Signature Page

Safety Evaluation of an Advanced Hybrid Closed Loop System Using Lyumjev with the Tandem t:slim X2 with Control-IQ in Adults, Adolescents and Children with Type 1 Diabetes

Protocol Identifying Number: TP-0009650

IDE Sponsor: Tandem Diabetes Care, Inc.

Version Number: v. 4.0

13 APR 2022

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Safety Evaluation of an Advanced Hybrid Closed Loop System Using Lyumjev with the Tandem t:slim X2 with Control-IQ in Adults, Adolescents and Children with Type 1 Diabetes

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KEY ROLES

Sponsor and Clinical Director	
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Title	Medical Director
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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ADE	Adverse Device Effect
AE	Adverse Event
BGM	Blood Glucose Meter
BMI	Body Mass Index
CFR	Code of Federal Regulations
CGM	Continuous Glucose Monitoring
DCCT	Diabetes Control & Complications Trial
DKA	Diabetic Ketoacidosis
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
ICH	International Conference of Harmonization
IDE	Investigational Device Exemption
IRB	Institutional Review Board
RBM	Risk-Based Monitoring
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
T1D	Type 1 Diabetes
UADE	Unanticipated Adverse Device Effect

SITE PRINCIPAL INVESTIGATOR STATEMENT OF COMPLIANCE

Protocol Title: Safety Evaluation of an Advanced Hybrid Closed Loop System Using Lyumjev with the Tandem t:slim X2 with Control-IQ in Adults, Adolescents and Children with Type 1 Diabetes

Protocol Version/Date: 4.0 13 APR 2022

I have read the protocol specified above. In my formal capacity as a Site Principal Investigator, my duties include ensuring the safety of the study participants enrolled under my supervision and providing the Jaeb Center for Health Research, which serves as the Coordinating Center for the protocol, with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site.

This trial will be carried out in accordance with ICH E6 Good Clinical Practice (GCP) and as required by the following: United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

Also, the trial will be carried out in accordance with ICH E6 Good Clinical Practice (GCP), and the Declaration of Helsinki.

As the Principal Investigator, I will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), or other approved Ethics Committee, except where necessary to eliminate an immediate hazard(s) to the trial participants.

All key personnel (all individuals responsible for the design and conduct of this trial) have completed Human Participants Protection Training and Good Clinical Practice Training. Further, I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Investigator's Signature _____ Date: _____ / _____ / _____
dd mmm yyyy

Investigator's Name: _____

Site Name/Number: _____

PROTOCOL SUMMARY

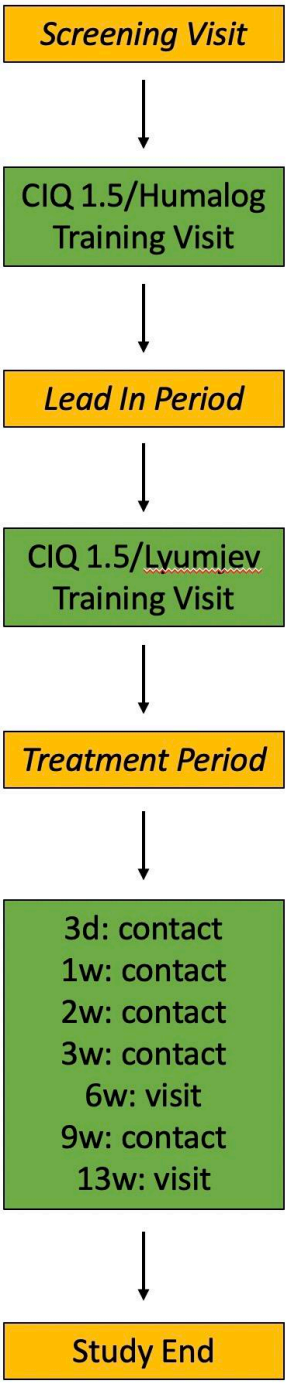
PARTICIPANT AREA	DESCRIPTION
Study Sponsor	Tandem Diabetes Care, Inc.
Protocol Number	TP-0009650
Protocol Title	Safety Evaluation of an Advanced Hybrid Closed Loop System Using Lyumjev with the Tandem t:slim X2 with Control-IQ in Adults, Adolescents and Children with Type 1 Diabetes
Précis	This is a prospective, multi-center (US only), single-arm study in adults and children (ages 6 to <81 years) with type 1 diabetes (T1D) who are current users of the t:slim X2 pump with Control-IQ technology to evaluate the safety of Lyumjev in the Control-IQ 1.5 System to achieve labeling updates for Lyumjev and the t:slim X2 insulin pump with Control-IQ 1.5 technology. Participants will be current Control-IQ users who will use Humalog with the study pump (Control-IQ 1.5) during a ~16 day lead-in during which pump setting adjustments may be made in response to observed trends. This will be followed by a 3-month outpatient treatment period in which participants will use the study pump with Control-IQ 1.5 and Lyumjev insulin. Exercise and meal challenges will be performed during the lead-in period and the main study period.
Products	Hybrid Closed Loop System: • t:slim X2 pump with Control-IQ 1.5 technology • Dexcom G6 system Lyumjev (insulin lispro-aabc)
Objectives	To evaluate the safety of Lyumjev (insulin lispro-aabc) use in the Tandem t:slim X2 insulin pump with Control-IQ 1.5 technology in adult and pediatric participants with diabetes in an outpatient setting to support system labeling.
Number of Sites	~10-15 clinical sites in the US.
Study Design	Single-arm prospective safety trial
Number of Participants	Up to 200 participants commencing treatment period so that at least 160 complete study (at least 80 participants age 6-<14 years old, and at least 80 participants age 14+). At least 20 participants will be age 14-<18 years of age. • Goal to have at least 1/3 of all completers with HbA1c ≥7.5% • Goal to have at least 10 completers with basal insulin rate >3 units/hour (for at least part of the day) Enrollment will be staged, starting with the 14+ cohort. After a cumulative 10,000 hours of use are reached in the age 14+ cohort, a Trial Level Safety Review of all adverse events and device issues will be performed before opening enrollment to the 6-13 year old cohort.
Participant Population:	**Eligibility to enroll in the study will be assessed based on the following inclusion criteria:** 1. Age 6 to <81 years 2. Diagnosis of type 1 diabetes for at least 1 year 3. Currently using Control-IQ technology for at least 3 months, with system use (active closed loop) for at least 85% of the possible time in 14 days prior to enrollment 4. Total daily insulin dose (TDD) at least 2 U/day 5. HbA1c < 10.5% 6. Residing full-time in the United States, with no anticipated travel outside the United States during the period of study participation.

PARTICIPANT AREA	DESCRIPTION
	7. For participants <18 years old, living with one or more parent/legal guardian knowledgeable about emergency procedures for severe hypoglycemia, able to contact the participant in case of an emergency, and willing to use the Dexcom Follow app (with push notifications turned on) for the duration of the study. 8. If >18 years old, participant has someone who lives within 30 minutes of them who is willing to be contacted if the study team can't reach the participant in case of a suspected medical emergency. 9. Participant has agreed to participate in the study; and has read, understood and signed the informed consent form (ICF) and assent, if applicable; and has agreed to follow all study procedures, including: • suspending use of any personal CGM for the duration of the clinical trial once the study CGM is in use • switching to or continuing to use Humalog during the lead-in period • switching to Lyumjev for the main study period. • willing and able to perform the study exercise and meal challenges. 10. Investigator has confidence that the participant can successfully operate all study devices and is capable of adhering to the protocol, including ability to respond to alerts and alarms, and to provide basic diabetes self-management. 11. Participant and/or parent/legal guardian have the ability to read and understand English **Eligibility to enroll in the study will be assessed based on the following exclusion criteria:** 1. More than 1 episode of diabetic ketoacidosis (DKA) in the past 6 months 2. More than 1 episode of severe hypoglycemia (needing assistance) in the past 6 months 3. Inpatient psychiatric treatment in the past 6 months 4. History of drug abuse (defined as any illicit drug use) or history of alcohol abuse prior to screening or unwillingness to agree to abstain from illicit drugs throughout the study. 5. For Female: Currently pregnant or planning to become pregnant during the time period of study participation • *A negative pregnancy test will be required for all females of child-bearing potential (menarchal)* • *Counseling on appropriate birth control options will be provided to females with child-bearing potential in the event the participant does not have an acceptable plan.* 6. Adults lacking the capacity to provide consent and/or follow study procedures in the opinion of the investigator 7. Concurrent use of any non-insulin glucose-lowering agent, other than metformin (for example, GLP-1 agonists, Symlin, DPP-4 inhibitors, SGLT-2 inhibitors, sulfonylureas). 8. Hemophilia or any other bleeding disorder 9. Hemoglobinopathy 10. History of heart, liver, lung or kidney disease determined by investigator to interfere with the study 11. History of allergic reaction to Humalog or Lyumjev 12. Use of glucocorticoids, beta blockers or other medications determined by investigator to interfere with study 13. Abnormal screening electrocardiogram consistent with increased risk during exercise, such as arrhythmia, ischemia, or prolonged QTc interval (>450 ms)

