# Signature Page

# Tandem Freedom Feasibility Trial #2

## Protocol Identifying Number: TP-0020402

## Sponsor: Tandem Diabetes Care, Inc.

## Version Number: v1.0

## 20 NOV 2024

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|---|---|
| **Principal Investigator** | |
| **Name, degree**<br>**Title** | Martin de Bock, FRACP PhD<br>Associate Professor, University of Otago, Christchurch |
| **Signature/Date** | Martin de Bock<br>Martin de Bock (Nov 22, 2024 13:28 GMT+13)<br>Nov 22, 2024 |
| **Medical Monitor** | |
| **Name, degree**<br>**Title** | Jordan Pinsker, MD<br>Chief Medical Officer, Tandem Diabetes Care |
| **Signature/Date** | Jordan Pinsker<br>Jordan Pinsker (Nov 21, 2024 16:30 PST)<br>Nov 21, 2024 |
| **Sponsor Representative** | |
| **Name, degree**<br>**Title** | Ravid Sasson-Katchalski, PhD<br>Senior Director, Clinical Affairs, Tandem Diabetes Care |
| **Signature/Date** | Ravid Katchalski<br>Ravid Katchalski (Nov 21, 2024 16:54 PST)<br>Nov 21, 2024 |

**Protocol Revision History**

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| 1.0 | 20 NOV 2024 | Initial Version |

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# LIST OF ABBREVIATIONS

| ABBREVIATION | DEFINITION |
|---|---|
| **ADE** | Adverse Device Effect |
| **AE** | Adverse Event |
| **CFR** | Code of Federal Regulations |
| **CGM** | Continuous Glucose Monitoring |
| **CLC** | Closed-Loop Control |
| **DKA** | Diabetic Ketoacidosis |
| **eCRF** | Electronic Case Report Form |
| **GCP** | Good Clinical Practice |
| **HbA1c** | Hemoglobin A1c |
| **HDEC** | Health and Disability Ethics Committees |
| **ICH** | International Conference of Harmonisation |
| **QC** | Quality Control |
| **SAE** | Serious Adverse Event |
| **UADE** | Unanticipated Adverse Device Effect |

# Site Principal Investigator Statement of Compliance

| | |
|---|---|
| Protocol Identifying Number: | TP-0020402 |
| Protocol Name: | Tandem Freedom Feasibility Trial #2 |
| Protocol Version / Date: | 1.0 / 20 NOV 2024 |

The Principal Investigators (undersigned) hereby declare that they have read this protocol and agree to its contents.

The investigator agrees that the study will be conducted according to the applicable New Zealand regulations (Medsafe and Health and Disability Ethics Committee), International Conference on Harmonization (ICH) guidelines on Good Clinical Practice (GCP) and the principles of the World Medical Association Declaration of Helsinki 2008. The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations.

By written consent to this protocol, the investigators agree to the above and to fully co-operate with all monitoring and audits in relation to this trial by allowing direct access to all documentation, including source data, by authorized individuals representing Tandem Diabetes Care, Inc., HDEC, Medsafe New Zealand, and/or by the US Federal, State and local regulatory authorities.

**Investigator Name:** _____

**Investigator Signature:** _____

**Date (DD/MMM/YYYY):** _____

# PROTOCOL SUMMARY

| | |
|---|---|
| **Study Sponsor** | Tandem Diabetes Care, Inc. |
| **Protocol Number** | TP-0020402 |
| **Protocol Title** | Tandem Freedom Feasibility Trial #2 |
| **Précis** | This feasibility study is a prospective, single arm study evaluating the Tandem Freedom system compared to a Control-IQ technology run-in phase in adults with type 1 diabetes.<br>Existing Control-IQ technology users will use Control-IQ technology at home for 1 week, then will use Tandem Freedom in a supervised hotel setting with Dexcom follow active.<br>The goal of Tandem Freedom is to use the system without requiring meal boluses. |
| **Products** | Investigational Device: t:slim X2 insulin pump with Tandem Freedom Algorithm |
| **Objectives** | The objective of the study is to assess the feasibility of the Tandem Freedom system, by assessing safety and performance in a short-term supervised setting in adults with type 1 diabetes under direct clinical supervision. |
| **Number of Sites** | 1 Clinical Site in New Zealand |
| **Study Design** | Single arm, prospective feasibility study to assess safety. |
| **Number of Participants** | Up to 20 participants signing consent to use the study devices, with a goal that at least 10 complete the study. |
| **Participant Population:** | **Eligibility to enroll in the study will be assessed based on the following inclusion criteria:**<br>1. Age ≥18 years old<br>2. Diagnosis of type 1 diabetes for at least 1 year<br>3. Current Control-IQ user, having been prescribed Control-IQ for at least 3 months<br>4. HbA1c ≤ 10%, recorded in the last 3 months<br>5. Investigator has confidence that the participant can successfully operate all study devices and is capable of adhering to the protocol, including performing the hotel observed setting portion of the study.<br>6. Willing to use only aspart (novorapid) or lispro (humalog) insulin with the study pump, with no use of long-acting basal insulin injections, or inhaled insulin with the study pump.<br><br>**Eligibility to enroll in the study will be assessed based on the following exclusion criteria:**<br>1. More than 1 episode of diabetic ketoacidosis (DKA) in the past 6 months<br>2. More than 1 episode of severe hypoglycemia (needing assistance) in the past 6 months<br>3. Inpatient psychiatric treatment in the past 6 months<br>4. For Female: Currently pregnant or planning to become pregnant during the time period of study participation<br>a. *A negative pregnancy test will be required for all females of child-bearing potential*<br>*b. Counseling on appropriate birth control options will be provided to all females of child-bearing potential*<br>5. 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).<br>6. Hemophilia or any other bleeding disorder<br>7. Hemoglobinopathy<br>8. History of heart, liver, lung or kidney disease determined by investigator to interfere with the study |

