The International Diabetes Closed Loop (iDCL) trial: Clinical Acceptance of the Artificial Pancreas

A Pilot Test of t:slim X2 with Control-IQ Technology

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TABLE OF ACRONYMS

Acronym	Abbreviation For
AP	Artificial Pancreas
BG	Blood Glucose
BT/BTLE	Bluetooth, Bluetooth low energy
CRF	Case Report Form
CGM	Continuous Glucose Monitoring
CLC	Closed-Loop Control
CSII	Continuous Subcutaneous Insulin Injection
CTR	Control-to-Range
DiAs	Diabetes Assistant
DKA	Diabetic Ketoacidosis
EC	European Commission
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
ID	Identification
iDCL	International Diabetes Closed Loop
IDE	Investigational Device Exemption
IOB	Insulin-on-Board
IQR	Interquartile Range
JDRF	Juvenile Diabetes Research Foundation
NIH	National Institutes of Health
POC	Point-of-Care
QA	Quality Assurance
QC	Quality Control
RBM	Risk-Based Monitoring
SAP	Sensor-Augmented Pump
SD	Standard Deviation
TDD	Total Daily Dose
UI	User Interface
UVA	University of Virginia

CHAPTER 1: INTRODUCTION

1.1. Background and Rationale

The Tandem X2 insulin pump with Control-IQ Technology is a third-generation closed-loop control (CLC) system retaining the same control algorithm that was initially tested by UVA's DiAs system and then implemented in the inControl system. DiAs is described in 13 IDEs (see IDEs 1-12 and 14 in the list below) and inControl is described in IDEs G160097, G160181, G150240, G140169/S010. For complete algorithmic and clinical background, we refer to these IDEs and to a number of scientific publications that describe glycemic control outcomes and clinical impressions from the use of these systems (see list of 25 peer-reviewed papers and scientific presentations under Bibliography). Overall, this control algorithm has been implemented in two mobile platforms (DiAs and inControl) and has been tested in 30 clinical trials by 450 adults and children with type 1 diabetes for over 280,000 hours of use to date in the U.S. and overseas.

As described in the Background, this project is a result from a sequence of clinical trials that have tested extensively the control system in over 280,000 hours of outpatient human use and in several centers in the U.S. and overseas. The following 16 IDEs reflect this progress:

1. IDE #G110095: Feasibility study of closed loop control in type 1 diabetes using heart rate monitoring as an exercise marker, approved 10/08/2011;
2. IDE #G120032: Early feasibility (pilot) study of outpatient control-to-range; 3/2/2012;
3. IDE #G120210: Early feasibility study 2 of outpatient control-to-range; 10/12/2012;
4. IDE #G130118: DiAs control-to-range nocturnal closed-loop camp study; 6/19/2013;
5. IDE #G130121: Optimizing closed-loop control of type 1 diabetes mellitus in adolescents; 6/19/2013;
6. IDE# G130142: Closed loop control in adolescents using heart rate as exercise indicator; 7/16/13;
7. IDE #G130143: Early feasibility study of adaptive advisory/automated (AAA) control of type 1 diabetes; 7/19/2013;
8. IDE #G140066: Full day and night closed-loop with DiAs platform; 5/9/14.
9. IDE #G140068: Unified Safety System (USS) Virginia Closed Loop versus sensor augmented pump therapy overnight in type 1 diabetes; 5/14/2014;
10. IDE #G140089: Outpatient control-to-range: Safety and efficacy with day-and-night in-home use; 6/6/2014;
11. IDE #G140169: Unified Safety System (USS) Virginia Closed-Loop versus Sensor Augmented Pump (SAP) therapy for hypoglycemia reduction in type 1 diabetes; 10/3/2014.
12. IDE #G150221: Reducing risks and improving glucose control during extended exercise in youth with T1DM: The AP Ski Camp; 11/09/2015;
13. IDE #G150240: Project Nightlight: Efficacy and system acceptance of dinner/night vs. 24 hr closed loop control; 11/12/2015;
14. IDE #G160047: Closed-loop in young children 5-8 years old using DiAs platform; 03/29/2016;
15. IDE #G160097: Clinical Acceptance of the Artificial Pancreas: the International Diabetes Closed-Loop (iDCL) Trial/Research Site Training Protocol; 06/03/16.
16. IDE#G160181: PROTOCOL 1 for "Clinical Acceptance of the Artificial Pancreas: The International Diabetes Closed Loop (iDCL) Trial; 09/21/16