PARTICIPANT AREA	DESCRIPTION
	(Screening ECG only required for participants age > 50, duration of diabetes > 20 years, or history of coronary artery disease) 14. Significant chronic kidney disease (which could impact CGM accuracy in investigator's judgment) or hemodialysis 15. History of adrenal insufficiency 16. History of abnormal TSH consistent with hypothyroidism or hyperthyroidism that is not appropriately treated 17. History of gastroparesis 18. A condition, which in the opinion of the investigator or designee, would put the participant or study at risk 19. Participation in another pharmaceutical or device trial at the time of enrollment or anticipated for during the time period of study participation 20. Employed by, or having immediate family members employed by Tandem Diabetes Care, Inc., Eli Lilly and Co., or TypeZero Technologies, LLC, or having a direct supervisor at place of employment who is also directly involved in conducting the clinical trial (as a study investigator, coordinator, etc.); or having a first-degree relative who is directly involved in conducting the clinical trial
Participant Duration	Approximately 15 weeks (~16 days for run in period followed by 13 weeks of study device use with Lyumjev).
Study Endpoints	The adult and pediatric populations will be combined for primary analysis. Separate secondary analyses also will be performed for the adult and pediatric cohorts. CGM metric analyses will be analyzed separately for the challenge days and subsequent nights and not included in the overall analyses. Primary Safety Endpoints: • Severe hypoglycemia (with cognitive impairment such that assistance of another individual is needed for treatment) during study compared with data on severe hypoglycemic events reported by T1D Exchange clinic registry over a 3-month time period. • Diabetic ketoacidosis • Unanticipated adverse device effects • Other serious adverse events • Adverse drug reactions Secondary Safety Endpoints: • All adverse events (including infusion site reactions) • CGM hypoglycemia outcomes (compared with baseline run-in data and separately when possible with 4 weeks of pre-study CGM data collected at enrollment) ◆ Overall % time <54 mg/dL ◆ Postprandial % time <54 mg/dL (30 min, ≤1, ≤2, ≤4, >1 to ≤2 and >2 to ≤4hr) ◆ Overall and postprandial % time <70 mg/dL ◆ Rate of hypoglycemia events defined as 15 or more consecutive minutes <54 mg/dL Exploratory: • Postprandial incremental area under the glucose curve (4 hr) • Peak postprandial glucose • Times in ranges-overall and postprandial (70-180 mg/dL, >180 mg/dL, >250 mg/dL, 70-140 mg/dL) • Mean glucose • Rate of hyperglycemia events, defined as 90 or more minutes >300 mg/dL within 120 minutes

PARTICIPANT AREA	DESCRIPTION
	• Overall variability (CV and SD) • HbA1c change from baseline • Patient-reported outcomes Exercise and Meal Challenges: • Endpoints will be CGM metrics and safety outcomes as indicated above • Separate analyses conducted for the overnight following the challenge
Protocol Overview/Synopsis	After consent is obtained, eligibility will be assessed. Eligible participants will enter the Lead-in Period. <u>Lead-in Period</u>: The lead-in Period will last approximately 16 days, and may begin the same day the screening visit is completed. Participants will switch from their current Control-IQ system to the study pump (Control-IQ 1.5 technology) and study sensor, and will be trained by qualified study staff on the new study devices including use of Humalog (insulin lispro injection). Study participation will require use of the Control-IQ technology with at least 85% of active closed loop over ~16 days of the lead-in period. The lead-in period data collection may be repeated if this threshold is not met. A study meal challenge and exercise challenge will be performed with Humalog during the lead in period. Those day and overnight periods will be analyzed separately. <u>Treatment Period</u>: Participants will return to clinic to undergo device training with Lyumjev in the study pump. Participants will then use the study pump and the investigational insulin for ~90 days during the study period. Participants will have a phone follow up visit at 1 week and 3 weeks, a clinic follow up visit at 6 weeks, a phone follow up visit at 9 weeks, and a final clinic visit at ~13 weeks. Participants will use the t:slim X2 insulin pump with Control-IQ technology turned on with the investigational insulin. It is acceptable to use manual mode when there is a loss of CGM data. Weekly phone/email/text contacts will be performed as part of the comprehensive plan to monitor for adverse events, to include infusion site reactions. Each participant will perform 3 meal and 3 exercise challenges during Lyumjev use. An assessment of adverse events, using open ended questions to capture hyperglycemic and hypoglycemic events, and their underlying cause and relationship to the study device, study insulin or other parts of the system (such as the infusion set), will occur at all visits/contacts. <u>Study Safety Plan</u>: Participants will be given a blood glucose and ketone meter to use throughout the study, and will be trained on their use by qualified staff. BGM readings will be performed in accordance with the study safety plan and per CGM manufacturer instructions. Ketone readings will be performed per the study safety plan. Site investigators may adjust insulin delivery profile settings as needed throughout the study in accordance with their clinical practice.

SCHEMATIC OF STUDY DESIGN



SCHEDULE OF STUDY VISITS AND PROCEDURES

	Screening Visit	CIQ 1.5/ Humalog Training Visit	CIQ 1.5/ Lyumjev Training Visit	Control-IQ Use							
		Lead-In	Start Main Trial ~16 days after start of Lead-In	3d	1w	2w	3w	6w	9w	13w	UV
Visit (V) or Contact (C)	V	V	V	C	C	C	C	V	C	V	V/C
Informed Consent/Assent	X										
Eligibility Assessment	X										
Medical history/ physical exam[a]	X			X	X	X	X	X	X	X	X
Height, weight, blood pressure and pulse	X		X								
HbAlc (POC or local lab)	X										
ECG [b]	X										
Questionnaires/Surveys (PRO Assessments)[c]	X									X	
Pregnancy test (females of child-bearing potential)	X		X								
Assessment of Device Use	X		X								
Study system training		X	X								
HbA1c (Central Lab)			X							X	
AE Assessment		X	X	X	X	X	X	X	X	X	X
Upload device data from home				X	X	X	X		X		X
Download device data at clinic visit	X	X	X					X		X	X

[a] A qualified medical professional must perform a medical assessment at each office visit. During each office visit, the skin surrounding the infusion sites should be assessed as part of a focused physical exam. This also applies for all phone visits converted to an office visit, as well as unscheduled visits that occur in the office.

[b] ECG performed at screening for participants age >50 years, duration of diabetes > 20 years, or history of coronary artery disease

[c] TRIM-D, Trim-DD (Diabetes Device), ITSQ (Insulin Treatment Satisfaction Questionnaire)

Chapter 1: Background Information

1.1 Introduction

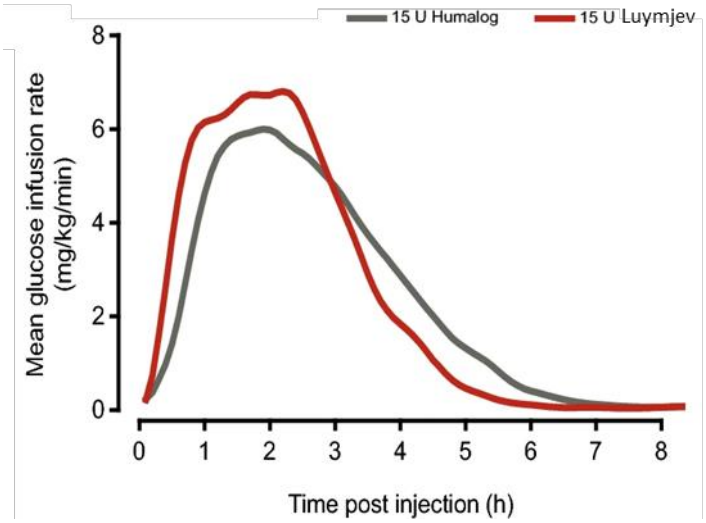
1.1.1 Tandem X2 Insulin Pump with Control-IQ Technology

The Tandem X2 insulin pump with Control-IQ technology is an FDA-approved closed-loop control (CLC) system based on the control algorithm developed and initially tested in the University of Virginia's DiAs system and then implemented in the inControl system (TypeZero, Technologies, Inc.). Use of the Control-IQ system has been extensively tested in adults and children with type 1 diabetes (T1D), demonstrating its efficacy and safety when used with insulin lispro (Humalog) or insulin aspart (Novolog).[1,2] The system is currently approved for ages 6 years and older and it is use in younger children is currently being studied (clinical trials.gov NCT04796779). There are over 150,000 users of the system since it became commercially available in 2020. A recent evaluation of real-world use of the system in 9,451 users age ≥6 years with at least 12 months of system use found results comparable to those found in the randomized trials.[3]

Since the initial approval of the system, modifications have been made in the software, which is referred to as version 1.5. These modifications include modest usability improvements and other enhancements intended to further reduce risk.

