

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

3 A Pivotal Study of t:slim X2 with Control-IQ Technology

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22

23

**TABLE OF CONTENTS**

24 **CHAPTER 1: BACKGROUND INFORMATION ..... 15**

25 1.1 Introduction ..... 15

26 1.2 Rationale ..... 18

27 1.3 Potential Risks and Benefits of the Investigational Device ..... 18

28 1.3.1 Known Potential Risks ..... 18

29 1.3.1.1 Venipuncture Risks ..... 18

30 1.3.1.2 Fingerstick Risks ..... 18

31 1.3.1.3 Subcutaneous Catheter Risks (CGM) ..... 18

32 1.3.1.4 Risk of Hypoglycemia ..... 18

33 1.3.1.5 Risk of Hyperglycemia ..... 20

34 1.3.1.6 Risk of Device Reuse ..... 20

35 1.3.1.7 Questionnaire ..... 20

36 1.3.1.8 Other Risks ..... 20

37 1.3.2 Known Potential Benefits ..... 21

38 1.3.3 Risk Assessment ..... 21

39 1.4 General Considerations ..... 21

40 **CHAPTER 2: STUDY ENROLLMENT AND SCREENING ..... 22**

41 2.1 Participant Recruitment and Enrollment ..... 22

42 2.1.1 Informed Consent and Authorization Procedures ..... 22

43 2.2 Participant Inclusion Criteria ..... 23

44 2.3 Participant Exclusion Criteria ..... 23

45 2.4 Screening Procedures ..... 24

46 2.4.1 Data Collection and Testing ..... 24

47 **CHAPTER 3: RUN-IN PHASE ..... 26**

48 3.1 Run-in Phase Overview ..... 26

49 3.2 Optimization of Insulin Pump Settings ..... 29

50 **CHAPTER 4: RANDOMIZATION VISIT ..... 31**

51 4.1 Randomization Visit ..... 31

52 4.1.1 HbA1c ..... 31

53 4.1.2 Baseline C-Peptide Assessment ..... 31

54 4.1.3 Randomization ..... 31

55 4.1.4 Questionnaires ..... 31

56 **CHAPTER 5: RANDOMIZED TRIAL PROCEDURES ..... 32**

57 5.1 Procedures for the CLC Group..... 32

58 5.1.1 Study System Training ..... 32

59 5.1.2 Home Use of the Study System..... 34

60 5.1.3 Study Device Download..... 34

61 5.1.4 1-Week Phone Contact..... 34

62 5.1.5 2-Week Visit (Training Review and Insulin Pump Optimization)..... 34

63 5.2 Procedures for the SAP Group ..... 35

64 5.2.1 Study Device Data Download ..... 35

65 5.2.2 1-Week Phone Contact..... 35

66 5.2.3 2-Week Visit (Training Review and Insulin Pump Optimization)..... 35

67 5.3 Follow-up Visits and Phone Contacts for Both Groups ..... 36

68 5.3.1 Follow-up Visits ..... 36

69 5.3.1.1 Procedures at Follow-up Visits..... 36

70 5.3.2 Phone Contacts ..... 37

71 5.4 Early Termination Visit (If Applicable) ..... 37

72 5.5 Unscheduled Visits ..... 37

73 5.6 Participant Access to Study Device at Study Closure ..... 37

74 **CHAPTER 6: STUDY DEVICES..... 38**

75 6.1 Description of the Investigational Device ..... 38

76 6.1.1 Insulin Pump..... 38

77 6.1.2 Continuous Glucose Monitoring ..... 38

78 6.1.3 Blood Glucose Meter and Strips..... 38

79 6.1.4 Ketone Meter and Strips..... 38

80 6.1.5 Study Device Accountability Procedures ..... 38

81 6.1.6 Blood Glucose Meter Testing..... 38

82 6.1.7 Blood Ketone Testing..... 38

83 6.2 Safety Measures..... 39

84 6.2.1 CGM Calibration..... 39

85 6.2.2 System Failure..... 39

86 6.2.3 Hypoglycemia Threshold Alert and Safety Protocol..... 39

87 6.2.4 Hyperglycemia Threshold Alert and Safety Protocol..... 39

88 **CHAPTER 7: TESTING PROCEDURES AND QUESTIONNAIRES ..... 41**

89 7.1 Laboratory Testing ..... 41

90 7.2 Questionnaires ..... 41

91 **CHAPTER 8: ADVERSE EVENTS, DEVICE ISSUES, AND STOPPING RULES ..... 45**

92	8.1 Adverse Events.....	45
93	8.1.1 Definitions.....	45
94	8.1.2 Reportable Adverse Events.....	46
95	8.1.2.1 Hypoglycemic Events.....	46
96	8.1.2.2 Hyperglycemic Events/Diabetic Ketoacidosis.....	46
97	8.1.3 Relationship of Adverse Event to Study Device.....	47