| | |
|---|---|
| | 9. History of allergic reaction to Humalog or Novorapid<br>10. Use of any medications determined by investigator to interfere with study<br>11. Significant chronic kidney disease (which could impact continuous glucose monitoring (CGM) accuracy in investigator's judgment) or hemodialysis<br>12. Concurrent use of any medication that could interfere with the study CGM, such as hydroxyurea<br>13. History of adrenal insufficiency<br>14. History of abnormal TSH consistent with hypothyroidism or hyperthyroidism that is not appropriately treated<br>15. History of gastroparesis<br>16. A condition, which in the opinion of the investigator or designee, would put the participant or study at risk<br>17. Participation in another pharmaceutical or device trial at the time of enrollment or anticipated for during the time period of study participation<br>18. Employed by, or having immediate family members employed by Tandem Diabetes Care, Inc., 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 2 weeks |

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| **Study Endpoints** | The two study periods are:<br>1) Control-IQ run-in period<br>2) The Tandem Freedom hotel observed period<br><br>Primary Endpoints for each period:<br>1. Number of severe hypoglycemia events (with cognitive impairment such that assistance of another individual is needed for treatment)<br>2. Number of diabetic ketoacidosis events<br><br>Secondary Endpoints for each period:<br>1. All device-related adverse events<br>2. CGM hypoglycemia outcomes<br>a. Overall % time <3.0 mmol/L<br>b. Overall % time <3.9 mmol/L<br>3. Times in ranges-overall (3.9 - 10.0 mmol/L, >10.0 mmol/L, >13.9 mmol/L, 3.9 - 7.9 mmol/L)<br>4. Mean glucose<br>5. Glycemic variability (CV and SD)<br><br>Due to the small sample size and feasibility nature of the study, primarily descriptive statistics will be used. |
| **Protocol Overview/Synopsis** | After consent is signed, eligibility will be assessed.<br><br><u>Run-In Period</u>:<br>After eligibility is assessed, participants will be given a study Dexcom G6 sensor, and will continue to use their Control-IQ system for 7 +/- 3 days at home.<br>Participants will be instructed to bolus for meals as they normally do.<br>Participants will be required to change their CGM sensor 48 +/- 12 hours before the hotel study.<br><br><u>Hotel Observed Session</u><br>Participants will then be admitted for the hotel observed setting for 4 nights.<br>On Day 1, participants will arrive before lunch, where they will bolus for the lunchtime meal as per their usual carb ratio and bolus routine with their home pump.<br>Participants will be switched the Tandem Freedom system, waiting for at least 2 hours after lunch before starting the Freedom system , which uses a t:slim X2 insulin pump and a nearly identical interface participants are familiar with from their home pump, but is now running a new algorithm that is designed to be used without a requirement for meal boluses.<br>Study staff will enable Dexcom follow from participants phones to study medical providers, who will also be physically present.<br>Study staff will program the Tandem Freedom pump TDI average from the last 7-days as shown in their home Control-IQ pump, a sleep schedule, and then enable Tandem Freedom for closed-loop. All participants will be encouraged to use TruSteel infusion sets to minimize chance of occlusion during the study,<br>Participants will bolus for all meals for the remainder of Day 1, entering carbohydrates as they would usually estimate and adjusting their overall bolus amount if needed. All boluses will be reviewed with study staff.<br>On Day 2 - 4, participants will eat meals and snacks as they usually would, but will be encouraged to not bolus for any meals. If a user or study staff feel a meal or correction bolus is needed, the investigator will make this determination and allow for boluses as they determine are needed. |