1.1.2 Lyumjev Insulin

Lyumjev™ is a rapid-acting human insulin analog indicated to improve glycemic control in adults with diabetes mellitus. It has a faster onset of action and shorter duration of action than Humalog® (insulin lispro). Insulin lispro appears in the bloodstream approximately 1 minute after injection of Lyumjev, 5 minutes faster than Humalog. In pharmacodynamic euglycemic clamp studies comparing Lyumjev and Humalog, onset of action was 10-min faster and duration of action was 44 minutes shorter with Luymjev compared to Humalog across all populations and dose range.[4] Lyumjev may be given as part of a multiple daily insulin regimen or administered via continuous subcutaneous insulin infusion. This is the first clinical trial evaluating Lyumjev with Control-IQ technology.



The differences in insulin lispro PK profiles between LY900014 and Humalog following SC injection were similar in children, adolescents, and adults. LY900014 demonstrated an accelerated insulin lispro absorption with a reduction in the late exposure and an overall shorter PK duration compared to Humalog. Following a single subcutaneous bolus infusion with CSII therapy, there was a trend towards an accelerated absorption of insulin lispro and the duration of exposure was shorter with LY900014 whilst maintaining a similar overall exposure and maximum concentration compared to Humalog in children and adolescents with type 1 diabetes (Lilly Internal data).

1.2 Rationale

The rationale for the study is based on the premise that use of an insulin with a more rapid onset of action in a CLC system may reduce hyperglycemic excursions, particularly after meals, and may also reduce the risk of hypoglycemia due to shorter duration of action. The initial needed determination is that use of Lyumjev in the Control-IQ system is safe.

1.3 Potential Risks and Benefits

Risks and Benefits are detailed below. Loss of confidentiality is a potential risk; however, data are handled to minimize this risk. Hypoglycemia, hyperglycemia and ketone formation are always a risk in participants with type 1 diabetes and participants will be monitored for these events.

1.3.1 Known Potential Risks

1.3.1.1 Blood Draw

A venipuncture and/or fingerstick will be performed to obtain blood for HbA1c measurement. Venipuncture can cause 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. A fingerstick frequently causes transient pain and there may be a small, localized bruise, which may be followed by a small scar that may persist for several weeks. The risk of local infection is less than 1 in 1000 with either venipuncture or fingerstick.

1.3.1.2 CGM and Pump Catheter Risks

There is a small risk of bleeding where the sensor or infusion set is inserted. There is a small risk for developing a local skin infection at the site of CGM sensor placement of pump infusion set placement. This may be associated with swelling, redness and pain; and may require antibiotic therapy. Rarely, a 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.

Some participants may develop skin irritation or allergic reactions to the adhesives used to secure the CGM, or to secure the insulin infusion sets for the continuous subcutaneous insulin infusion. If these reactions occur, different adhesives or “under-taping” (such as with IV 3000, Tegaderm, etc.) will be tried, sites will be rotated frequently, and a mild topical steroid cream or other medication may be required. Skin irritation or allergic reactions at the infusion site could also occur with infusion of insulin. As a new insulin is being used in this study, this is a possible risk.

1.3.1.3 Hypoglycemia

As with any person having type 1 diabetes and using insulin, there is always a risk of having hypoglycemia. The frequency of hypoglycemia should be no more and possibly less than it would be as part of daily living. Symptoms of hypoglycemia can include sweating, jitteriness, and not feeling well. There is the possibility of fainting or seizures (convulsions) and that for a few days the participant may

not be as aware of symptoms of hypoglycemia. A CGM functioning poorly and significantly over-reading glucose values could lead to inappropriate insulin delivery.

1.3.1.4 Risk of Hyperglycemia

Hyperglycemia and ketonemia could occur if insulin delivery is attenuated or suspended for an extended period or if the pump or infusion set is not working properly. A CGM functioning poorly and significantly under-reading glucose values could lead to inappropriate suspension of insulin delivery.

1.3.1.5 Risk of Device Reuse

The study CGM system is labeled for single use only. The sensor (the component of the system that enters the skin) will be single use only. The receiver, if used, is a hand-held device. The transmitter and receiver may be reused during the study after cleaning the device using a hospital-approved cleaning procedure. The transmitter is attached to the sensor but does not enter the skin. Participants will be informed that FDA or relevant national authorities have approved these devices for single use and that by using them among multiple patients, bloodborne pathogens (i.e. Hepatitis B) may be spread through the use of multiple users.

The study insulin pump is labeled for single-patient use. During the study, this device may be reused after cleaning adhering to a hospital-approved cleaning procedure. All infusion set equipment will be single patient use only (infusion set insertion kits, tubing, cartridges etc.) Participants will be informed that FDA or relevant national authorities typically approve the insulin pump device for single use and that by using them among multiple patients, bloodborne pathogens (i.e. Hepatitis B) may be spread through the use of multiple users.

The study blood glucose meter and blood ketone meter are labeled for single-patient use. During the study, only one person can use each device as there are rare risks that bloodborne pathogens (i.e. Hepatitis B) may be spread through the use of multiple users.

1.3.1.6 Questionnaires

As part of the study, participants (or their parent/legal guardian) will complete questionnaires which include questions about their private attitudes, feelings and behavior related to the investigational equipment as well as managing diabetes. It is possible that some people may find these questionnaires to be mildly upsetting. Similar questionnaires have been used in previous research and these types of reactions have been uncommon.

1.3.1.7 Potential Risks of the CLC System

Even though the study system has been tested prior to this study, there is still a risk that parts of the system may not function properly. The following are possible reasons the system may deliver too much insulin or incorrectly stop insulin delivery:

- CGM sensor reads higher or lower than the actual glucose level which increases risk for hypoglycemia and hyperglycemia with automated insulin delivery system;
- Device malfunctions that could produce a suspension of insulin delivery or over delivery of insulin.

1.3.1.8 Potential Risks of Using Lyumjev

Potential adverse reactions with Lyumjev are similar to other insulins: hypoglycemia, hypokalemia, allergic reactions, injection-site reactions, lipodystrophy, localized cutaneous amyloidosis, pruritus, rash,

weight gain, and peripheral edema. Infusion site reactions and discomfort will be carefully monitored for in the study.

1.3.1.9 Other Risks

Data downloaded from the CGM, pump, and the home glucose and ketone meter will be collected for the study. The downloaded data from the participant's home pump will include data from prior to the date of the screening visit and will include data from the period beyond the last 4 weeks prior to screening. Some people may be uncomfortable with the researchers' having such detailed information about their daily diabetes habits.

1.3.2 Benefits

Participants may achieve better glucose control than they are currently achieving using the Control IQ system. It is expected that this protocol will yield increased knowledge about using the Control-IQ system with Lyumjev insulin that will lead to its becoming approved for use.

The individual participant may not benefit from study participation.

1.3.3 Risk Assessment

Based on the facts that (1) study participants are already using the Control-IQ system, (2), mitigations are in place, and have been tested in prior studies using the investigational device system in the home setting, that limit the likelihood of excessive insulin dosing or prolonged withdrawal of insulin, and (3) rapid reversal of hypoglycemia and hyperglycemia can be achieved, it is the assessment of the investigators that this protocol falls under DHHS 46.405 which is a greater than mimimal risk, but also presents prospect of direct benefit to the participants.

1.4 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).

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

The protocol is considered a significant risk device study, due to the fact that the intervention is experimental. Therefore, an investigational device exemption (IDE) from the U.S. Food and Drug Administration (FDA) is required to conduct the study.

Chapter 2: Study Enrollment and Lead-in Period

2.1 Participant Recruitment and Enrollment

Enrollment will proceed with the goal of having up to 200 participants commencing the treatment period so that at least 160 participants complete the trial (approximately 80 participants age 6-<14 years of age, and approximately 80 partipants age 14+). At least 20 participants will be age 14-<18 years of age. A maximum of 200 individuals may be enrolled into screening (ie, be consented) in the study in order to achieve this goal.

Study participants will be recruited from ~10-15 clinical centers in the United States 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.

In addition, there will be a study-wide goal to have at least 1/3 of completers with baseline HbA1c ≥7.5%; and at least 10 completers with basal insulin rate >3 units/hour (for at least part of the day).

Enrollment will be staged, starting with the 14+ cohort. After a cumulative 10,000 hours of use are reached in the age 14+ cohort, a Trial Level Safety Review of all adverse events and device issues will be performed before opening enrollment to the 6-13 year old cohort. Participants in this review will include the Medical Monitor, Sponsor personnel, and a medical representative from Eli Lilly. The decision to proceed with enrollment of younger participants will be driven by the totality of the safety data including any relevant device or drug
data.

2.1.1 Informed Consent and Authorization Procedures

Potential eligibility 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, electronic informed consent will be obtained.

For potential study participants ≥18 years old, the study protocol will be discussed with the potential study participant by study staff. The potential study participant will be given the Informed Consent Form to read. Potential study participants will be encouraged to discuss the study with family members and their personal physicians(s) before deciding whether to participate in the study. If the potential study participant agrees to participate, the Informed Consent Form will be electronically signed through the JCHR website.