98	8.1.4 Intensity of Adverse Event.....	47
99	8.1.5 Coding of Adverse Events.....	49
100	8.1.6 Outcome of Adverse Event.....	49
101	8.2 Reportable Device Issues.....	50
102	8.3 Pregnancy Reporting.....	50
103	8.4 Timing of Event Reporting.....	50
104	8.5 Stopping Criteria.....	51
105	8.5.1 Participant Discontinuation of Study Device.....	51
106	8.5.2 Criteria for Suspending or Stopping Overall Study.....	51
107	8.6 Independent Safety Oversight.....	52
108	8.7 Risks.....	52
109	<b>CHAPTER 9: MISCELLANEOUS CONSIDERATIONS.....</b>	<b>53</b>
110	9.1 Drugs Used as Part of the Protocol.....	53
111	9.2 Prohibited Medications, Treatments, and Procedures.....	53
112	9.3 Participant Compensation.....	53
113	9.4 Participant Withdrawal.....	53
114	9.5 Confidentiality.....	53
115	<b>CHAPTER 10: STATISTICAL CONSIDERATION.....</b>	<b>55</b>
116	10.1 Statistical and Analytical Plans.....	55
117	10.2 Statistical Hypotheses.....	55
118	10.3 Sample Size.....	55
119	10.4 Outcome Measures.....	55
120	10.4.1 Primary Efficacy Endpoint.....	55
121	10.4.2 Secondary Efficacy Endpoints.....	56
122	10.4.2.1 Secondary Efficacy Endpoints Included in Hierarchical Analysis.....	56
123	10.4.2.2 Other Secondary Efficacy Endpoints.....	56
124	10.4.2.3 Safety Analyses.....	57
125	10.4.3 CGM Metrics Calculations.....	58
126	10.5 Analysis Datasets and Sensitivity Analyses.....	58
127	10.5.1 Per Protocol Analyses.....	58

128 10.5.2 Other Sensitivity Analyses ..... 58

129 10.6 Analysis of the Primary Efficacy Endpoint ..... 59

130 10.7 Analysis of the Secondary Endpoints ..... 59

131 10.7.1 Hierarchical Analyses ..... 59

132 10.7.2 Other Endpoint Analyses ..... 61

133 10.8 Safety Analyses ..... 62

134 10.9 Intervention Adherence ..... 63

135 10.10 Adherence and Retention Analyses ..... 63

136 10.11 Baseline Descriptive Statistics ..... 63

137 10.12 Device Issues ..... 64

138 10.13 Planned Interim Analyses ..... 65

139 10.14 Subgroup Analyses ..... 65

140 10.15 Multiple Comparison/Multiplicity ..... 66

141 10.16 Exploratory Analyses ..... 66

142 **CHAPTER 11: DATA COLLECTION AND MONITORING ..... 67**

143 11.1 Case Report Forms and Device Data ..... 67

144 11.2 Study Records Retention ..... 67

145 11.3 Quality Assurance and Monitoring ..... 67

146 11.4 Protocol Deviations ..... 68

147 **CHAPTER 12: ETHICS/PROTECTION OF HUMAN PARTICIPANTS ..... 69**

148 12.1 Ethical Standard ..... 69

149 12.2 Institutional Review Boards ..... 69

150 12.3 Informed Consent Process ..... 69

151 12.3.1 Consent Procedures and Documentation ..... 69

152 12.3.2 Participant and Data Confidentiality ..... 69

153 **CHAPTER 13: REFERENCES ..... 71**

154

155

**LIST OF ABBREVIATIONS**

ABBREVIATION	DEFINITION
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

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**Signature Page**

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

A Pivotal Study of t:slim X2 with Control-IQ Technology

**Protocol Identifying Number: DCLP3**

**IND/IDE Sponsor: University of Virginia**

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**5 NOV 2018**

<b>JCHR Principal Investigator</b>	
<b>Name, degree</b>	John W. Lum, M.S.
<b>Signature / Date</b>	
<b>Protocol Chair/Director</b>	
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<b>Signature / Date</b>	

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171 **SITE PRINCIPAL INVESTIGATOR STATEMENT OF COMPLIANCE**

172 Protocol Title: **The International Diabetes Closed Loop (iDCL) trial: Clinical Acceptance of**  
173 **the Artificial Pancreas - A Pivotal Study of t:slim X2 with Control-IQ Technology**