We further reference pre-submission Q170885 and our discussion with FDA on July 18, 2017 regarding the structure of studies intended to test inControl implemented on t:slim X2. Based on the input provided by the Agency, we defined a series of three studies leading to a future pivotal trial of this system. The flowchart of these studies is included in Figure 1:

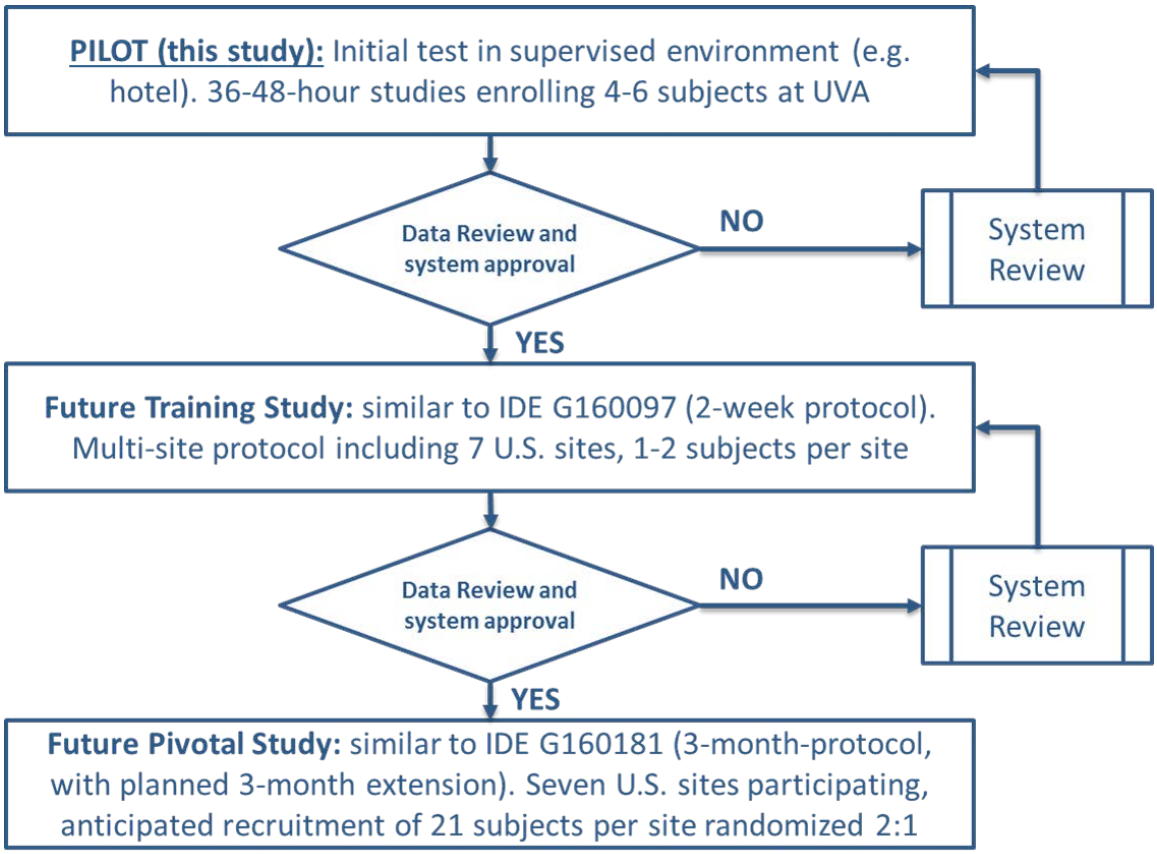

Figure 1: Sequence of planned studies leading to a future pivotal trial of the Tandem X2 insulin pump with Control-IQ Technology. Each study will have a separate IDE submission

Closed-Loop Control System

The Closed-Loop Control System contained in t-slim X2 with Control-IQ Technology is described in Master File MAF-2032/A003. Control-IQ Technology is derived from inControl previously described in IDE# G160097,G160181, G150240 and G140169/S010. The CLC is an "artificial pancreas" (AP) application that uses advanced closed loop control algorithms to automatically manage blood glucose levels for people with Type 1 Diabetes. The system modulates insulin to keep blood glucose in a targeted range. The system components include the t:slim X2 with Control-IQ Technology and the Dexcom CGM G6 (Figure 2).