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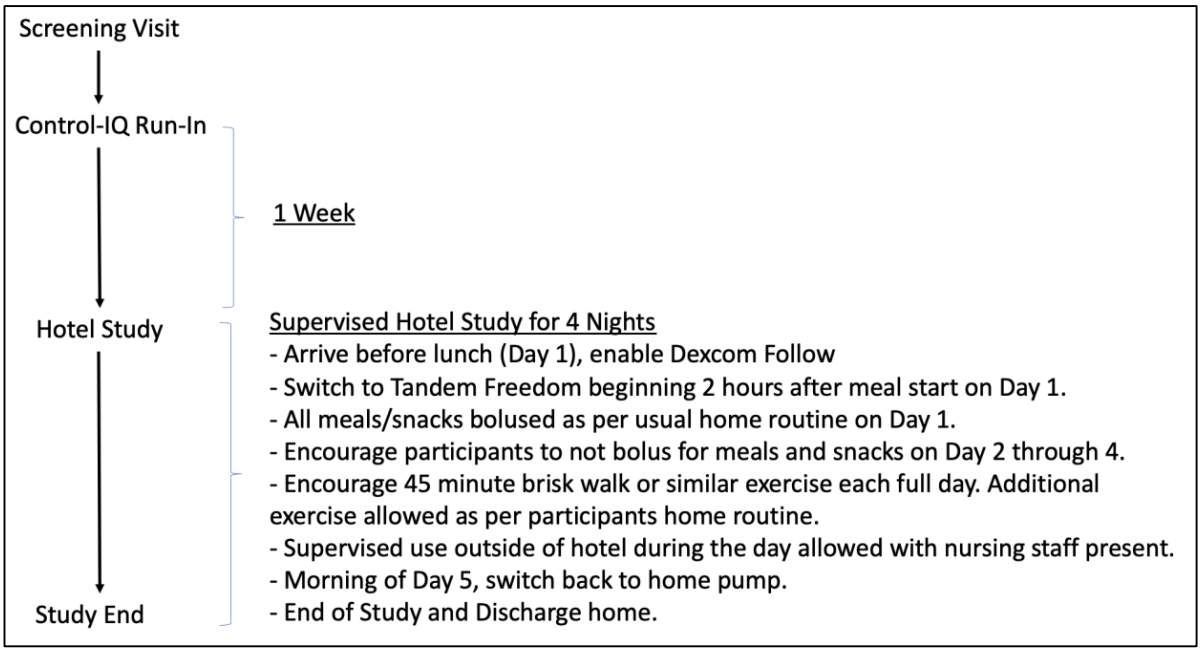
| | Participants will be provided 3 meals a day plus may have snacks per their normal routine. Participants may adjust their meals per their normal routine.<br>Participants will also be encouraged to perform a supervised brisk walk or similar exercise of at least 45 minutes each full day (Day 2 to Day 4), at approximately the same time each day. Additional exercise per the participants usual routine will be allowed as long as study staff are notified.<br>On the morning of Day 5, participants will switch back to their home pump and complete their participation in the study.<br><u>Study Safety Plan</u>:<br>Participants will use their personal blood glucose and ketone meter throughout the study.<br>Fingerstick blood glucose readings will be performed in accordance with the study protocol and as per CGM manufacturer instructions.<br>Ketone readings will be performed per the study protocol.<br>Site investigators may reset the TDI derived insulin delivery profile as needed throughout the study in accordance with their clinical practice.<br>Real-time CGM alerts will be sent to study staff during the inpatient observed hotel phase per the study safety guidelines. |

# SCHEMATIC OF STUDY DESIGN



# SCHEDULE OF STUDY VISITS AND PROCEDURES

| **Visit Number** | **1** | **2** | **3** |
|---|---|---|---|
| | **Screening Visit** | **Control-IQ Run-In Period[2] 7 Days (+/- 3 days)** | **Hotel Study for 4 Nights** |
| **Visit (V) or Contact (C)** | **V** | **C[2]** | **V** |
| Informed Consent | **X** | | |
| Eligibility Assessment | **X** | | |
| Medical history/demographics/ physical exam | **X** | | |
| Height, weight, blood pressure and pulse | **X** | | |
| HbA1c (point of care or local lab)[1] | **X** | | |
| Pregnancy test (females of child-bearing potential) | **X** | | |
| Exercise Challenge | | | **Encourage 45 minutes of exercise per day on Days 2 - 4** |
| AE/Device Issue Assessment | | **X[3]** | **X** |
| Upload and Review Device Data | **X** | **X** | **X** |

[1]May use prior HbA1c value recorded in the last 3 months.

[2]Participants have up to 2 weeks after screening to begin the Control-IQ Run-In Period.

[3]Participants will call study staff for any issues related to the protocol or devices during the Control-IQ run in period.

# Chapter 1: Background Information

## 1.1 Introduction

### 1.1.1 Disease Background

Type 1 diabetes affects 1.25 million people in the United States. Approximately 70% of individuals with type 1 diabetes report poor metabolic control, and do not meet the American Diabetes Association's recommended goal of hemoglobin A1c (HbA1c) level of 7.0%. These findings indicate the need for better approaches to type 1 diabetes management.

### 1.1.2 Tandem X2 Insulin Pump and Tandem Freedom Control Algorithm

The Tandem X2 insulin pump with Control-IQ technology is an approved closed-loop control (CLC) system. Use of the Control-IQ system has been extensively tested in adults and children with type 1 diabetes, demonstrating its efficacy and safety when used with insulin lispro (Humalog) or insulin aspart (Novorapid).[1,2] 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]

A next generation CLC algorithm, the Tandem Freedom System, is now being evaluated to remove the burden of meal bolusing. The system is designed to not require meal insulin boluses as part of its design. This algorithm is now running in the t:slim X2 insulin pump.

A prior study with the Tandem Freedom system was completed in the supervised setting in New Zealand in June 2024 (NCT06428591). Ten adults with type 1 diabetes (average age 30 years old [range 18 – 64 years old], duration of diabetes 18 +/- 13 years, total daily insulin 62 +/- 23 units/day [range 28 – 106 units/day], current Control-IQ users for 1.4 +/- 0.5 years, HbA1c 6.8 +/- 0.7% [range 6.0 – 7.9] completed the study. After a Control-IQ run-in period at home, participants were admitted to the hotel for the supervised study, where they used the Tandem Freedom system first with boluses for one day, then without boluses for one, eating large meals and performing exercise each day.

The study showed participants achieved 61.8% time in range 3.9-10.0 mmol/L at home using Control-IQ technology during the run-in week, 82.4% time in range 3.9-10.0 mmol/L using Freedom for 24 hours with boluses, and 54.7% time in range 3.9-10.0 mmol/L using Freedom for 24 hours without meal boluses. There were no severe hypoglycemia or DKA events, and no serious adverse events. As participants were able to achieve nearly the same time in range without bolusing with Freedom as they achieved with bolusing with Control-IQ, the results from this study support continued development and evaluation in a second study.

## 1.2 Rationale

The objective of this study is to assess the feasibility of the Tandem Freedom system, by assessing safety and performance in a short-term supervised second feasibility study. The study will occur in a supervised, hotel setting with medical staff present, with existing Control-IQ users with type 1 diabetes already familiar with the t:slim X2 insulin pump, to further determine how Tandem Freedom functions with unbolused meals and exercise.