174 Protocol Version/Date: v10.0/5 NOV 2018

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

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

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

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

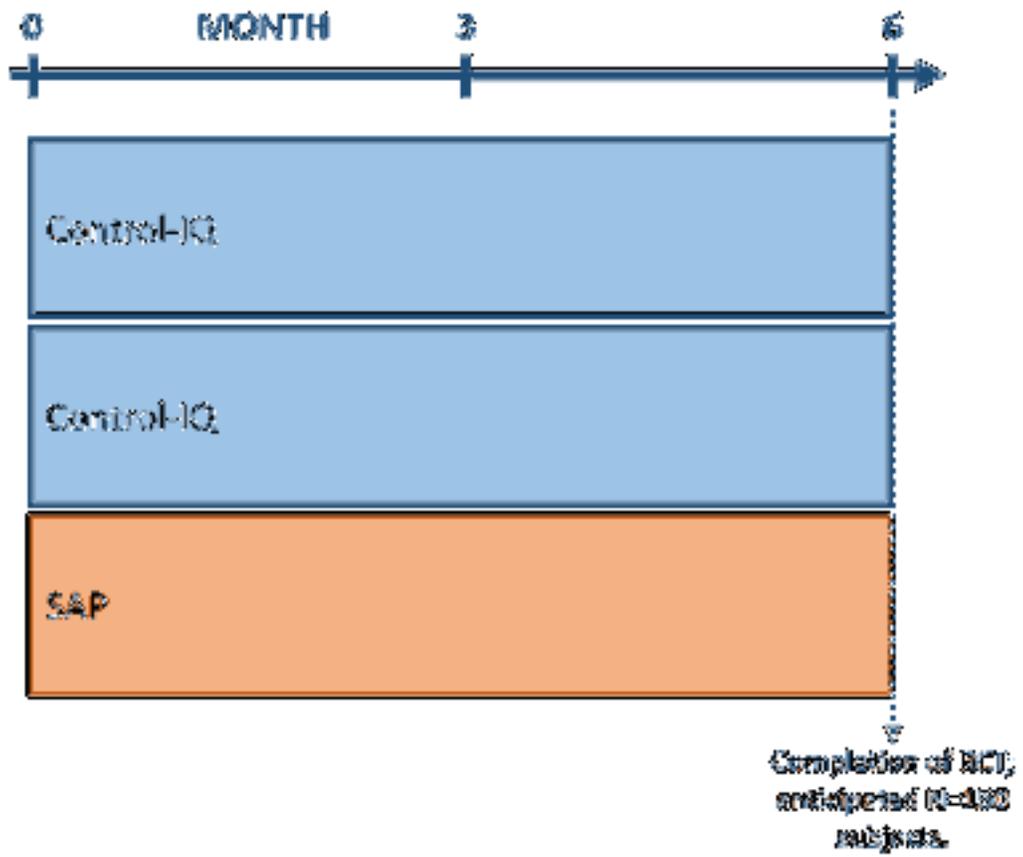
193 Investigator's Signature \_\_\_\_\_ Date: \_\_\_\_ / \_\_\_\_ / \_\_\_\_  
194 dd mmm yyyy