Figure 2: t:slim X2 with Control-IQ and Dexcom G6 system

1.2. Synopsis of Study Protocol

1.2.1. Study Objective

The objective of the study is for clinical staff to gain experience using the proposed artificial pancreas system named t:slim X2 with Control-IQ Technology and assess usability in a supervised setting prior to initiating home use in a Training protocol (IDE submission pending).

1.2.2. Major Eligibility Criteria

- Clinical diagnosis of type 1 diabetes, treated with insulin for at least 1 year
- Use of an insulin infusion pump for at least 6 months
- Age 18 to <75 years old
- Hemoglobin A1c <10.5%
- Currently using no insulins other than one of the following rapid-acting insulins at the time of enrollment: insulin lispro (Humalog), insulin aspart (Novolog), or insulin glulisine (Apidra). Willingness to switch to lispro (Humalog) or aspart (Novolog) if using glulisine (Apidra).
- No more than one episode of diabetic ketoacidosis (DKA) or severe hypoglycemia involving a seizure of loss of consciousness in the 6 months prior to enrollment
- Total daily insulin dose at least 10 units/day and ≤ 100 U/day

1.2.3. Sample Size

This protocol will be conducted at the University of Virginia only and may enroll up to 20 total subjects with the goal that at least 4 subjects will complete the entire study. .

1.2.4. Protocol Summary

Subject participation will last approximately 36-48 hours in a supervised setting using the study CGM and study pump as detailed in Figure 3 below.

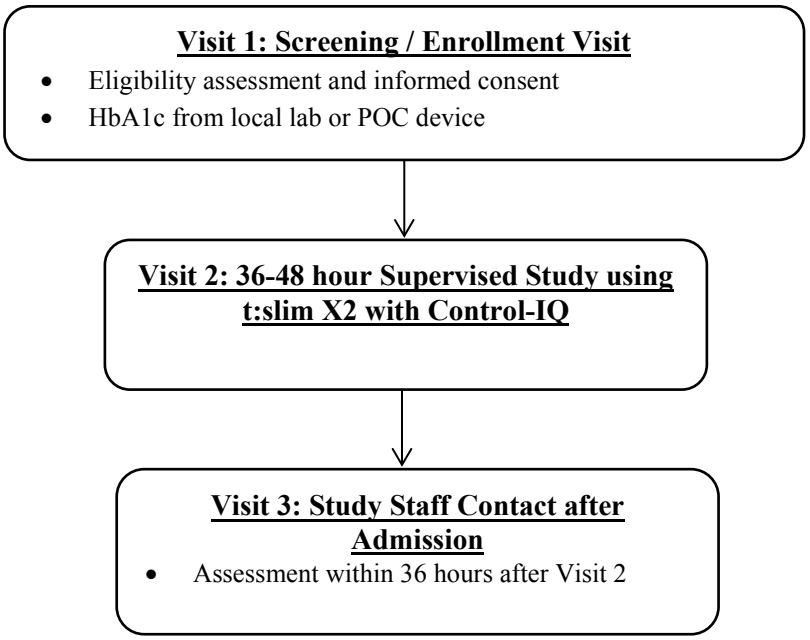

Figure 3: Enrollment Flow Diagram

1.2.5. **Outcomes**

The primary outcome is a qualitative assessment of the system's suitability for use in an in-home clinical trial based on the results of the Technology Acceptance questionnaire and feedback from clinical staff.

Descriptive analyses for secondary safety and efficacy measures will be tabulated for each subject as described in CHAPTER 7: STATISTICAL CONSIDERATIONS.

1.3. **General Considerations**

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

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

There is no restriction on the number of subjects to be enrolled by each site towards the overall recruitment goal.

The protocol is considered a significant risk device study, due to the fact that the closed-loop system is experimental. Therefore, an IDE from the FDA is required to conduct the study.

CHAPTER 2: VISIT 1: SUBJECT SCREENING AND ENROLLMENT

2.1. Study Population

This protocol will be conducted at the University of Virginia only and may enroll up to 20 total subjects with the goal that at least 4 subjects will complete the entire study. The number of subjects is a convenience sample not based on statistical principles.