## 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. As all participants

will be existing Control-IQ users, and familiar with infusion set care and pump use, this helps to minimize risk.

### 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 Continuous Glucose Monitoring (CGM) sensor placement and at the 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.

#### 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. The study exercise challenges could increase the risk of hypoglycemia.

#### 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. Not performing premeal insulin boluses in the hotel setting could increase the risk of hyperglycemia. Encouraging participants to use TruSteel infusion sets in the study will minimize the risk of hyperglycemia from occlusions.

#### 1.3.1.5 Risk of Device Reuse

All devices will be used by a single study participant only. There will be no device reuse.

#### 1.3.1.6 Potential Risks of the CLC System

Even though the study system has been tested prior to this study, including completion of a prior 10 participant first in human 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.

#### 1.3.1.7 Other Risks

Data downloaded from pump (to include CGM values) will be collected for the study. The downloaded data from the participant's home devices at the screening visit may include data from the period beyond the last 2 weeks prior to screening, but will be de-identified. Data from the home glucose and ketone meters will be reviewed for adverse events only, and an export of those devices is not required for the study. 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 their home insulin pump.

The individual participant may not benefit from study participation.

### 1.3.3 Risk Assessment

Based on the facts that (1) individuals with diabetes experience mild hypoglycemia and hyperglycemia frequently as a consequence of the disease and its management, (2) mitigations are in place, including direct medical supervision in the hotel setting and all participants are current Control-IQ users, 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 Sponsor that this protocol is an investigation involving a minor increase over minimal risk. In addition, it is the belief of the Sponsor that this study also presents prospect of direct benefit to the participants and general benefit to others with diabetes.

## 1.4 General Considerations

The study is being conducted in compliance 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).

Per Medsafe guidelines Part 11, the investigator device (Tandem Freedom System) in the study will be labelled "To be used by qualified investigators only".

# Chapter 2: Study Enrollment and Lead-in Period

## 2.1 Participant Recruitment and Enrollment

Enrollment will proceed with the goal of having up to 20 participants screened, so that at least 10 complete the study.

All participants will be existing Control-IQ users to assure familiarity with the t:slim X2 insulin pump.

Study participants will be recruited from a single clinical center as a convenience sample.

### 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, written informed consent will be obtained.

For potential study participants, 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.

A copy of the consent form will be provided to the participant, and another copy will be added to the participant's study record.

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

## 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 ≥18 years old
2. Diagnosis of type 1 diabetes for at least 1 year
3. Current Control-IQ user, having been prescribed Control-IQ for at least 3 months
4. HbA1c ≤ 10%
5. Investigator has confidence that the participant can successfully operate all study devices and is capable of adhering to the protocol, including performing the hotel observed setting portion of the study.
6. Willing to use only aspart (novorapid) or lispro (humalog) insulin with the study pump, with no use of long-acting basal insulin injections, or inhaled insulin with the study pump.

### 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. For Female: Currently pregnant or planning to become pregnant during the time period of study participation
    a. *A negative pregnancy test will be required for all females of child-bearing potential*
    b. *Counseling on appropriate birth control options will be provided to all females of child-bearing potential*
5. 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).
6. Hemophilia or any other bleeding disorder
7. Hemoglobinopathy
8. History of heart, liver, lung or kidney disease determined by investigator to interfere with the study
9. History of allergic reaction to Humalog or Novorapid
10. Use of any medications determined by investigator to interfere with study
11. Significant chronic kidney disease (which could impact CGM accuracy in investigator's judgment) or hemodialysis
12. Concurrent use of any medication that could interfere with the study CGM, such as hydroxyurea
13. History of adrenal insufficiency
14. History of abnormal TSH consistent with hypothyroidism or hyperthyroidism that is not appropriately treated
15. History of gastroparesis
16. A condition, which in the opinion of the investigator or designee, would put the participant or study at risk
17. Participation in another pharmaceutical or device trial at the time of enrollment or anticipated for during the time period of study participation
18. Employed by, or having immediate family members employed by Tandem Diabetes Care, Inc., 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 Visit 1: Screening Visit

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 (study nurse). Height, weight and vital signs may be recorded by appropriately delegated office staff.

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

- Inclusion and exclusion criteria assessed
- Demographics (age, sex, ethnicity and socioeconomic information)

- Participant initials to verify electronic case report form (eCRF) entry is associated with the correct individual
- Contact information (retained at the site and not entered into study database)
- Medical history
- 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 for all females of childbearing potential who are premenopausal and not surgically sterile
- Current device download of the participant's home insulin pump (with included CGM device data), for up to the last two weeks of data if available. Site will also record average total daily dose, average percent basal, and average percent bolus insulin from the last 2 weeks.

Screening procedures will last approximately 1-2 hours. The screening visit must occur in clinic and cannot be performed remotely.

### 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.

# Chapter 3: Study Visits

## 3.1 Visit 2: Start Control-IQ Run-In

After screening, participants will have a clinic visit at which they will be given the study CGM (Dexcom G6) and begin the run-in period. The run-in period will be 7 +/- 3 days.

This device training visit should be completed within 2 weeks of screening, and may be performed the same day as the screening visit. If not completed within 2 weeks of screening, re-review of screening results by the investigator should be performed, who may ask for repeated testing as per investigator judgement. The device training visit must occur in clinic and cannot be performed remotely.

Participants will receive additional supplies for blood glucose and ketone testing if needed.

Participants will continue to use their home insulin pump (t:slim X2 insulin pump with Control-IQ technology) during the run-in phase. Participants will switch the CGM to the study provided CGM sensor and transmitter.