195 Investigator's Name: \_\_\_\_\_

196 Site Name/Number: \_\_\_\_\_

## PROTOCOL SUMMARY

PARTICIPANT AREA	DESCRIPTION
<b>Title</b>	The International Diabetes Closed Loop (iDCL) Trial: Pivotal Trial of t:slim X2 with Control-IQ Technology
<b>Précis</b>	A randomized controlled trial of 6 month at home closed loop system vs. sensor-augmented pump.
<b>Investigational Device</b>	t:slim X2 with Control-IQ and Dexcom G6 system
<b>Objectives</b>	The objective of the study is to assess efficacy and safety of a closed loop system (t:slim X2 with Control-IQ Technology) in a large randomized controlled trial.
<b>Study Design</b>	Randomized Clinical Trial with 2:1 randomization to intervention with the closed loop system vs. sensor-augmented pump for 6 months. See Figure 1.
<b>Number of Sites</b>	Seven US clinical sites
<b>Endpoint</b>	The primary outcome is time in target range 70-180 mg/dL measured by CGM in CLC group vs. SAP group at 6 months
<b>Population</b>	<p><b>Key Inclusion Criteria</b></p> <ul style="list-style-type: none"> <li>• Type 1 Diabetes</li> <li>• Ages 14 and older</li> </ul> <p><b>Key Exclusion Criteria</b></p> <ul style="list-style-type: none"> <li>• Use of any non-insulin glucose-lowering agents except metformin</li> </ul>
<b>Sample Size</b>	Up to seven clinical sites in the United States may enroll up to 225 total participants with the goal of randomizing 168 participants such that at least 150 participants complete the 6-month randomized trial.
<b>Treatment Groups</b>	<p>Randomized Trial</p> <ul style="list-style-type: none"> <li>• Intervention Group: t:slim X2 with Control-IQ Technology and Study CGM.</li> <li>• Control Group: Sensor-augmented pump (SAP) with no automated insulin delivery, and study CGM</li> </ul>
<b>Participant Duration</b>	6-8 months
<b>Protocol Overview/Synopsis</b>	After consent is signed, eligibility will be assessed. Eligible participants not currently using an insulin pump and Dexcom G4, G5, or G6 CGM with minimum data requirements will initiate a run-in phase of 2 to 8 weeks that will be customized based on whether the participant is already a pump or CGM user. Participants who skip or successfully complete the run-in will be randomly assigned 2:1 to the use of closed-loop control (CLC group) using t:slim X2 with Control-IQ Technology vs SAP for 6 months.



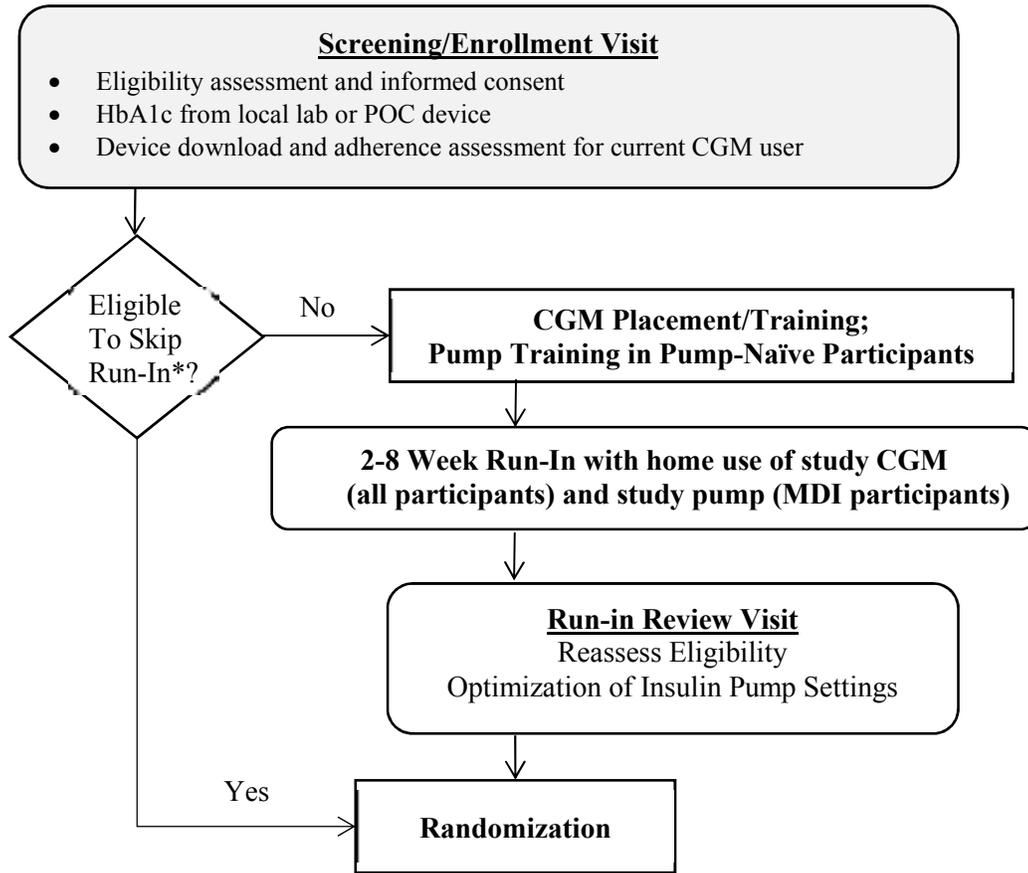
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Figure 1: Study Design: Participants Randomized 2:1 Control-IQ vs. SAP

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**SCHEMATIC OF STUDY DESIGN**