2.2. Eligibility and Exclusion Criteria

2.2.1. Eligibility

To be eligible for the study, a subject must meet the following criteria:

1) Clinical diagnosis, based on investigator assessment, of type 1 diabetes for at least one year and using insulin for at least 1 year
2) Use of an insulin pump for at least 6 months with established parameters for basal rate(s), carbohydrate ratio(s) and insulin sensitivity factor(s) for at least 3 months.
3) Age 18.0 to <75.0 years
4) Hemoglobin A1c <10.5%
5) For females, not currently known to be pregnant
   If female and sexually active, must agree to use a form of contraception to prevent pregnancy while a subject in the study. A negative serum or urine pregnancy test will be required for all premenopausal women who are not surgically sterile. Subjects who become pregnant will be discontinued from the study. Also, subjects who during the study develop and express the intention to become pregnant within the timespan of the study will be discontinued.
6) Willingness to suspend use of any personal CGM for the duration of the clinical trial once the study CGM is in use
7) Investigator has confidence that the subject can successfully operate all study devices and is capable of adhering to the protocol
8) Currently using no insulins other than one of the following rapid-acting insulins at the time of enrollment: insulin lispro (Humalog), insulin aspart (Novolog), or insulin glulisine (Apidra). Willingness to switch to lispro (Humalog) or aspart (Novolog) if using glulisine (Apidra).
9) Total daily insulin dose (TDD) at least 10 U/day and ≤100 U/day
10) Weight at least 25 kg and not greater than 140 kg

2.2.2. Exclusion

The presence of any of the following is an exclusion for the study:

1) More than one episode of diabetic ketoacidosis (DKA) in the 6 months prior to enrollment
2) More than one episode of severe hypoglycemia involving seizure or loss of consciousness in the 6 months prior to enrollment
3) Concurrent use of any non-insulin glucose-lowering agent (including GLP-1 agonists, Symlin, DPP-4 inhibitors, SGLT-2 inhibitors, biguanides, sulfonylureas and naturaceuticals).
4) Hemophilia or any other bleeding disorder
5) A condition, which in the opinion of the investigator or designee, would put the subject or study at risk
6) Participation in another pharmaceutical or device trial at the time of enrollment or during the study

7) Employed by, or having immediate family members employed by Tandem Diabetes Care, Inc. 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. **Authorization Procedures**

Written informed consent must be obtained prior to performing any study specific procedures with the subject that are not part of the subject's routine care.

For eligible subjects, the study will be discussed with the subject and the subject will be provided with an Informed Consent Form to read and will be given the opportunity to ask questions. If the subject agrees to participate, the Informed Consent Form will be signed. A copy of the consent form will be provided to the subject.

2.4. **Screening and Enrollment Visit Logistics**

Potential subjects 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. Subject exclusion will be at the discretion of the investigator based on study inclusion/exclusion criteria.

Subjects who do not initially meet study eligibility requirements may be rescreened once at later date per investigator discretion.

2.4.1. **Data Collection and Testing**

A standard physical exam (including vital signs, 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:

- Subject fully informed about the study and informed consent form signed according to IRB requirements
- Inclusion and exclusion criteria assessed
- Demographics (date of birth, gender, race and ethnicity)
- Contact information
- Diabetic history
- Medical history
- Substance use history (drinking, smoking, and drug habits)
- Concomitant medications
- Physical examination to include:
    - Weight, height
    - Vital signs including measurement of temperature, blood pressure and pulse
- HbA1c level measured using the DCA2000 or comparable point of care device or local lab (used to assess eligibility)
    - Measurement must be made within two weeks prior to enrollment

    - Measurement performed as part of usual clinical care prior to obtaining informed consent for participation in the trial may be used
- Urine or serum pregnancy test for all premenopausal women who are not surgically sterile

Screening procedures will last approximately 1-2 hours.

CHAPTER 3: VISIT 2: 36-48-HOUR SUPERVISED STUDY

3.1. Timing

Visit 2 may immediately follow Visit 1. The visit will last approximately 36-48 hours and encompass two overnight periods. This visit will occur in an outpatient transitional setting such as a local hotel. Below is the name and address of one possible location. This hotel is 3.3 miles from the UVa Emergency Department.