Participants may contact study providers at any time for questions during the Control-IQ Run-In period.

Participants will be required to change their CGM sensor 48 +/- 12 hours before the hotel study.

## 3.2 Visit 3: Hotel Supervised Study for 4 Nights

### 3.2.1 General Guidelines

Upon arrival, the following procedures will be performed:

• Current device download of the participant's home insulin pump (with included CGM device data). Site will record average total daily dose, average percent basal, and average percent bolus insulin from the last 7 days from the pump screen.

• Assessment of device issues that have occurred.

• Assessment of adverse events, using open ended questions to capture hyperglycemic and hypoglycemic events during the Run-In Phase.

On Day 1, participants will arrive before lunch, where they will bolus for the lunchtime meal as per their usual carb ratio and bolus routine with their home pump.

Participants will be switched the Tandem Freedom system, waiting for at least 2 hours after lunch before starting the Freedom pump (Investigational Device).

Study staff will use the TDI from the last 7 days as shown on the participants home pump to initialize the system, although they may adjust this value per clinical judgement, and re-initialize the system based on an updated TDI use at any time during the study.

A sleep schedule will be set from 11 PM to 6 AM so sleep activity automatically activates in the evening and deactivates in the morning.

During this phase of the study, participants will be monitored in person by study staff, and remotely monitored by the study team with Dexcom Follow, 24 hours per day. Pump and CGM alerts will be set to annunciate throughout the study. Dexcom follow alerts will be sent to study staff for CGM values <3.9 mmol/L mg/dL and >16.7 mmol/L mg/dL at any time.

Participants will be provided 3 meals a day plus may have snacks per their normal routine. Participants may adjust their meals per their normal routine.

Food diary showing the start time of all meals, as well as the number of carbohydrates, fat and protein consumed, will be recorded by study staff.

During the hotel study, the following hyper and hypoglycemic treatment plan will be used:

**Table 1.** Hypoglycemia and Hyperglycemia Prevention and Treatment Plan during the supervised, hotel study.

| Condition | Action Taken |
|---|---|
| CGM reading <3.9 mmol/L | A confirmatory fingerstick measurement will be performed.<br><br>If fingerstick glucose ≥3.9 mmol/L, and participant is not having any symptoms, no treatment is required. However, treatment may be initiated by the investigator (recommended ~4-16 g fast acting carbohydrate, but may be adjusted per investigator discretion). Participants will then perform a follow-up fingerstick measurement 10 to 15 minutes after treatment if CGM <3.9 mmol/L mg/dL.<br><br>If fingerstick glucose <3.9 mmol/L, treatment will be initiated by the investigator (recommended ~4-16 g fast acting carbohydrate, but may be adjusted per investigator discretion). Participants will then perform a follow-up fingerstick measurement 10 to 15 minutes after treatment if CGM <3.9 mmol/L.<br><br>This protocol will be repeated until CGM is ≥ 3.9 mmol/L or the fingerstick is ≥3.9 mmol/L per standard clinical treatment for hypoglycemia. |
| Any time a participant has subjective symptoms of hypoglycemia | A fingerstick blood glucose measurement will be performed. Fast-acting carbohydrates may be given to any participant who is symptomatic or requests treatment, even before a confirmatory fingerstick is performed. |
| CGM reading is >16.7 mmol/L for more than 2 hours | A confirmatory fingerstick measurement will be performed.<br><br>If the participant 's BG is confirmed to be >16.7 mmol/L, then ketones will be checked using the study-approved ketone meter. |
| BG confirmed >16.7 mmol/L mg/dL for more than 2 hours and ketones are <0.6 mmol/L | A manual correction bolus may be delivered via the pump if BG is not beginning to trend downward, but this may be adjusted as per investigator discretion, based on insulin-on-board and clinical judgement. Fingerstick BG and ketone measurements will be repeated after 1 hour. If a correction dose of insulin is given, the dose may be adjusted by the investigator.<br><br>If BG fails to decrease by a minimum of 2.8 mmol/L in 1 hour after a correction dose is given, then study staff will |

| | |
|---|---|
| | replace the participant's infusion set with a new infusion set and the correction bolus will be repeated, per the investigator's discretion. The decision to change out the infusion set and giving a correction dose may adjusted per investigator discretion, based on insulin-on-board and clinical judgement. |
| BG confirmed >16.7 mmol/L for more than 2 hours and ketones are ≥0.6 mmol/L | A manual correction bolus may be delivered via injection to assure proper absorption in the setting of likely infusion set failure. The decision to give a manual correction bolus by injection may be adjusted by investigator discretion, based on insulin-on-board and clinical judgement.<br><br>Fingerstick BG and ketone measurements will be repeated after approximately 1 hour.<br><br>After a manual correction bolus, the study staff will replace the participant's infusion set, if they believe it is contributing to the hyperglycemia, with a new infusion set and the correction bolus will be repeated per the investigator's discretion. Closed loop will be disabled by the investigator for the next 4 hours and until BG has returned to <10 mmol/L. |
| Participant loses consciousness or has a seizure, or participant is unable to take oral carbohydrates | 1 mg of IM glucagon or 3 mg nasal glucagon will be administered and 111 will be called. The study will be stopped immediately until sponsor conducts a full investigation to determine the root cause for the compromised system performance and is able to address all issues. Sponsor will also communicate the results of this root cause investigation to regulatory bodies and to study investigators. |

Meal boluses and all interaction with the pump will be supervised by study staff to ensure that the correct number of carbohydrate grams are entered into the bolus calculator and the correct dose is given.