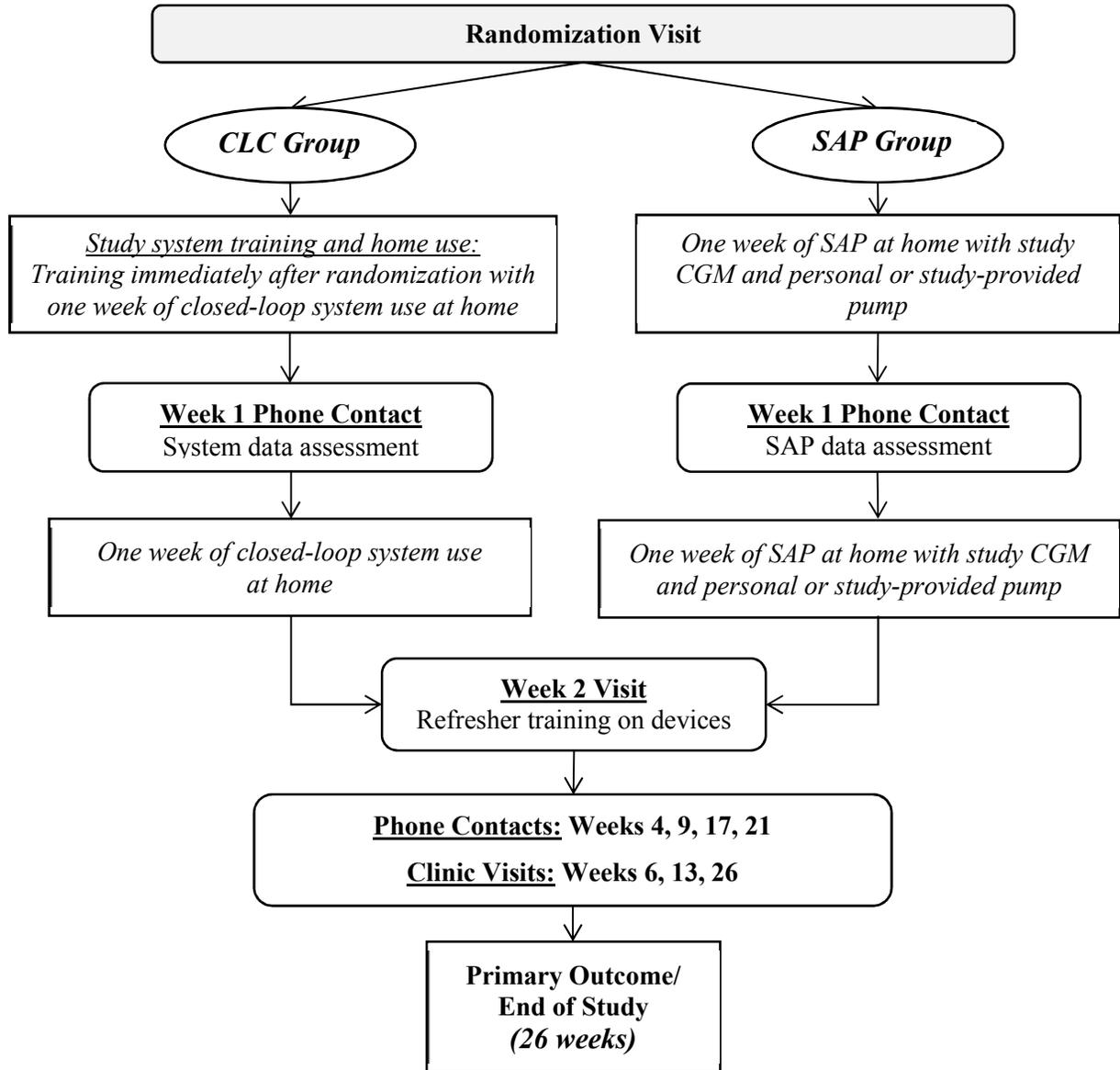


\*Current use of insulin pump and Dexcom G4, G5, or G6 CGM with readings captured on at least 11 out of the previous 14 days

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**Figure 2: Schematic of Study Design (Pre-Randomization)**



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Figure 3. Schematic of Study Design (Post-Randomization)

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**Table 1. Schedule of Study Visits and Procedures**

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	Pre	Pre	0	1w	2w	4w	6w	9w	13w	17w	21w	26w
<b>Visit (V) or Phone (P)</b>	V	V	V	P	V	P	V	P	V	P	P	V
<b>Comment</b>	Screen/ Enroll	Run-in	Rand									
<b>Eligibility Assessment</b>	X	X	X									
<b>HbA1c (DCA Vantage or similar point of care device, or local lab)</b>	X		X						X			X
<b>HbA1c (Central lab)</b>			X						X			X
<b>C-peptide (Central lab) and blood glucose assessment</b>			X									
<b>Pregnancy test (females of child-bearing potential)</b>	X		X						X			
<b>Device Data download(s)</b>	X	X	X	X	X	X	X	X	X	X	X	X
<b>Review diabetes management and AEs</b>		X	X	X	X	X	X	X	X	X	X	X
<b>Questionnaires as defined in section 7.2</b>			X						X			X