Hyatt Place Charlottesville
The Shops at Stonefield
2100 Bond Street
Charlottesville, VA 22901

3.2. Procedures upon Arrival to the Study Site

The subjects will be assessed with vital signs. Subjects will not be allowed to initiate the study in the presence of fever or other significant illness within 24-hours of admission. A fingerstick BG and fingerstick ketone measurement will be performed and Glycemic Guidelines followed (Appendix A-11). Female subjects of childbearing potential will perform a urine pregnancy test. If positive, the subject will discontinue study participation. The subject will be asked to seek confirmation of the test and the appropriate medical care.

3.3. Study Device Initiation and Training

Subjects will receive study system training by a qualified trainer. The study system includes the Tandem t:slim X2 with Control-IQ technology and associated Dexcom G6 CGM.

Study Pump and CGM training will include:

- The subject will be fully instructed on the study insulin pump. A qualified staff member will conduct the training and in particular discuss differences from their home pump in important aspects such as calculation of insulin on board and correction boluses. Additional topics not limited to but may include: infusion site initiation, cartridge/priming procedures, setting up the pump, charging the pump, navigation through menus, bolus procedures including stopping a bolus, etc.
- The study team will assist the subject in study pump infusion site initiation and will start the subject on the study pump. The study pump will be programmed with the subject's usual basal rates and pump parameters. The subject's personal pump will be removed.
- The subject will be encouraged to review the literature provided with the pump and infusion sets after the training is completed.
- The subject will learn how to calibrate the CGM unit during the study.
- The subject will learn how to access the CGM trace via the t:slim X2 with Control-IQ user interface.
- Subjects will be asked to perform fingerstick blood glucose measurements in accordance with the labeling of the study CGM device.

Pump training specific to the Control-IQ Technology functions will include:

- How to turn on and off Control-IQ technology.
- How to understand when Control-IQ is increasing or decreasing basal rates.
- How to administer a meal or correction bolus on the t:slim X2 with Control-IQ system
- What to do when exercising while using the system.
- How to enable the sleep function and set the sleep schedule.
- The subject will be assessed for understanding of the system interface and how to react to safety/alert messages.
- The subject will be given a User Guide as a reference.

Blood glucose testing

- All study blood glucose meters will be QC tested with at least two different concentrations of control solution if available at the start of the admission. A tested meter will not be used in a study if it does not read within the target range at each concentration per manufacturer labeling.
- Subjects will be reminded to use the study blood glucose meter for all fingerstick BGs during the study.

Blood ketone testing

- All study blood ketone meters will be QC tested with at least two different concentrations of control solution if available at the start of the admission. A tested meter will not be used in a study if it does not read within the target range at each concentration per manufacturer labeling
- Subjects will be instructed to perform blood ketone testing as described in Appendix A-11 or Section 4.1.4 **Hyperglycemia Safety Protocol**.

3.4. Procedures during Study

Study subjects will have restaurant meals and offered any snacks per their usual routine. Subjects will participate in supervised exercise per their usual routine (e.g. walking 30-45 minutes). Subjects will simulate an infusion site change and a sensor change during the study.

3.5. Procedures for Monitoring

Subjects will be asked to perform fingersticks prior to meals and any user-initiated correction boluses. Subjects will be asked to perform a fingerstick in the event of a Control-IQ Low Alert or Control-IQ High Alert. Glycemic Guidelines (Appendix A-11) will be followed during the admission.

CGM will be recorded from the study system by the study staff at least every 2 hours during the day and every 3 hours at night.

Bolus history will be recorded from the study system by the study staff at least every 2 hours during the day and every 3 hours at night.

Subjects will be instructed to notify staff of any alerts/alarms received.

3.6 Qualifications and Role of the Staff

There will be at least two study staff present at all times at the study site, at least one of whom will be clinical staff (e.g. nurse, physician, nurse practitioner). There will be a physician available either on-site or nearby off-site at all times. Glucagon for the emergency treatment of hypoglycemia will be available on-site.

3.7 Visit 3: Follow-up Visit

Subjects will be contacted by study staff within 36 hours of discharge to assess for any adverse events, significant hypoglycemia or significant hyperglycemia.

CHAPTER 4: SAFETY MEASURES

4.1 Safety Measures

4.1.1 CGM Calibration

Throughout the study, subjects will be instructed to calibrate the study CGM in accordance with manufacturer labelling.