For potential participants under 18 years of age, 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 meeting the IRB's minimum age of assent will be given a Child Assent Form to read and discuss with his/her parents and study personnel. If the parent and child agree to participate, the child will provide explicit verbal assent and the Informed Consent Form will be electronically signed by the parent through the JCHR website. Both the parent and the Investigator must attest that the child provided explicit assent. A failure to object or a lack of response shall not be construed to be assent.

A copy of the consent form (and assent form as applicable) will be provided to the participant or 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/parent will be asked to sign an authorization for release of personal information. The investigator, or his or her designee, 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 and authorization have been signed by all applicable parties.

Participants who turn 7 during the course of the study will need to read the Child Assent Form and provide explicit verbal assent as attested by the parent and Investigator. Participants who turn 18 during the course of the study will need to re-consent and provide re-authorization with an adult Informed Consent Form.

2.2 Participant Eligibility Criteria

2.2.1 Inclusion Criteria

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

1. Age 6 to <81 years
2. Diagnosis of type 1 diabetes for at least 1 year
3. Currently using Control-IQ technology for at least 3 months, with CGM data recorded indicative of system use (active closed loop) for at least 85% of the possible time in 14 days prior to enrollment
4. Total daily insulin dose (TDD) at least 2 U/day
5. HbA1c < 10.5%
6. Residing full-time in the United States, with no anticipated travel outside the United States during the period of study participation.
7. For participants <18 years old, living with one or more parent/legal guardian knowledgeable about emergency procedures for severe hypoglycemia and able to contact the participant in case of an emergency, and willing to use the Dexcom Follow app (with push notifications turned on) for the duration of the study.
8. If >18 years old, participant has someone who lives within 30 minutes of them who is willing to be contacted if the study team can't reach the participant in case of a suspected medical emergency.
9. Participant has agreed to participate in the study; and has read, understood and signed the informed consent form (ICF) and assent, if applicable; and has agreed to follow all study procedures, including:
    - suspending use of any personal CGM for the duration of the clinical trial once the study CGM is in use
    - switching to or continuing to use Humalog during the lead-in period
    - switching to Lyumjev for the main study period.
    - willing and able to perform the study exercise and meal challenges.
10. Investigator has confidence that the participant can successfully operate all study devices and is capable of adhering to the protocol, including ability to respond to alerts and alarms, and to provide basic diabetes self-management.
11. Participant and/or parent/legal guardian have the ability to read and understand English

2.2.2 Exclusion Criteria

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

1. More than 1 episode of diabetic ketoacidosis (DKA) in the past 6 months
2. More than 1 episode of severe hypoglycemia (needing assistance) in the past 6 months
3. Inpatient psychiatric treatment in the past 6 months
4. History of drug abuse (defined as any illicit drug use) or history of alcohol abuse prior to screening or unwillingness to agree to abstain from illicit drugs throughout the study.
5. For Female: Currently pregnant or planning to become pregnant during the time period of study participation
    - *A negative pregnancy test will be required for all females of child-bearing potential (menarchal)*
    - *Counseling on appropriate birth control options will be provided to females with child-bearing potential in the event the participant does not have an acceptable plan.*
6. Adults lacking the capacity to provide consent and/or follow study procedures in the opinion of the investigator
7. Concurrent use of any non-insulin glucose-lowering agent, other than metformin (for example, GLP-1 agonists, Symlin, DPP-4 inhibitors, SGLT-2 inhibitors, sulfonylureas).
8. Hemophilia or any other bleeding disorder
9. Hemoglobinopathy
10. History of heart, liver, lung or kidney disease determined by investigator to interfere with the study
11. History of allergic reaction to Humalog or Lyumjev
12. Use of glucocorticoids, beta blockers or other medications determined by investigator to interfere with study
13. Abnormal screening electrocardiogram consistent with increased risk during exercise, such as arrhythmia, ischemia, or prolonged QTc interval (>450 ms) (Screening ECG only required for participants age > 50 years, duration of diabetes > 20 years, or history of coronary artery disease)
14. Significant chronic kidney disease (which could impact CGM accuracy in investigator's judgment) or hemodialysis
15. History of adrenal insufficiency
16. History of abnormal TSH consistent with hypothyroidism or hyperthyroidism that is not appropriately treated
17. History of gastroparesis
18. A condition, which in the opinion of the investigator or designee, would put the participant or study at risk
19. Participation in another pharmaceutical or device trial at the time of enrollment or anticipated for during the time period of study participation

20. Employed by, or having immediate family members employed by Tandem Diabetes Care, Inc., Eli Lilly and Co., or TypeZero Technologies, LLC, or having a direct supervisor at place of employment who is also directly involved in conducting the clinical trial (as a study investigator, coordinator, etc.); or having a first-degree relative who is directly involved in conducting the clinical trial

2.3 Screening Procedures

After informed consent has been signed, 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 local laboratory testing if needed to screen for exclusionary medical conditions.

2.3.1 Data Collection and Testing

A standard physical exam (including vital signs and height and weight measurements) will be performed by the study investigator or designee (a physician, fellow, nurse practitioner or a physician assistant).

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
- Substance use history (drinking, smoking, and drug habits)
- Concomitant medications
- Physical examination to include:
  - Weight, height
  - Vital signs including measurement of blood pressure and pulse
- Blood draw (venipuncture or fingerstick) for local HbA1c measurement
- Urine pregnancy test (test not required for any female that has not reached menarche, is surgically sterile, or is at least 1 year post-menopausal)
  - For those not excluded from testing, counseling on appropriate birth control options will be provided in the event the participant does not have an acceptable plan.
- ECG performed at screening for participants age > 50 years, duration of diabetes > 20 years, or history of coronary artery disease
- Completion of the following patient-reported outcomes (PRO) surveys by the participant (age 14+) or parent: TRIM-D, Trim-DD (Diabetes Device), ITSQ (Insulin Treatment Satisfaction Questionnaire)

Screening procedures will last approximately 1-2 hours.

2.4 Screen Failures

Individuals who do not initially meet study eligibility requirements may be rescreened one more time at a later date per investigator discretion.

2.5 Lead-in Period

All participants will complete the Lead-in Period as an outpatient for approximately 16 days. The Lead-in Period may begin the same day the screening visit is completed or within 4 weeks after informed consent is signed. The lead-in period will last at least 16 days and no more than 21 days.

At the initiation of the Lead-in Period (CIQ 1.5/ Humalog Training Visit), participants will switch from their current Control-IQ system to the study pump (Control-IQ 1.5 technology), study sensor, and study-provided Humalog (insulin lispro injection). Training will be provided by qualified study staff on the study pump, the study CGM sensor, the study glucose meter, and the study ketone meter. The study investigator may adjust insulin delivery profile settings as indicated.

During the lead-in period, each participant will perform one meal and exercise challenge to determine a baseline using Humalog and Control-IQ 1.5. Those day and overnight periods will be analyzed separately. Procedures are described in section 5.1. A minimum of 48 hours will occur between all challenges for each participant.

After 16 days (and up to 21 days), the participant will have a visit. System use will be assessed and to proceed to the Treatment Period, it is necessary that a participant used the Control-IQ system, with at least 85% of system use (active closed loop) reported over the time of the lead-in period (ie, minimum of 85% of 14 days).

The lead-in period data collection may be repeated if this threshold is not met.

Chapter 3: Treatment Period

3.1 CIQ 1.5/ Lyumjev Training Visit

At the end of the Lead-in Period, participants will have a clinic visit at which their use of the CIQ 1.5 system with Humalog will be assessed. Participants who successfully used the system with at least 85% of system use (active closed loop) will undergo device training with Lyumjev in the study pump.

A blood sample (venipuncture or fingerstick) will be obtained to send to the central laboratory for HbA1c measurement.

Participants will receive supplies for blood glucose and ketone testing. QC testing will be performed on the meters before they are dispensed.

3.1.1 Training on System Use

All participants will receive study system training from a qualified trainer. Since all of the participants will be experienced Control-IQ users, the amount of training will be customized for each participant. For pediatric participants, a parent (or legal guardian) will be required to attend the training procedures.

At a minimum training will include the following:

- Calibration of the CGM in accordance with manufacturer labeling
- Use of Lyumjev in the study pump
- Procedures for treating severe hypoglycemia
- Procedures for identifying potential infusion set failure and steps to take including the checking of the blood ketone level and changing the infusion set

The participant will be given a User Guide as a reference as well as Hypoglycemia and Hyperglycemia Guidelines.

Participants will be instructed to download the study device prior to each phone contact or office visit.

The participant will be instructed to use the system in closed-loop mode except 1) when no calibrated CGM sensor is available or 2) if insulin is delivered by any means other than the study pump (e.g. injection of subcutaneous insulin via syringe in the event of infusion site failure). If insulin is delivered by any means other than the study pump, participant will be instructed to turn off Control-IQ for four hours.

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.