When meal boluses are given, participants will give the bolus per their usual meal bolus timing, but not more than 15 minutes before the meal.

At least one member of the study medical staff (Physician, NP, PA, or other qualified clinician) will always be present on site.

During the study session, participants may change our their study sensor or their infusion site as needed per their usual care. Participants will be encouraged to use TruSteel infusion sets for the duration of the study.

Insulin and glucose data from the screening visit, as well as follow up visits and at the start of the hotel session, will be reviewed and the site investigator may adjust insulin delivery profile settings as needed in accordance with their clinical practice.

### 3.2.2 Day 1

Following the Control-IQ run-in phase, participants will commence the hotel supervised phase.

On Day 1, participants will arrive before lunch, where they will bolus for the lunchtime meal as per their usual carb ratio and bolus routine with their home pump.

Participants will be switched the Tandem Freedom system and be encouraged to use the TruSteel infusion set, waiting for at least 2 hours after lunch before starting the Freedom pump (Investigational Device).

Study staff will use the TDI from the last 7 days as shown on the participants home pump to initialize the system, although they may adjust this value per clinical judgement, and re-initialize the system based on an updated TDI at any time during the study.

A sleep schedule will be set from 11 PM to 6 AM so sleep activity automatically activates in the evening and deactivates in the morning.

Participants will bolus for all meals for the remainder of Day 1, entering carbohydrates as they would usually estimate and adjusting their overall bolus amount if needed.

Participants may perform low-intensity activity (e.g., walking) at any time during day 1.

No meals should occur after sleep activity is enabled.

### 3.2.3 Days 2 through 4 – Full Days

Sleep activity will be disabled upon waking up if not already automatically de-activated per the sleep schedule.

On Days 2 - 4, participants will eat meals and snacks as they usually would, but will be encouraged to NOT BOLUS for all meals and snacks. If a user or study staff feel a meal or correction bolus is needed, the investigator will make this determination and allow for boluses as they determine are needed.

Participants will also be encouraged to perform a supervised brisk walk or similar exercise of at least 45 minutes each full day (Day 2 to Day 4) under staff supervision, at approximately the same time each day. Additional exercise per the participants usual routine will be allowed as long as study staff are notified. Exercise activity should be used for this exercise, to start 30-90 minutes before exercise, and turned off after exercise is complete, as determined by the investigator.

Exercise does not have to be performed, but will be encouraged. Exercise will be cancelled or stopped 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 any other symptoms, as determined by the investigator.

Participants may perform low-intensity activity (e.g., walking) at any time during the hotel study.

Supervised outings may occur with study staff present to areas outside of the hotel during the daytime. Realtime CGM alerts will remain in place, and the same hypoglycemia/hyperglycemia treatment guidelines apply as in the hotel setting.

No meals should occur after sleep activity is enabled.

### 3.2.4 Day 5 – Morning

Sleep activity will be disabled upon waking up if not already automatically de-activated per the sleep schedule.

After waking up, participants will switch back to their home Control-IQ pump, and may have breakfast prior to leaving the hotel.

Participants may be discharged if their CGM is ≥4.4 mmol/L for at least 15 minutes.

## 3.3 Unscheduled Visits

Participants may have unscheduled visits during the study run-in period if required for additional questions or other unanticipated needs per the study investigator discretion.

At each contact, study staff will perform an:

• Assessment of device issues that have occurred

• Assessment of adverse events, using open ended questions to capture hyperglycemic and hypoglycemic events during the Run-In Phase.

# Chapter 4: Study Devices and Drugs

## 4.1 Study Devices

### 4.1.1 Insulin Pump

For the hotel supervised session, participants will use the study provided Tandem t:slim X2 insulin pump with the Tandem Freedom System/algorithm (Investigational Device).

### 4.1.2 Continuous Glucose Monitoring

The study CGM is the commercial version of the Dexcom G6 (Dexcom, Inc), which includes a transmitter and sensors. The CGM sensor will be replaced at least once every 10 days.

### 4.1.3 Blood Glucose and Ketone Meter

For blood glucose and ketone testing, participants will use their home meter, the CareSens Dual Blood Glucose and Ketone Testing Monitor (i-SENS, Inc).

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

Blood ketone levels will be measured when needed to evaluate prolonged hyperglycemia.

### 4.1.4 Study Device and Drug Accountability Procedures

Device accountability and inventory will be documented to include detailed inventory records of the study CGM supplies, and Tandem insulin pump system.

### 4.1.5 Participant Access to Study Device at Study Closure

Participant will return the investigational study device (insulin pump) at study closure. Participant may keep any extra ketone and glucose testing strips they were issued, and any issued remaining pump and CGM supplies that are not marked for investigational use.

# Chapter 5: Testing Procedures

## 5.1 Laboratory Testing

### 5.1.1 HbA1c

HbA1c measurement will be performed locally in clinic or at a laboratory at the screening visit if no prior HbA1c measurement is available from the last 3 months.

### 5.1.2 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.

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

## 6.1 Unanticipated Problems

Site investigators will promptly report to the Sponsor on an eCRF all unanticipated problems meeting the criteria below. 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 HDEC (Health and Disability Ethics Committees)-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 Sponsor will report to the appropriate regulatory authorities if the event 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).

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 Issues 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 malfunction 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 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.
- Skin reactions from sensor or pump infusion set placement are only reportable if severe and/or required treatment.

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

### 6.2.3 Hypoglycemic Events

Hypoglycemia 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), an Adverse Event Form should be completed. 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 6.2.5) 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 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 all of the following are present, or judged likely to have been present based on available data:

- 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 AE, or as a SAE as defined in section 6.2.1, an Adverse Event Form should be completed. 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 6.2.5) 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 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 HDEC and Medsafe reporting.