4.1.2 Insulin Dosing

When Control-IQ is turned on, subjects are expected to input carbohydrates in order to bolus for a meal and may also administer correction boluses if desired. In case of a system crash or any interruption of communication between t:slim X2 with Control-IQ and the CGM, the pump will revert to open-loop basal delivery within a short period of time. The system has a Max Insulin Alert that is triggered when the 2-hour insulin delivery has administered 50% of the Total Daily Insulin (TDI). No further insulin will be delivered until this condition is no longer present.

4.1.3 Hypoglycemia Safety Protocol

All subjects will be required to set the CGM hypoglycemia threshold alarm to a value no less than 60 mg/dl.

The t:slim X2 with Control-IQ system will issue a hypoglycemia alarm (Control-IQ Low Alert) if the CGM is <70 mg/dL or when the system predicts BG <70 mg/dL within the next 15-30 minutes when exercise is not activated.

If the subject receives a hypoglycemia alarm from t:slim X2 with Control-IQ, a message appears on the 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 user. The user is prompted to test blood sugar and treat with carbs.

4.1.4 Hyperglycemia Safety Protocol

Subjects will be required to set the CGM hyperglycemia threshold alarm to a value no greater than 300 mg/dl.

The t:slim X2 with Control-IQ system will issue a predictive hyperglycemia alarm (Control-IQ High Alert) if the system detects prolonged resistance to insulin treatment and the BG is estimated to be above 200 mg/dL.

If the subject receives a hyperglycemia alarm from t:slim X2 with Control-IQ, a message appears on the 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 user. The user is prompted to check the site for occlusion and test blood glucose.

If a subject's CGM reading is ≥300 mg/dL for over 1 hour, or ≥400 mg/dL at any point, the following steps will be taken:

- 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, study staff will assist subject in taking correction insulin or changing the pump infusion set.
- If a subject administers correction insulin via insulin syringe, subjects will be instructed to turn Control-IQ off for a few hours and can be restarted per study physician evaluation within 4 hours.

4.1.5 **Study Data Monitoring**

Study staff will download the t:slim X2 at the completion of the admission. These data will be reviewed by the study team. The study pumps following completion of an admission will be sent to Tandem for further analysis of pump function.

4.1.6 **CGM Sensor Connection Failure**

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

4.1.7 **Control-IQ Connection Failure**

If the study system is unable to activate Control-IQ for any reason, the pump will automatically revert to preprogrammed basal insulin delivery without any need for instruction from the user.

4.1.8 **Study System Failure**

If the t:slim X2 detects a system error that does not allow the pump to operate, the Malfunction Alarm will display and the subject will be instructed to contact Tandem Technical Support and the study team.

CHAPTER 5: ADVERSE EVENTS, DEVICE ISSUES, POTENTIAL RISKS, AND STOPPING RULES

5.1 **Adverse Event Definition**

A reportable adverse event for this protocol includes any untoward medical occurrence that meets criteria for a serious adverse event or any unanticipated medical occurrence in a study subject that is study- or device-related, including severe hypoglycemia as defined below and severe hyperglycemia/diabetic ketoacidosis (DKA) as defined below. Skin reactions from sensor placement are only reportable if severe and/or required treatment.

Hypoglycemic events are recorded as Adverse Events (severe hypoglycemic event) if 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 subject 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 coma. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. If plasma glucose measurements are not available during such an event, neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

Hyperglycemic events are recorded as Adverse Events (severe hyperglycemic event) if the event involved DKA, as defined by the Diabetes Control and Complications Trial (DCCT) and described below, or in the absence of DKA if evaluation or treatment was obtained at a health care provider facility for an acute event involving hyperglycemia or ketosis.

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 <15; and
- Treatment provided in a health care facility

5.2 **Recording of Adverse Events**

Throughout the course of the study, all efforts will be made to remain alert to possible adverse events or untoward findings. The first concern will be the safety of the study subject, and appropriate medical intervention will be made.

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

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

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

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

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

The intensity of adverse events will be rated on a three-point scale: (1) mild, (2) moderate, or (3) severe. It is emphasized that the term severe is a measure of intensity: 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.

Adverse events will be coded using the MedDRA dictionary.

Adverse events that continue after the study subject's discontinuation or completion of the study will be followed until their medical outcome is determined or until no further change in the condition is expected.

5.3 Reporting Serious Adverse Events or Unexpected Adverse Device Effects

A serious adverse event is any untoward occurrence that:

- Results in death.
- Is life-threatening; (a non-life-threatening event which, had it been more severe, might have become life-threatening, is not necessarily considered a serious adverse event).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions (sight threatening).
- Is a congenital anomaly or birth defect.
- Is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

An Unanticipated Adverse Device Effect is defined as 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 subjects (21 CFR 812.3(s)).