Participants will be provided with contact information and will be asked to call the study clinical staff for any health-related issues and for technical issues with the system. Participants may use the study pump without Control-IQ activated and study CGM during periods of component disconnections or technical difficulties.

Adult participants may use available manufacturer-provided CGM software and features of the study CGM related to mobile data access or remote monitoring, but will be instructed not to use any third-party components for this purpose. For pediatric participants, the parent/caregiver will use the Dexcom Follow app (with push notifications turned on) for the duration of the study.

The t:connect mobile app from Tandem Diabetes Care will not be available for use during the trial, and will not pair to the study pump.

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.

Following the CIQ 1.5/Lyumjev Training Visit, participants will use the study pump and the investigational insulin for ~90 days during the Treatment Period.

3.1.2 Training on Management of Hypoglycemia

The t:slim X2 with Control-IQ system will issue a predictive hypoglycemia alert (Control-IQ Low Alert) when the system predicts BG <70 mg/dL within the next 15 minutes (<80 mg/dL when exercise mode is activated). Participants will be permitted to change the CGM low glucose threshold alert setting on their device or mobile app, but will be instructed to choose a value no less than 70 mg/dL.

If the participant receives a Control-IQ Low Alert, a message appears on the user interface (UI) that is accompanied by vibration followed by vibrations and/or sound if not acknowledged by the user in 5 minutes. This alert remains on the screen until acknowledged by the participant. The user is prompted to test blood glucose and treat with carbohydrate.

The participant and companion if available will be instructed that if severe hypoglycemia occurs, the study pump's insulin delivery should be suspended and glucagon administration if the participant is unable to consume carbohydrate.

Participants will be required to have a home glucagon emergency kit. Participants who currently do not have one will be given a prescription for the glucagon emergency kit.

3.1.3 Training on Management of Hyperglycemia

The t:slim X2 with Control-IQ system will issue a predictive hyperglycemia alert (Control-IQ High Alert) when the system has increased insulin delivery, but detects a CGM value above 200 mg/dL and does not predict the value will decrease in the next 30 minutes. 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 the participant receives a Control-IQ High Alert, a prompt appears on the user interface to check the site for occlusion and test blood glucose.

If a participant's CGM reading is >300 mg/dL for more than 60 minutes or is ≥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 ≥ 0.6 mmol/L (or ≥ 2.5 mmol\L at any time), take correction insulin, change insulin (pump) infusion site and contact study staff. Continue to monitor their glucose and blood ketone levels until they return to normoglycemia and ketones are < 0.6 mmol/l.
    - If ketones are <0.6 mmol/l, they will be advised to continue to monitor their glucose until it returns to normoglycemia and to repeat the ketone measurement in 90 minutes if necessary
- If correction insulin is administered via insulin syringe, turn Control-IQ off for four hours and until glucose level has returned to <180 mg/dL.

3.1.4 Participant Reporting of Infusion Set Insertion Reactions

Participants will receive a weekly contact (phone, email and/or text message) to assess any issues related to their current infusion site.

Participants will be instructed to take a photo at time of removal of the first 2 infusion sets and subsequently photo at the time of removal only if there is redness on skin when the infusion set is removed. Additional photos may be needed if during a virtual visit, video is not available.

3.1.5 Adjustments in Insulin Pump Settings

Insulin and glucose data from the Lead-in Period will be reviewed and the site investigator may adjust insulin delivery profile settings as needed in accordance with their clinical practice.

3.2 Study Visits and Phone Contacts

Participants will have a phone (or video-conference) follow-up visit at 3 days, 1 week, 2 weeks, and 3 weeks, a clinic follow-up visit at 6 weeks, a phone follow-up visit at 9 weeks, and a final clinic visit at 13 weeks, within the windows specified below.

TARGET DAY/WEEK	VISIT OR PHONE	TARGET WINDOW (AROUND TARGET DAY/WEEK)
3 day	P	±1 day
1 week	P	±2 days
2 week	P	±2 days
3 weeks	P	±7 days
6 weeks	V	±7 days
9 weeks	P	±7 days
13 weeks	V	91-98 days

If necessary, visits should be completed out-of-window rather than missed. A visit is not considered missed until the next visit/phone window opens.

The goal will be for all participants to complete all scheduled visits. However, participants who (because of unforeseen circumstances or due to changes in contact precautions that may be needed during the evolving COVID-19 pandemic) are unable or unwilling to return for all follow-up visits will be permitted to return for key visits only as an alternative to withdrawal from the study. When a participant is placed into this status, missed visits will not be recorded as protocol deviations (since they would not be recorded as protocol deviations if the participant was dropped from the study).

Additional office visits may occur as needed.

3.2.1 Procedures During Phone Contacts

Phone contacts can be with or without video. Phone contacts will include the following:

- Assessment of device issues that have occurred
- Assessment of adverse events (such as hyperglcyemia, hypoglcyemia, and infusion set reactions) using open ended questions, and their underlying cause and relationship to the study device, study insulin or other parts of the system (such as the infusion set).

- Completion of a detailed case report form with respect to any infusion site reactions that have occurred.

For the first three contacts (3 day, 1 week, 2 week), if a video virtual visit can be done, visual inspection will be performed of the current and most recent infusion set insertion site. If video is not possible, then the participant will be requested to take a photo of the current and most recent infusion set insertion sites.

3.2.2 Procedures at Study Visits

The following procedures will be performed at each visit, unless otherwise specified:

- Review of study device data
- Assessment of compliance with study device use by review of any available device data
- Assessment of device issues that have occurred
- Assessment of adverse events, using open ended questions to capture hyperglycemic and hypoglycemic events, and their underlying cause and relationship to the study device, study insulin or other parts of the system (such as the infusion set).
- A focusesd physical exam to include skin and infusion sites will be performed at each in person visit.
- Completion of a detailed case report form with respect to any infusion site reactions that have occurred.

At 13 weeks, the following additional procedures will be performed:

- Blood draw (venipuncture or fingerstick) for HbA1c measurement at central lab (13 weeks only)
- Completion of the following PRO surveys by the participant (age 14+) or parent: TRIM-D, Trim-DD (Diabetes Device), ITSQ (Insulin Treatment Satisfaction Questionnaire)

3.2.3 Unscheduled Visits

Participants may have unscheduled visits during the study period if required for additional device training or other unanticipated needs per the study investigator discretion.

3.3 Exercise and Meal Challenges

Participants will complete 3 meal and 3 exercise challenges during Lyumjev use. Procedures are described in section 5.1.

3.4 Early Discontinuation of Study Device

Participants who discontinue the study device prior to 13 weeks, either by choice or by investigator decision, will be asked to come for an end of study visit and then will be dropped from the study. If the visit occurs at 6 weeks or after, blood will be drawn for the central-lab HbA1c measurement and the PROs will be completed.

Chapter 4: Study Devices and Drugs

4.1 Study Devices

The investigational device (CLC system) includes an insulin pump and a continuous glucose monitor.

4.1.1 Insulin Pump

The study system will include the Tandem t:slim X2 with Control-IQ technology.

4.1.2 Continuous Glucose Monitoring

The study CGM that is part of the CLC system is the Dexcom G6, which includes a transmitter and sensors. The CGM sensor will be replaced at least once every 10 days.

4.1.3 Blood Glucose Meter

The study blood glucose meter is the Contour® NEXT (Ascencia Diabetes Care).

Blood glucose levels will be measured using the study's blood glucose meter (glucometer) and the CGM device will be calibrated if needed using the study glucometer and strips in accordance with the manufacturer's labeling.

4.1.4 Ketone Meter

The study blood ketone meter is the Precision Xtra Blood Glucose and Ketone Monitoring System (Abbott Diabetes Care).

Blood ketone levels will be measured when needed to evaluate prolonged hyperglycemia. The blood glucose meter component of the Precision Xtra device will not be used.

4.2 Study Drug

The study drug is Lyumjev (insulin lispro-aabc). The drug is a formulation of insulin lispro that includes the addition of two excipients, treprostinil and sodium citrate. Treprostinil enhances absorption by local vasodilatation without eliciting a systemic effect while citrate further enhances the speed of absorption.

- **Acquisition**

  Study drug will be shipped by Eli Lilly to the study's central pharmacy for distribution to the clinical sites.

- **Formulation, Appearance, Packaging, and Labeling**

  LYUMJEV (insulin lispro-aabc) injection is a sterile, aqueous, clear, and colorless solution for subcutaneous or intravenous administration. Each mL of LYUMJEV U-100 contains 100 units of insulin lispro-aabc and the inactive ingredients: glycerol (12.1 mg), magnesium chloride hexahydrate (1.02 mg), metacresol (3.15 mg), sodium citrate dihydrate (4.41 mg), treprostinil sodium (1.06 mcg), zinc oxide (content adjusted to provide 39 mcg zinc ion), and Water for Injection, USP.

- **Product Storage and Stability**

  Dispense in the original sealed carton with the enclosed Instructions for Use.