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## Chapter 1: Background Information

210

### 1.1 Introduction

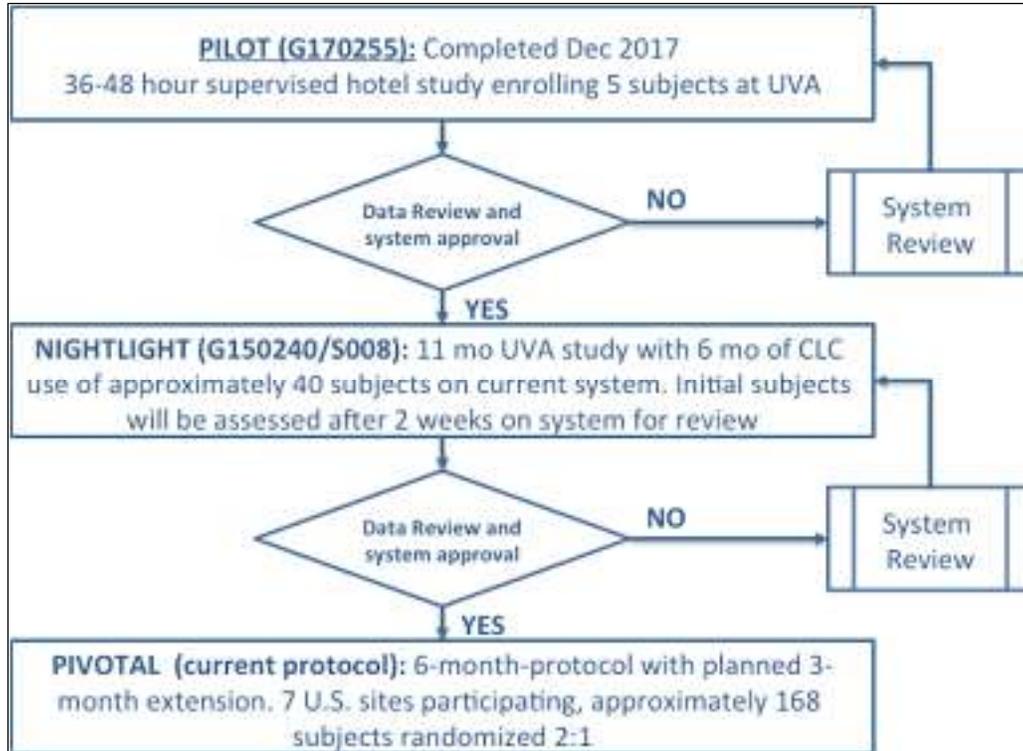
211 The Tandem X2 insulin pump with Control-IQ Technology is a third-generation closed-loop  
 212 control (CLC) system retaining the same control algorithm that was initially tested by UVA's  
 213 DiAs system and then implemented in the inControl system. DiAs is described in 13 IDEs  
 214 (see IDEs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

222 As described in the Background, this project is a result from a sequence of clinical trials that  
 223 have tested extensively the control system and in several centers in the U.S. and overseas. The  
 224 following 18 IDEs reflect this progress:

- 225 1. IDE #G110095: Feasibility study of closed loop control in type 1 diabetes using heart rate  
 226 monitoring as an exercise marker, approved 10/08/2011;
- 227 2. IDE #G120032: Early feasibility (pilot) study of outpatient control-to-range; 3/2/2012;
- 228 3. IDE #G120210: Early feasibility study 2 of outpatient control-to-range; 10/12/2012;
- 229 4. IDE #G130118: DiAs control-to-range nocturnal closed-loop camp study; 6/19/2013;
- 230 5. IDE #G130121: Optimizing closed-loop control of type 1 diabetes mellitus in adolescents;  
 231 6/19/2013;
- 232 6. IDE# G130142: Closed loop control in adolescents using heart rate as exercise indicator;  
 233 7/16/13;
- 234 7. IDE #G130143: Early feasibility study of adaptive advisory/automated (AAA) control of  
 235 type 1 diabetes; 7/19/2013;
- 236 8. IDE #G140066: Full day and night closed-loop with DiAs platform; 5/9/14.
- 237 9. IDE #G140068: Unified Safety System (USS) Virginia Closed Loop versus sensor  
 238 augmented pump therapy overnight in type 1 diabetes; 5/14/2014;
- 239 10. IDE #G140089: Outpatient control-to-range: Safety and efficacy with day-and-night in-home  
 240 use; 6/6/2014;
- 241 11. IDE #G140169: Unified Safety System (USS) Virginia Closed-Loop versus Sensor  
 242 Augmented Pump (SAP) therapy for hypoglycemia reduction in type 1 diabetes; 10/3/2014.
- 243 12. IDE #G150221: Reducing risks and improving glucose control during extended exercise in  
 244 youth with T1DM: The AP Ski Camp; 11/09/2015;
- 245 13. IDE #G150240: Project Nightlight: Efficacy and system acceptance of dinner/night vs. 24 hr  
 246 closed loop control; 11/12/2015;