Serious or unexpected related adverse events will be reported to the local IRB's online adverse event website.

The principal investigator is responsible for reporting serious study-related adverse events and abiding by any other reporting requirements specific to the local Institutional Review Board.

5.4 **Device Issues**

Device malfunctions (failure of device to perform as intended) will be reported to the manufacturer, irrespective of whether associated with an adverse event. However, CGM sensors lasting fewer than 10 days and tape adherence issues will not be reported unless associated with an adverse event. Additionally, t:slim X2 with Control-IQ component disconnections will not be reported unless associated with an adverse event.

5.5 **Medical Monitor**

The Medical Monitor will be informed of all serious adverse events and any unanticipated adverse device events that occur during the study.

5.6 **Potential Risks and Side Effects**

Loss of confidentiality is a potential risk; however, data are handled to minimize this risk. Hyperglycemia and ketone formation are always a risk in subjects with type 1 diabetes and subjects will be closely monitored for this. When wearing sensors and insulin infusion sets there is always a risk of skin rashes, allergic reactions to the tape, or infections at the insertion site. There is always a risk for a small piece of a sensor remaining under the skin or a sensor or infusion set breaking off under the skin.

5.6.1 **Fingerstick Risks**

About 1 drop of blood will be removed by fingerstick for measuring blood sugars and sometimes HbA1c or other tests. This is a standard method used to obtain blood for routine hospital laboratory tests. Pain is common at the time of lancing. In about 1 in 10 cases, a small amount of bleeding under the skin will produce a bruise. A small scar may persist for several weeks. The risk of local infection is less than 1 in 1000. This should not be a significant contributor to risks in this study as fingersticks are part of the usual care for people with diabetes.

5.6.2 **Subcutaneous Catheter Risks (CGM)**

Subjects using the CGM will be at low risk for developing a local skin infection at the site of the sensor needle placement. If a catheter is left under the skin for more than 24 hours it is possible to get an infection where it goes into the skin, with swelling, redness and pain. There may be bleeding where the catheter is put in and bleeding under the skin causes a bruise (1 in 10 risk).

Study staff should verbally alert the subject that on rare occasions, the CGM may break and leave a small portion of the sensor under the skin that may cause redness, swelling or pain at the insertion site. The subject should be further instructed to notify the study coordinator immediately if this occurs.

5.6.3 **Risk of Hypoglycemia**

As with any person having type 1 diabetes and using insulin, there is always a risk of having a low blood sugar (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. Just as at home, there is the possibility of fainting or seizures (convulsions) and that for a few days the subject 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.

5.6.4 **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.

5.6.5 **Risk of Device Reuse**

The study CGM system is intended for single use only. The sensor (the component of the system that enters the skin) will be single use only. 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 and the receiver is a hand held device. Subjects 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 intended 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.) Subjects will be informed that FDA or relevant national authorities typically approves insulin pump 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 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.

5.6.6 **Questionnaire**

As part of the study, subjects will complete a Technology Acceptance Questionnaire which includes questions about their private attitudes, feelings and behavior related to t:slim X2 with Control-IQ. 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.

5.6.7 **Other Risks**

Some subjects 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.

Whenever the skin is broken there is the possibility of an infection. The CGM and pump infusion sites are inserted under the skin. It is possible that any part that is inserted under the skin may cause an infection. These occur very infrequently, but, if an infection was to occur, oral and/or

topical antibiotics can be used. The risk of skin problems could be greater if you use a sensor for longer than it is supposed to be used. Therefore, subjects will be carefully instructed about proper use of the sensor.

Data downloaded from the CGM, pump, and the home glucose and ketone meter will be collected for the study as measures of diabetes self-management behaviors. Some people may be uncomfortable with the researchers' having such detailed information about their daily diabetes habits.

5.7 **Risk Assessment**

Based on the facts that (1) adults and adolescents with diabetes experience mild hypoglycemia and hyperglycemia frequently as a consequence of the disease and its management, (2) the study intervention involves periodic automated insulin dosing that may increase the likelihood of hypoglycemia, and periodic automated attenuation of insulin delivery that may increase the likelihood of hyperglycemia, (3) mitigations are in place, and have been tested in prior studies using similar investigational device system in the home setting, that limit the likelihood of excessive insulin dosing or prolonged withdrawal of insulin, and (4) 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 minor increase over minimal risk. In addition, it is the belief of the investigators that this study also presents prospect of direct benefit to the subjects and general benefit to others with diabetes.