  Refrigerate unopened LYUMJEV vials between 36°F to 46°F (2°C to 8°C) until time of use and keep in the original carton to protect from light. Do not freeze or use LYUMJEV if it has been

frozen. Do not expose to direct heat. Discard opened or unopened LYUMJEV vials stored at room temperature below 86°F (30°C) after 28 days.

Change the LYUMJEV U-100 in the pump reservoir at least every 9 days, or according to the pump user manual, whichever is shorter, or after exposure to temperatures that exceed 98.6°F (37°C).

	Not in-use (Unopened)		In-use (Opened)	
	Room Temperature (below 86 F [30 C])	**Refrigerated (36 F to 46 F [2 C to 8 C])**	**Room Temperature (below 86 F [30 C])**	**Refrigerated (36 F to 46 F [2 C to 8 C])**
10 mL vial [a,b]	28 days	Until expiration date	28 days	28 days

a In-use (opened) vials, whether or not refrigerated, must be used within 28 days.
b When stored at room temperature, LYUMJEV can only be used for a total of 28 days including both not in-use (unopened) and in-use (opened) storage time.

4.3 Study Device and Drug Accountability Procedures

Device and drug accountability procedures will be detailed in the clinical center procedures manual.

4.4 Participant Access to Study Device at Study Closure

Participants will return all investigational study devices and supplies (insulin pump, CGM and related supplies, and unused insulin) at their final visit. Participant may keep the study ketone meter and study glucometer if these devices are not marked for investigational use only.

Chapter 5: Testing Procedures and Questionnaires

5.1 Meal and Exercise Challenges

Participants will complete 1 missed meal bolus and 1 exercise challenge during the Humalog lead-in period, then 3 meal and 3 exercise challenges during Lyumjev use.

A minimum of 48 hours will occur between all challenges for each participant.

Participants will be instructed to communicate with study staff within one day prior to each challenge to review procedures and to have a contact with study staff after the completion of each challenge.

5.1.1 Meal Challenges

The same meal should be used for each of the four meal challenges—either lunch or dinner (participant choice).

For the lead-in phase meal challenge, no bolus will be given for the meal.

During Lyumjev use, the three meal challenges will consist of:

- No bolus for the meal
- 50% bolus - calculate the bolus dose using the bolus calculator, and deliver half the recommended dose of insulin.
- Full bolus for the meal based on calculated bolus dose using the bolus calculator.

For each meal challenge, participants will:

1. Be in a fasting state for two hours prior to consuming the meal and the last manual insulin bolus more than two hours ago.
2. Only begin the meal challenge if the glucose is between 70 mg/dL and 200 mg/dL. *Subjects with hyperglycemia > 200mg/dL will reschedule their challenge for another time. If < 70 mg/dL, carbohydrate treatment can be given and then continue.*
3. Consume at least 50 grams carbohydrate for the meal. *Each participant will use the same meal for all of their meal challenges in the study. Participants will be encouraged to use the same frozen entrée of their choice for consistency.*
4. Write down the start and end time of eating the meal, as well as the meal content (to include amount of carbohydrate, protein and fat) on the study provided logbook.
5. Not give an additional bolus for up to 3 hours after the meal challenge, unless BG is above 300 mg/dL for more than 1 hour, or symptoms of hyperglycemia develop.
6. Not take additional carbohydrates for up to 3 hours after the meal challenge, unless BG is < 70 mg/dL, or symptoms of hypoglycemia develop.
7. Not exercise for 3 hours after the meal challenge.

For pediatric participants, caregivers/parents will be instructed to:

- Be physically present with the participant and monitor CGM glucose during the 3 hours of each meal bolus challenge timeline.
- Follow the study hypoglycemia and hyperglycemia safety guidelines, as well as the above guidelines for the challenge.

- Be in same residence with the participant for the overnight period after the challenges and to continue to monitor the participant.

5.1.2 Exercise Challenges

For each exercise challenge, participants will:

1. Have extra carbohydrate containing snacks and glucagon on hand during and after exercise.
2. Per their usual routine and investigator guidance, consider activation of "exercise activity" on the pump up to 45 minutes ahead of actual exercise, to allow for less insulin on board when starting exercise.
3. Consider reducing the last meal bolus prior to exercise as a way to reduce insulin on board and limit hypoglycemia.
4. Perform two hours of exercise, including at least one hour of moderate activity
5. Only begin exercise if CGM glucose is ≥ 120 mg/dL and CGM glucose is not trending downward.
6. Write down the time of last meal and amount and time of last insulin dose, type of exercise performed, as well as the start and stop time of each exercise session in the study logbook *(as this may not correlate exactly with exercise activity use on the pump)*.
7. Stop the exercise challenges at any point for injury or development of new symptoms (development of chest pain/pressure, feeling unwell, development of hypoglycemic symptoms, undue shortness of breath, signs of poor perfusion (leg pain/claudication), or for any other reason.
8. Notify the site within 24 hours after completion of each exercise challenge if they develop new symptoms and review guidance on the need to stop future exercise challenges if any adverse events or new symptoms occurred per clinician judgement based on the severity of symptoms.

For pediatric participants, caregivers/parents will be instructed to:

- Be physically present with the participant and monitor CGM glucose during and through 2 hours after the exercise challenge completes.
- Follow the study hypoglycemia and hyperglycemia safety guidelines, as well as the above guidelines for the challenge.
- Be in same residence with the participant for the overnight period after the challenges to continue to monitor the participant.

5.2 Laboratory Testing

5.2.1 HbA1c

HbA1c measurement will be performed locally at the Screening visit.

An additional blood sample will be obtained (venipuncture or fingerstick) and sent to central lab at the CIQ 1.5/Lyumijev Training visit and at the 13-week visit.

5.2.2 Urine Pregnancy

Urine pregnancy testing performed locally at clinical site for females of child-bearing potential at the Screening visit and anytime pregnancy is suspected.

5.3 Questionnaires

Questionnaires are completed during Screening and at the time of the 13-week visit. Each questionnaire is described briefly below. Questionnaires will be completed by participants age 14 years and older, and by parent/guardian for younger participants. The procedures for administration are described in the study procedures manual.

Each questionnaire is described briefly below. The procedures for administration are described in the study procedures manual.

MEASURE	DESCRIPTION
Treatment Related Impact Measure of Diabetes (TRIM-D)	28-item measure with 5 domains assessing treatment burden, daily life, diabetes management, compliance and psychological health. Higher score indicates a better health state
Treatment Related Impact Measure of Diabetes Device (TRIM-DD)	8-item measure with 2 domains assessing Device Bother and Device Function. Higher score indicates a better health state
Insulin Treatment Satisfaction Questionnaire (ITSQ)	22-item measure with a 5-factor structure assessing insulin satisfaction: satisfaction with insulin delivery device, glycemic control, hypoglycemic control, convenience of regimen and lifestyle flexibility. Scores range from 0 to 100 with higher score indicating a better health state

Chapter 6: Unanticipated Problem, Adverse Event, and Device Issue Reporting

6.1 Unanticipated Problems

Site investigators will promptly report to the Coordinating Center on an eCRF 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 a pharmacy or laboratory. These instances must be reported to the JCHR IRB within seven calendar days of recognition. The Director of the Human Research Protection Program (HRPP) will report to the appropriate regulatory authorities to fulfill the obligations of the HRPP if the IRB determines that the event indeed meets the criteria of an Unanticipated Problem requiring additional reporting.

6.2 Adverse Events

6.2.1 Definitions

Adverse Event (AE): Any untoward medical occurrence (including laboratory findings) associated with study procedures, the use of a device, biologic in a study participant, including any comparator used, irrespective of the relationship between the adverse event and the device(s) under investigation (referred to as *Adverse Reaction* when caused by a drug).

Serious Adverse Event (SAE): Any untoward medical occurrence that meets at least one of the following:

- 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).

Suspected Adverse Reaction: any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug (21 CFR 312.32(a)).

Suspected Unexpected Serious Adverse Reaction (SUSAR): any adverse event considered to be related to a drug that is both unexpected and meets criteria for an SAE. *Unexpected* means that the adverse reaction is not listed in the investigator brochure or protocol 21 CFR 312.32(a).

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 investigational plan or application (including a supplementary plan or application), 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 section 6.2.2).

Comparator: Medical device, therapy (e.g. active treatment, normal clinical practice), placebo or no treatment, used in the control group in a clinical investigation. (ISO 14155:2020)

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.

Use Error: User action or lack of user action while using the medical device (3.34) that leads to a different result than that intended by the manufacturer or expected by the user. Includes the inability of the user to complete a task. Use errors can result from a mismatch between the characteristics of the user, user interface, task or use environment. Users might be aware or unaware that a use error has occurred. An unexpected physiological response of the patient is not by itself considered a use error. A malfunction of a medical device that causes an unexpected result is not considered a use error. (ISO 14155:2020)

6.2.2 Reportable Adverse Events

A reportable adverse event includes all events meeting the definition of an adverse event, except for the following:

- Hypoglycemia and hyperglycemia not meeting the criteria below will not be recorded as adverse events unless associated with an Adverse Device Effect or discontinuation of the study device or study drug.
- Skin reactions from sensor or pump infusion set placement are only reportable as everse advents if severe and/or required treatment (see section 6.2.5).