- 247 14. IDE #G160047: Closed-loop in young children 5-8 years old using DiAs platform;
- 248 03/29/2016;
- 249 15. IDE #G160097: Clinical Acceptance of the Artificial Pancreas: the International Diabetes
- 250 Closed-Loop (iDCL) Trial/Research Site Training Protocol; 06/03/16.
- 251 16. IDE#G160181: PROTOCOL 1 for “Clinical Acceptance of the Artificial Pancreas: The
- 252 International Diabetes Closed Loop (iDCL) Trial; 09/21/16
- 253 17. IDE#G170255: Protocol 3 for “Pilot Trial of t:slim X2 with Control-IQ
- 254 Technology”;11/16/17 and IDE#G170255/S001 Protocol 3 for “Training Study of t:slim X2
- 255 with Control-IQ Technology”; 11/16/17
- 256 18. IDE#G170267: “Real-Time Monitoring and Glucose Control During Winter-Sport Exercise
- 257 in Youth with Type 1 Diabetes: The AP Ski Camp Continued”; 11/21/17

258 We further reference pre-submission Q170885 and our discussion with FDA on July 18, 2017  
 259 regarding the structure of studies intended to test inControl implemented on t:slim X2. Based on  
 260 the input provided by the Agency, we initially defined a series of three studies leading to a future  
 261 pivotal trial of this system (36-48 hr Pilot Study, 2 week at home Training Study, followed by  
 262 the Pivotal Trial). Since the time of the initial discussion, we have concluded a successful Pilot  
 263 of 5 Adult (December 2017) and a Ski Camp with 12 Teenagers (January 2018) on the System.  
 264 We have also received approval for the use of this system in a long-term home study (Project  
 265 Nightlight/G#150240/S008). The Project Nightlight Study will now replace the previous  
 266 Training Study as noted in Figure 4.



267  
 268 **Figure 4: Sequence of planned studies leading to this pivotal trial of the**  
 269 **Tandem X2 insulin pump with Control-IQ Technology**

270 A successful pilot of 5 Adults (mean age 52.8 yrs; 3F/2M, mean A1c 6.5%) with Type 1  
 271 Diabetes was completed in December 2017. In this pilot study, the system was challenged with  
 272 a variety of scenarios including: Pump disconnection, CGM sensor removal without stopping  
 273 session, CGM sensor change, Basal Rate change, Cartridge Change, Extended Bolus, Calibration  
 274 at non-ideal conditions, Stopping Control-IQ, Reset Sleep Time, Restaurant Meals and Exercise  
 275 (treadmill/walk). The study demonstrated excellent connectivity with 98% time in closed-loop  
 276 control and 94% time CGM is available during 196 hours of use.

277 **Table 2. Pilot Study results based on time in closed-loop**

METRIC (COMPUTED DURING CLOSED-LOOP USE)	OVERALL	DAYTIME	NIGHTTIME
<b>Mean glucose (mg/dL)</b>	<b>129</b>	<b>135</b>	<b>121</b>
Coefficient of variation (median)	27%	27%	21%
% below 54 mg/dL (median)	0.7%	0.0%	0.0%
% below 60 mg/dL (median)	1.1%	2.0%	0.0%
% below 70 mg/dL (median)	2.9%	4.1%	1.0%
<b>Percent in range 70-180 mg/dL (mean)</b>	<b>87%</b>	<b>82%</b>	<b>94%</b>
% above 180 mg/dL (median)	5%	8%	6%
% above 250 mg/dL (median)	0%	0%	0%
% above 300 mg/dL (median)	0%	0%	0%

278 **Closed-Loop Control System**

279 The Closed-Loop Control System contained in t-slim X2 with Control-IQ Technology is  
 280 described in Master File MAF-2032/A008. Control-IQ Technology is derived from inControl  
 281 previously described in IDE# G160097, G160181, G150240 and G140169/S010. The CLC is  
 282 an “artificial pancreas” (AP) application that uses advanced closed loop control algorithms to  
 283 automatically manage blood glucose levels for people with Type 1 Diabetes. The system  
 284 modulates insulin to keep blood glucose in a targeted range. The system components include  
 285 the t:slim X2 with Control-IQ Technology and the Dexcom CGM G6.