5.8 **Study Stopping Criteria**

5.8.1 **Criteria for Individual Subjects**

Rules for stopping the study for an individual subject are as follows:

1. System or controller malfunctions that impose on the safety of the subject, unless the problem can be clearly identified and the system definitively repaired
2. Severe hypoglycemia or hyperglycemia/DKA (not associated with infusion set failure) as defined in Section 5.1
3. The subject requests that the treatment be stopped
4. Subject pregnancy

5.8.2 **Criteria for Suspending/Stopping Overall Study**

In case of a system malfunction resulting in a severe hypoglycemia or severe hyperglycemia event (as defined in Section 5.1) that is thought to be device-related (either due to excess insulin administration or suspension due to system malfunction) and occurs more than one time, the overall study will be suspended while the problem is diagnosed. In addition, the study could be suspended if the manufacturer of any constituent study device requires stoppage of device use for safety reasons (e.g. product recall). The study 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.

As stated in section 5.5, the medical monitor will be informed of all serious adverse events and any unanticipated adverse device events that occur during the study. The medical monitor will request suspension or outright stoppage of the study if deemed necessary based on the totality of safety data available.

CHAPTER 6: MISCELLANEOUS CONSIDERATIONS

6.1 Benefits

One purpose of this research is to reduce the frequency of hypoglycemia and severe hypoglycemic events. Hypoglycemia is the number one fear of many individuals and families with someone who has type 1 diabetes and this fear often prevents optimal glycemic control.

It is expected that this protocol will yield increased knowledge about using an automated closed-loop to control the glucose level. This research is a definitive step on the path towards development of a fully closed-loop system. The individual subject may not benefit from study participation.

6.2 Subject Compensation

Subjects will be paid $150 for completing the Pilot Study.

- Visit #2 (Supervised Hotel Study): $125
- Visit #3 (Follow-Up Visit) - $25

6.3 Subject Withdrawal

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

6.4 Confidentiality

For security and confidentiality purposes, subjects will be assigned an identifier that will be used instead of their name. De-identified data will be shared with the Jaeb Center for Health Research in Tampa, FL. De-identified data will also be provided to Tandem for system evaluation purposes.

CHAPTER 7: STATISTICAL CONSIDERATIONS

The intent of this protocol is to introduce the t:slim X2 with Control-IQ system prior to proceeding in a subsequent short-term home trial, which will be submitted with a separate protocol and IDE application. The number of subjects is a convenience sample not based on statistical principles.

We will observe, record, and tabulate any t:slim X2 with Control-IQ errors that would inform us whether system fixes would be needed prior to its deployment in the home trial. We will tabulate technical performance metrics including:

- % time in closed-loop and any other relevant operational modes
- % time CGM data available to the controller
- Rate of relevant failure events and alarms per 24 hours

In addition, descriptive glycemic analyses for secondary efficacy measures will be tabulated for each subject based on CGM data, including:

- mean glucose
- percentage of readings in the target range of 70-180 and 70-140 mg/dl
- glucose variability measured with the standard deviation and coefficient of variation
- percentage of readings <70, 60, and 54 mg/dl
- nadir
- AUC glucose <70, 60, and 54 mg/dl
- low blood glucose index
- percentage of readings >180, 250, and 300 mg/dl
- AUC glucose >180 mg/dl
- high blood glucose index

The technical performance, errors, and glycemic analyses will be split by time of the day: daytime vs. nighttime

CHAPTER 8: DATA COLLECTION AND MONITORING

8.1 **Case Report Forms and Device Data**

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

8.2 **Document Storage and Retention**

- The Investigator will retain all records and documents pertaining to this study. They will be available for inspection by the appropriate regulatory agencies. In addition, the Investigator will retain the source documents from which the information entered on the CRFs was derived. These records are to be retained in a secure storage facility maintained by the investigational center until 3 years (or longer/shorter if local laws require) after approval of the above-listed study devices or termination of the study, whichever is longer. The investigator should take measures to prevent accidental or early destruction of the clinical study related materials.

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