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.

6.2.3 Hypoglycemic Events

Hypoglycemia not associated with an Adverse Device Effect or discontinuation of the study device or study drug is only reportable as an adverse event when one of the following criteria is met:

- a hypoglycemic event occurred meeting the following definition of severe hypoglycemia: 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 glucose measurements are not available during such an event, neurological recovery attributable to the restoration of glucose to normal is considered sufficient evidence that the event was induced by a low glucose concentration.
- evaluation or treatment was obtained at a health care provider facility for an acute event involving hypoglycemia, or the participant contacted the site and received guidance following the occurrence of an acute event involving hypoglycemia

When a severe hypoglycemia event occurs (as defined above), 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. When a severe hypoglycemia event occurs during use of a study device, it generally will be considered to be unrelated to the device (per section 6.2.6) if the device functioned as intended and there does not appear to be a flaw in how the device is intended to function.

6.2.4 Hyperglycemic/Ketotic Events

Hyperglycemia not associated with an Adverse Device Effect or discontinuation of the study device or study drug is only reportable as an adverse event when one of the following 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 ≥1.0 mmol/L, even if there was no communication with a health care provider at the time of the event

Hyperglycemic events are classified as DKA if the following are present:

- 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 (or CO2) <15; and
- Treatment provided in a health care facility

When a hyperglycemia/ketotic event qualifies as an SAE as defined in section 6.2.1, 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 6.2.1 is met.

When a hyperglycemia/DKA event occurs during use of a study device, it generally will be considered to be unrelated to the device (per section 6.2.6) if the device functioned as intended and there does not appear to be a flaw in how the device is intended to function.

6.2.5 Skin Reactions Related to Infusion Set

When a skin reaction related to the infusion set is considered to be mild or moderate in nature, an infusion site reaction case report form will be completed at each scheduled visit and phone contact, or in response to the weekly contact from the sites. When a skin reaction related to the infusion set is considered severe or treatment was received, an infusion site reaction case report form and an Adverse Event Form also will be completed.

6.2.6 Relationship of Adverse Event to Study Investigational Device

The study investigator will assess the relationship of any adverse event to the study device or study drug. The Medical Monitor also will make this assessment, which may or may not agree with that of the study investigator. Reporting requirements will be based on the Medical Monitor's assessment.

To ensure consistency of adverse event causality assessments, investigators should apply the following general guidelines when determining whether an adverse event is related to a study device or study drug:

Unrelated: The AE is clearly not related to a study drug/device and a likely alternative etiology exists such as an underlying disease, environmental or toxic factors or other therapy.

Unlikely Related: The AE does not follow a reasonable temporal sequence during or after use of study drug/device and a more likely alternative etiology exists such as an underlying disease, environmental or toxic factors, or other therapy.

Possibly Related: The AE occurred in a reasonable time during or after use of study drug/device; but could be related to another factor such as an underlying disease, environmental or toxic factors, or other therapy; and there is a possible, though weak, scientific basis for establishing a causal association between the AE and the study drug/device.

Probably Related: The AE occurred in a reasonable time during or after use of study drug/device; is unlikely to be related to another factor such as an underlying disease, environmental or toxic factors, or other therapy; and there is a plausible, though not strong, scientific basis for establishing a causal association between the AE and the study drug/device.

Definitely Related: The AE occurred in a reasonable time during or after use of study drug/device; cannot be explained by another factor such as an underlying disease, environmental or toxic factors, or therapy; and there is a strong scientific basis for establishing a causal association between the AE and the study drug/device.

Events determined to be *Possibly Related*, *Probably Related*, or *Definitely Related* will be considered 'Related' with respect to any required IRB and FDA reporting.

6.2.7 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.

6.2.8 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 risk information previously described in the protocol, labeling, or Investigator Brochure.

6.2.9 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 causality as well as whether an event is classified as a serious adverse event and/or an unanticipated adverse device effect.

6.2.10 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 as UADEs or related SAEs or SUSARs 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.

6.3 Reportable Device Issues

All UADEs and ADEs as defined in section 6.2.1 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.

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
- Pump infusion set insertion lasting fewer days than expected per manufacturer
- 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

6.4 Timing of Event Reporting

SAEs possibly related to a study device, study drug, or study participation and UADEs and SUSARs must be reported by the investigator 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 on the on line form within 7 days of the site becoming aware of the event.

The Coordinating Center will notify all participating investigators 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.

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. Where the JCHR IRB is the overseeing IRB, sites must report all serious, related adverse events within seven calendar days.

Upon receipt of a qualifying event, the Sponsor will investigate the event to determine if a UADE has occurred, and if indicated, report the results of the investigation to all overseeing IRBs, and the FDA within 10 working days of the Sponsor becoming aware of the UADE per 21CFR 812.46(b). A SUSAR must be reported within 7 calendar days if life threatening and 15 calendar days if not life threatening per 21 CFR 312.32(c)(2). The Sponsor in conjunction with the Medical Monitor must determine if the UADE presents an unreasonable risk to participants. If so, the Sponsor must ensure that all investigations, or parts of investigations presenting that risk, are terminated as soon as possible but no later than 5 working

days after the Sponsor makes this determination and no later than 15 working days after first receipt notice of the UADE.

The investigators are also required to report, without unjustified delay, all device deficiencies that could have led to a UADE, including device deficiencies, irrespective of whether an adverse event occurred.

6.5 Safety Oversight

The study Medical Monitor will review all adverse events and adverse device events that are reported during the study and assess the relationship to the study device/drug. SAEs typically will be reviewed within 24 hours of reporting. Other AEs typically will be reviewed on a weekly basis. Additionally, the Medical Monitor will review compiled safety data at periodic intervals.

The Sponsor will be informed of all reported adverse evens and the Medical Monitor's assessment of relationship to the study device/drug; and informed of all reported device issues.

6.6 Stopping Criteria

6.6.1 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 study device will be suspended while the problem is diagnosed. The UADE will be reported to the IRB and FDA. After assessment of the problem and any correction, use of the study device will not be restarted until approval is received from the IRB and FDA.

In the absence of a device malfunction, use of the study device 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 intervention. 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 pregnancy
- Two distinct episodes of DKA as defined in section 6.2.3
- Two distinct severe hypoglycemia events as defined in section 6.2.3
- One episode of DKA as defined in section 6.2.4 and one severe hypoglycemia event as defined in section 6.2.3

Each DKA, severe hypoglycemia event, or significant infusion site reaction will be reviewed by the Medical Monitor and by the Sponsor with respect to determination of cause and whether the occurrence of the event can be attributed to use of the study device or study drug.

An additional requirement for continued study device use following a single DKA or severe hypoglycemia event will be that the site investigator believes that the event is unlikely to recur and that it is safe for the participant to continue to use the system. Additionally, if the Medical Monitor determines that the occurrence of the event indicates that it is not safe for the participant to continue to use the study device, use will be discontinued.

6.6.2 Criteria for Suspending or Stopping Overall Study

In addition to the suspension of device use due to a UADE as described in section 6.2.1, study activities could be similarly 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 resume if the underlying problem can be corrected by a protocol or system modification that will not invalidate the results obtained prior to suspension.

In addition to the suspension of closed-loop mode use due to a UADE as described above, closed-loop system use will be suspended for a root cause analysis if there are 5 or more cases of severe hypoglycemia or five or more cases of hyperglycemia/ketotic events qualifying as SAEs across the entire study in participants who have initiated Control-IQ technology use.

For pediatric participants, the study will be suspended for that cohort for a root cause analysis if there are 3 or more cases of severe hypoglycemia or 3 or more cases of hyperglycemia/ketotic events qualifying as SAEs across the pediatric participants who have initiated Control-IQ technology use.

Chapter 7: Miscellaneous Considerations

7.1 Drugs Used as Part of the Protocol

Humalog (insulin lispro) will be used during the Lead-in Period and Lyumjev (insulin lispro-aabc) will be used during the Treatment Period.

7.2 Collection of Medical Conditions and Medications

Pre-Existing Conditions: 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) will be recorded.

Medical Conditions Developing During the Study: Medical conditions that develop or worsen during the study will be recorded as adverse events.

Medications: All medications for in use at the time of screening or added during the course of the study will be recorded. Nutraceuticals and preventative treatment also will be recorded. 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.

7.3 Prohibited Medications, Devices, Treatments, and Procedures

Treatment with any insulin other than study-provided insulin and treatment with a non-insulin glucose-lowering agent, other than metformin, is not permitted, including GLP-1 agonists, Symlin, DPP-4 inhibitors, SGLT-2 inhibitors, sulfonylureas.

The investigational study devices (t:slim X2 insulin pump, Dexcom CGM sensor) must be removed before magnetic resonance imaging (MRI), computed tomography (CT) or diathermy treatment. Participants may continue in the trial after temporarily discontinuing use if requiring one of the above.