### 6.2.6 Severity (Intensity) of Adverse Events

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

MILD: Usually transient, requires no special treatment, and does not interfere with the participant's daily activities.

MODERATE: Usually causes a low level of inconvenience, discomfort or concern to the participant and may interfere with daily activities, but is usually ameliorated by simple therapeutic measures and participant is able to continue in study.

SEVERE: Interrupts a participant's usual daily activities, causes severe discomfort, may cause discontinuation of study device, and generally requires systemic drug therapy or other treatment.

### 6.2.7 Expectedness

For a serious adverse event that is considered possibly related to study device, 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.

### 6.2.8 Coding of Adverse Events

Adverse events will be coded using the MedDRA dictionary.

### 6.2.9 Outcome of Adverse Events

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

- RECOVERED/RESOLVED – The participant recovered from the AE/SAE without sequelae. Record the AE/SAE stop date.
- RECOVERED/RESOLVED WITH SEQUELAE – The event persisted and had stabilized without change in the event anticipated. Record the AE/SAE stop date.
- FATAL – A fatal outcome is defined as the SAE that resulted in death. Only the event that was the cause of death should be reported as fatal. AEs/SAEs that were ongoing at the time of death; however, were not the cause of death, will be recorded as "resolved" at the time of death.
- NOT RECOVERED/NOT RESOLVED (ONGOING) – An ongoing AE/SAE is defined as the event was ongoing with an undetermined outcome.

  *An ongoing outcome will require follow-up by the site in order to determine the final outcome of the AE/SAE. The outcome of an ongoing event at the time of death that was not the cause of death, will be updated and recorded as "resolved" with the date of death recorded as the stop date.*

- UNKNOWN – An unknown outcome is defined as an inability to access the participant or the participant's records to determine the outcome (for example, a participant that was lost to follow-up).

If any reported adverse events are ongoing when a participant completes the study (or withdraws), adverse events classified 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 as both 'device issues' and adverse events, except for skin reactions from CGM sensor placement or pump infusion set placement that do not require pharmacologic treatment.

Device issues 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 protocol.
- Device issues clearly addressed in the protocol 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 must be reported by the site to the Sponsor within 1 working day of the site becoming aware of the event. This can occur via phone or email, or by completion of the appropriate eCRFs as applicable. If the form(s) are not initially completed, they 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 eCRF(s) within 7 days of the site becoming aware of the event.

The Sponsor 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 Sponsor 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.

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 the HDEC, and Medsafe within 10 working days of the Sponsor becoming aware of the UADE. The Sponsor 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 complaints and malfunctions that could have led to a UADE, including device complaints and malfunctions, irrespective of whether an adverse event occurred.

### 6.5 Safety Oversight

The study Sponsor's Medical Director or Chief Medical Officer will serve as Medical Monitor, and will review all reported adverse events, including all cases of severe hypoglycemia and DKA, and adverse device effects that are reported during the study. SAEs typically will be reviewed within 1 working day of reporting. Other AEs typically will be reviewed on a weekly basis.

The Medical Monitor will confirm the MedDRA code assigned and adjudicate events as specified in the safety management plan for relatedness to the study procedure and investigational device, assess seriousness and severity, and determine if the event the event is anticipated or unanticipated. Both the investigators and Medical Monitor's assessments will be recorded, however, the adjudication decision of the Medical Monitor will be used for the final classification of events, including relatedness to the study procedures and/or the investigational device, for the determination of safety endpoints and for all regulatory reports, product labeling, and publications or presentations. If there has been a discrepancy between the Medical Monitor and Coordinating Investigator when classifying an AE, it will be reported to HDEC.

## 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 for that participant while the problem is diagnosed.

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
- One distinct episode of DKA in the study treatment period as defined in section 6.2.4
- One distinct severe hypoglycemia event in the study treatment period as defined in section 6.2.3

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

### 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 6.6.1, 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.

Closed-loop system use will also be suspended if there are three or more cases of severe hypoglycemia or three or more cases of DKA across the entire study in participants who have initiated Tandem Freedom use. The HDEC and Medsafe will be notified. After assessment of the problem and any corrections are implemented, use of the closed-loop system may be restarted if approval is received from the HDEC and Medsafe.

# Chapter 7: Miscellaneous Considerations

## 7.1 Drugs Used as Part of the Protocol

Participants will use their own Humalog (insulin lispro) or Novorapid (insulin aspart) during the Run In and Treatment Period with the study devices.

## 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 developing during the study will be reviewed by the investigator for their relationship to the study device.

*Medications:* All medications 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 Humalog or Novorapid insulin with the study pumps is not permitted. Treatment with a non-insulin glucose -lowering agent, other than metformin, is not permitted, including GLP-1 receptor agonists, Symlin, DPP-4 inhibitors, SGLT-2 inhibitors, or sulfonylureas.

The investigational study device (t:slim X2 insulin pump with Tandem Freedom algorithm) and study sensor and transmitter (Dexcom CGM sensor and transmitter) must be removed before magnetic resonance imaging (MRI), computed tomography (CT), X-Rays, 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 HDEC 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.

# Chapter 8: Statistical Considerations

## 8.1 General Statistical Considerations

Summary statistics will be generated for all relevant variables. In the comparison of continuous variables, distributions will be tested for the normality assumption. If standard parametric techniques are found to be inadequate, an appropriate non-parametric technique will be used. Categorical variables will be presented using frequencies and percentages and compared using differences in proportions unless stated otherwise. For safety/adverse event reporting, both the number of overall events and the number of participants experiencing that event will be tabulated. No corrections will be made for multiple testing procedures.

