies may be performed, the exact nature of which will be determined at study end depending on study outcomes.

Chapter 11: Data Collection and Monitoring

11.1 Case Report Forms and Device Data

The main study data are collected through a combination of electronic case report forms (CRFs) and electronic device data files obtained from the study software and individual hardware components. These electronic device files and electronic CRFs from the study website are considered the primary source documentation.

When data are directly collected in electronic case report forms, this will be considered the source data.

11.2 Study Records Retention

Study documents should be retained for a minimum of 3 years. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the Coordinating Center, if applicable. It is the responsibility of the Coordinating Center to inform the investigator when these documents no longer need to be retained.

Auto-antibody and HbA1c results from the central labs may be returned to clinical sites during the study. C-peptide results from the central lab will not be returned to sites until study completion. Results from other samples sent to central labs will not be returned to sites.

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants.

11.3 Quality Assurance and Monitoring

Designated personnel from the Coordinating Center will be responsible for maintaining quality assurance (QA) and quality control (QC) systems to ensure that the clinical portion of the trial is conducted and data are generated, documented and reported in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirements. Adverse events will be prioritized for monitoring.

A risk-based monitoring (RBM) plan will be developed and revised as needed during the course of the study, consistent with the FDA "Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring" (August 2013). Study conduct and monitoring will conform with 21 Code of Federal Regulations (CFR) 812.

The data of most importance for monitoring at the site are participant eligibility and adverse events. Therefore, the RBM plan will focus on these areas. As much as possible, remote monitoring will be performed in real-time with on-site monitoring performed to evaluate the verity and completeness of the key site data. Elements of the RBM may include:

- Qualification assessment, training, and certification for sites and site personnel
- Oversight of Institutional Review Board (IRB) coverage and informed consent procedures

- Central (remote) data monitoring: validation of data entry, data edits/audit trail, protocol review of entered data and edits, statistical monitoring, study closeout
- On-site monitoring (site visits): source data verification, site visit report
- Agent/Device accountability
- Communications with site staff
- Patient retention and visit completion
- Quality control reports
- Management of noncompliance
- Documenting monitoring activities
- Adverse event reporting and monitoring

Coordinating Center representatives or their designees may visit the study facilities at any time in order to maintain current and personal knowledge of the study through review of the records, comparison with source documents, observation and discussion of the conduct and progress of the study.

11.4 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or procedure requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the monitoring plan.

Chapter 12: Ethics/Protection of Human Participants

12.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Participants of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

12.2 Institutional Review Boards

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

12.3 Informed Consent Process

12.3.1 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing.

The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

12.3.2 Participant and Data Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the Coordinating Center and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Coordinating Center.

The study monitor, other authorized representatives of the Coordinating Center, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Jaeb Center for Health Research (JCHR). This will not include the participant's contact or identifying information, unless otherwise specified in the informed consent form. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by JCHR research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the JCHR.

12.3.3 Future Use of Stored Specimens

Permission to collect and store blood samples for future use will be included in the informed consent. With the participant's approval, blood specimens will be labeled by study ID and stored at Indiana University and the University of Minnesota for use by researchers, including those outside of the study.

These samples could be utilized to learn more about causes of T1D, its complications (such as eye, nerve, and kidney damage) and other conditions for which individuals with diabetes are at increased risk, and how to improve treatment.

All studies will be performed after a written protocol for testing and analysis are approved by local IRB(s). Specimens will be transferred to research labs at research institutions as needed to perform the approved investigations.

The labs will be provided with a code-link for each participant that will allow linking the biological specimens with the clinical information collected during the trial, maintaining the masking of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage may not be possible after the study is completed.

Chapter 13: References

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