7.4 Rescue Medications, Treatments, and Procedures

Each participant will be required to have a glucagon preparation for rescue therapy for severe hypoglycemia.

7.5 Pregnancy Reporting

If pregnancy occurs, the participant will be discontinued from the study. The occurrence of pregnancy will be reported to the Coordinating Center within seven days and to the JCHR IRB as an Unanticipated Problem within seven calendar days.

7.6 Participant Compensation

Participant compensation will be specified in the informed consent form.

7.7 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.

7.8 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 8: Statistical Considerations

8.1 Statistical and Analytical Plans

The approach to sample size and statistical analyses are summarized below.

8.2 Statistical Hypotheses

The primary objective of the study is assessment of safety. Therefore, there is no formal statistical hypothesis testing for efficacy. Safety endpoints will be compared with historical published data.

8.3 Sample Size

The sample size of 160 completers of the trial was selected to have reasonable precision for assessing safety endpoints and is not based on statistical principles.

8.4 Outcome Measures

Key Safety Endpoints

- Severe hypoglycemia as defined in section 6.2.3
- Diabetic ketoacidosis as defined in section 6.2.4
- Unanticipated adverse device effects
- Other serious adverse events
- Adverse drug reactions

Secondary Safety Endpoints

- All reportable adverse events
- CGM hypoglycemia outcomes
  - Overall % time <54 mg/dL
  - Postprandial % time <54 mg/dL (30 min, ≤1, ≤2, ≤4, >1 to ≤2 and >2 to ≤4hr)
  - Overall and postprandial % time <70 mg/dL
  - Rate of hypoglycemia events defined as 15 or more consecutive minutes <54 mg/dL

Exploratory Endpoints

- Postprandial incremental area under the glucose curve (4 hr)
- Peak postprandial glucose
- Times in ranges-overall and postprandial (70-180 mg/dL, >180 mg/dL, >250 mg/dL, 70-140 mg/dL)
- Mean glucose
- Rate of hyperglycemia events, defined as 90 or more minutes >300 mg/dL within 120 minutes
- Overall variability (CV and SD)
- HbA1c change from baseline
- CGM metrics for hypoglycemia, hyperglycemia, and variability during daytime and nighttime

Patient-Reported Outcomes

- TRIM-D
- Trim-DD
- ITSQ

8.5 Analysis Datasets

For the main analyses, adult and pediatric participants will be pooled. Secondarily separate analyses will be conducted for adults (>18 years) and pediatric (<18 years) participants. Further exploratory analyses will be conducted within pediatric subgroups.

All participants who initiate the Treatment Period and use the study device with the study drug will be included in the safety analyses.

For inclusion in the analysis of CGM metrics, participants must have at least 24 hours of CGM data during the Treatment Period.

8.6 Statistical Methods

8.6.1 Analysis of the Safety Event Endpoints

Safety events (ie, not including CGM defined events) will be tabulated for each type of event as the number of events per participant, the number of participants with > 1 event, and the rate of events per 100 person-years.

Since study eligibility excluded participants with 2 or more severe hypoglycemia or DKA events in the prior 6 months, an unbiased comparison of the event rate during the Treatment Period with the pre-study event rate is not possible. Therefore, the severe hypoglycemia and DKA event rates will be compared with the T1D Exchange data,[5] which reported the frequency of 1 or more severe hypoglycemia and DKA events in the prior 3 months according to age group; this will allow for age-matching with this trial. The proportion of participants with events during the Treatment Period will be compared with the T1D Exchange frequency using Barnard's exact test. Study endpoint will be met if severe hypoglycemia and DKA event rates are not significantly higher during follow-up compared with T1D Exchange frequency.

8.6.2 Analysis of CGM Endpoints

CGM metrics will be computed for (1) 4 weeks pre-study (personal CGM), (2) Lead-in Period, and (3) Treatment Period. CGM metrics will be computed over 24 hours, during daytime (6am-11:59pm), during nighttime (12mn-5:59am), and during scheduled exercise and meal challenges.

The main statistical comparison will be made between the Treatment Period and the Lead-in Period. The lead-in period time for analysis will exclude the day and night of the baseline exercise and meal challenges. Additionally the Treatment Period will be compared with the pre-study CGM data.

Linear mixed models will be used to test the change from pre-Treatment Period to Treatment Period. Missing data will be handled by the method of direct likelihood, which assumes outcomes are missing at random and estimates follow-up values via maximimum likelihood. Sensitivity analyses will be performed to assess the robustness of the results under different missing data assumptions.

8.6.3 Analysis of HbA1c and PRO Measures

Linear mixed models will be used to test the change in HbA1c and PRO scores from baseline to 13 weeks. Missing data will be handled by the method of direct likelihood, which assumes outcomes are missing at random and estimates follow-up values via maximimum likelihood.

8.7 Intervention Adherence

The following tabulations will be performed:

- Sensor use–percent time of use
- Closed loop system use–percent time of use
- % time in different operational modes

8.8 Protocol Adherence and Retention

The following tabulations and analyses will be performed to assess protocol adherence for the study:

- Number of protocol deviations
- Flow chart accounting for all enrolled participants
- Number of and reasons for unscheduled visits and phone calls
- Number of participants who were enrolled but did not enter the Treatment Period and reasons
- Number of participants who stopped treatment and reasons

8.9 Baseline Descriptive Statistics

Baseline demographic and clinical characteristics of the cohort of participants who initiate the Treatment Period will be summarized in a table using summary statistics appropriate to the distribution of each variable. Descriptive statistics will be displayed by treatment group for the following:

- Age
- Sex
- Race/Ethnicity
- Socio-economic factors (income, education, and/or insurance status)
- Diabetes duration
- HbA1c
- BMI
- Total daily insulin
- Prior severe hypoglycemia and DKA events
- Baseline CGM metrics

8.10 Additional Tabulations and Analyses

The following data will be tabulated at baseline and at or over 13 weeks

- Insulin metrics (units/kg): total daily insulin, total daily basal insulin, total daily bolus insulin (plus total daily manual bolus, total daily automated bolus)
- Weight
- Number and type of infusion set reactions

8.11 Device Issues

The following tabulations will be performed with respect to device issues:

- Reported device issues according to type of issue

8.12 Planned Interim Analyses

No formal interim analyses are planned.

8.13 Subgroup Analyses

Results will be tabulated according to age group, HbA1c, and total daily insulin. Additional subgroups will be defined in the Statistical Analysis Plan.

8.14 Multiple Comparison/Multiplicity

Safety event endpoints will not be corrected for multiple comparisons. For CGM, HbA1c, and PRO endpoint analyses, the false discovery rate will be controlled using the adaptive Two Stage Group Benjamini-Hochberg (TST GBH) method.[6,7]

8.15 Analysis of Meal and Exercise Challenges

The meal and exercise challenges will be analyzed with the same CGM metrics and safety outcomes above to be tabuled during, 2 hours after and overnight for each challenge, and will be detailed in the statistical analysis plan. Separate analysis will be conducted for each type of challenge.

Chapter 9: Data Collection and Monitoring

9.1 Case Report Forms and Other Data Collection

The main study data are collected on electronic case report forms (eCRFs). When data are directly collected in electronic case report forms, this will be considered the source data. For any data points for which the eCRF is not considered source (e.g. lab results that are transcribed from a printed report into the eCRF), the original source documentation will be maintained in the participant's study chart or medical record. This source must be readily verifiable against the values entered into eCRF. Even where all study data are directly entered into the eCRFs at office visits, evidence of interaction with a live subject must be recorded (e.g., office note, visit record, etc.).

Electronic device data files are obtained from the study software and individual hardware components. These electronic device files are considered the primary source documentation.

HbA1c measurements will be made by the central laboratory and the data will be transmitted to the Coordinating Center.

9.2 Study Records Retention

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.

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. 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 sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

9.3 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, as well as to ensure that the rights and wellbeing of trial participants are protected and that the reported trial data are accurate, complete, and verifiable. 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. This plan describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detil monitoring will be performed, and the distribution of monitoring reports.

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. The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

9.4 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. A significant (or major) deviation is any deviation that departs from the established materials in such a way that it poses an increase in the risk to subjects, adversely affects the welfare, rights, or safety of the research subjects, or negatively influences the scientific study integrity. As a result of a significant deviation, a corrective and preventive action plan shall 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 10: Ethics/Protection of Human Participants

10.1 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.

10.2 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.

10.3 Informed Consent Process

10.3.1 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's 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.

10.3.2 Participant and Data Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) 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 sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB, regulatory agencies or 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 the reviewing IRB, institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Coordinating Center. 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 the Coordinating Center 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 Coordinating Center.

10.3.3 Future Use of Stored Specimens and Data

Data collected for this study will be analyzed and stored at the Coordinating Center. After the study is completed, a dataset will be provided to the study Sponsor.

No biologic specimens will be stored.

Chapter 11: References

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