## 8.2 Statistical Hypotheses

The primary objective of the study is assessment of safety. Therefore, there are no formal statistical hypotheses associated with any of the endpoints. Outcomes will be primary descriptive in nature.

## 8.3 Sample Size

The sample size of at least 10 participants completing the trial is required. As this is a feasibility study assessing safety, this sample size is for a convenience sample and is not based on a power analysis.

## 8.4 Outcome Measures

The two study periods are:

1) Control-IQ at home run-in period.

2) The Tandem Freedom hotel observed period.

Primary Endpoints for each period:

1. Severe hypoglycemia (with cognitive impairment such that assistance of another individual is needed for treatment)
2. Number of diabetic ketoacidosis events

Secondary Endpoints for each period:

1. All device-related adverse events
2. CGM hypoglycemia outcomes
    a. Overall % time <3.0 mmol/L
    b. Overall % time <3.9 mmol/L
3. Times in ranges-overall (3.9-10 mmol/L, >10 mmol/L, >13.9 mmol/L, 3.9-7.9 mmol/L)
4. Mean glucose
5. Overall variability (CV and SD)

Due to the small sample size and feasibility nature of the study, primarily descriptive statistics will be used.

## 8.5 Baseline Descriptive Statistics

Baseline demographic and clinical characteristics of the cohort of participants will be summarized in a table using summary statistics appropriate to the distribution of each variable.

## 8.6 Additional Tabulations and Analyses

The following data will be tabulated at baseline, for the run-in period, and for the hotel supervised period

- Insulin metrics (units/kg): total daily insulin, total daily manual insulin.

## 8.7 Device Issues

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

- Number of device issues by type, and number of unique participants with each type of device issue

## 8.8 Multiple Comparison/Multiplicity

There are no adjustments performed for multiple comparisons.

## 8.9 Handling of Missing Data

All practical monitoring and follow-up steps will be taken to ensure complete and accurate data collection. All analyses will be based on available data only; no imputation for missing data is planned.

# 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). 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.

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

## 9.2 Study Records Retention

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

Study documents should be retained for a minimum of 10 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 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, 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 monitoring plan will be developed and revised as needed during the course of the study. Study conduct and monitoring will conform with 21 Code of Federal Regulations (CFR) 812 and Guideline on the Regulation of Therapeutic Products in New Zealand Part 11: Clinical trials – regulatory approval and good clinical practice requirements, including the Guideline for Good Clinical Practice E6(R2) (EMA/CHMP/ICH/135/1995). This plan will describe in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

A data management plan will be also be developed and revised as needed during the course of the study.

The data of most importance for monitoring at the site are participant eligibility and adverse events. Therefore, the monitoring 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 monitoring may include:

- Qualification assessment, training, and certification for sites and site personnel
- Oversight of HDEC coverage and informed consent procedures
- On-site monitoring (site visit): source data verification, data edits/audit trail, protocol review of entered data and edits, statistical monitoring, study closeout, site visit report
- Agent/Device accountability
- Communications with site staff
- Patient retention and visit completion
- Management of noncompliance
- Documenting monitoring activities
- Adverse event reporting and monitoring

Sponsor 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 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 participants, adversely affects the welfare, rights, or safety of the research participants, 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 HDEC 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 agrees that the study will be conducted according to the applicable New Zealand regulations (Medsafe and Health and Disability Ethics Committee), International Conference on Harmonization (ICH) guidelines on Good Clinical Practice (GCP) and the principles of the World Medical Association Declaration of Helsinki 2008. The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations.

## 10.2 Institutional Review Boards

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Health and Disability Ethics Committee (HDEC) for review and approval. Full HDEC approval must be obtained before any participant is enrolled. Only substantial amendments to the protocol will require HDEC review and approval before the changes are implemented to the study. All substantial changes to the consent form will be HDEC approved.

## 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 HDEC-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 HDEC, 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 HDEC, institutional policies, sponsor requirements, and applicable regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored by the study sponsor. 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 will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Sponsor.

### 10.3.3 Future Use of Stored Specimens and Data

After the study is completed, a de-identified dataset will be provided to the study Sponsor.

No biologic specimens will be stored.

# Chapter 11: References


1. Brown SA, Kovatchev BP, Raghinaru D, Lum JW, Buckingham BA, Kudva YC, Laffel LM, Levy CJ, Pinsker JE, Wadwa RP, Dassau E, Doyle FJ 3rd, Anderson SM, Church MM, Dadlani V, Ekhlaspour L, Forlenza GP, Isganaitis E, Lam DW, Kollman C, Beck RW; iDCL Trial Research Group. Six-month randomized, multicenter trial of closed-loop control in type 1 diabetes. N Engl J Med. 2019; 381:1707-1717.

2. Breton MD, Kanapka LG, Beck RW, Ekhlaspour L, Forlenza GP, Cengiz E, Schoelwer M, Ruedy KJ, Jost E, Carria L, Emory E, Hsu LJ, Oliveri M, Kollman CC, Dokken BB, Weinzimer SA, DeBoer MD, Buckingham BA, Cherñavvsky D, Wadwa RP; iDCL Trial Research Group. A randomized trial of closed-loop control in children with type 1 diabetes. N Engl J Med. 2020; 383:836-845.

3. Breton M, Kovatchev B. One year real-world use of the Control-IQ advanced hybrid closed loop technology. Diabetes Technol Ther. 2021;23:601-608.