286 **Figure 5. t:slim X2 with Control-IQ and Dexcom G6 system**  
 287

288 **1.2 Rationale**

289 The objective of this randomized clinical trial is to 1) assess the efficacy and safety of the  
290 Control-IQ closed loop system over a 6 month period, the data from which may be used for  
291 subsequent PMA application for this system and 2) investigate longer term use of the system  
292 compared with switching to sensor-augmented pump therapy.

293 **1.3 Potential Risks and Benefits of the Investigational Device**

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

297 **1.3.1 Known Potential Risks**

298 **1.3.1.1 Venipuncture Risks**

299 A hollow needle/plastic tube will be placed in the arm for taking blood samples. Blood draws  
300 can cause some common reactions like pain, bruising, or redness at the sampling site. Less  
301 common reactions include bleeding from the sampling site, formation of a small blood clot or  
302 swelling of the vein and surrounding tissues, and fainting.

303 **1.3.1.2 Fingertick Risks**

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

310 **1.3.1.3 Subcutaneous Catheter Risks (CGM)**

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

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

320 **1.3.1.4 Risk of Hypoglycemia**

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

326 of hypoglycemia. A CGM functioning poorly and significantly over-reading glucose values  
327 could lead to inappropriate insulin delivery.

328 **1.3.1.5 Risk of Hyperglycemia**

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

333 **1.3.1.6 Risk of Device Reuse**

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

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

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

350 **1.3.1.7 Questionnaire**

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

356 **1.3.1.8 Other Risks**

357 Some participants may develop skin irritation or allergic reactions to the adhesives used to secure  
 358 the CGM, or to secure the insulin infusion sets for the continuous subcutaneous insulin infusion.  
 359 If these reactions occur, different adhesives or “under-taping” (such as with IV 3000, Tegaderm,  
 360 etc.) will be tried, sites will be rotated frequently, and a mild topical steroid cream or other  
 361 medication may be required.

362 Whenever the skin is broken there is the possibility of an infection. The CGM and pump  
 363 infusion sites are inserted under the skin. It is possible that any part that is inserted under the  
 364 skin may cause an infection. These occur very infrequently, but, if an infection was to occur,  
 365 oral and/or topical antibiotics can be used. The risk of skin problems could be greater if you use  
 366 a sensor for longer than it is supposed to be used. Therefore, participants will be carefully  
 367 instructed about proper use of the sensor.

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

### 372 **1.3.2 Known Potential Benefits**

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

376 It is expected that this protocol will yield increased knowledge about using an automated  
377 closed-loop to control the glucose level and is intended to develop data to support a future  
378 PMA-application. The individual participant may not benefit from study participation.

### 379 **1.3.3 Risk Assessment**

380 Based on the facts that (1) adults and adolescents with diabetes experience mild hypoglycemia  
381 and hyperglycemia frequently as a consequence of the disease and its management, (2) the study  
382 intervention involves periodic automated insulin dosing that may increase the likelihood of  
383 hypoglycemia, and periodic automated attenuation of insulin delivery that may increase the  
384 likelihood of hyperglycemia, (3) mitigations are in place, and have been tested in prior studies  
385 using the investigational device system in the home setting, that limit the likelihood of excessive  
386 insulin dosing or prolonged withdrawal of insulin, and (4) rapid reversal of hypoglycemia and  
387 hyperglycemia can be achieved, it is the assessment of the investigators that this protocol falls  
388 under DHHS 46.405 which is a minor increase over minimal risk. In addition, it is the belief of  
389 the investigators that this study also presents prospect of direct benefit to the participants and  
390 general benefit to others with diabetes.

### 391 **1.4 General Considerations**

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

395 Whenever possible, data will be directly collected in electronic case report forms, which will be  
396 considered the source data.

397 There is no restriction on the number of participants to be enrolled by each site toward the  
398 overall recruitment goal.

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

402

## Chapter 2: Study Enrollment and Screening

403

### 2.1 Participant Recruitment and Enrollment

404 Enrollment will proceed with the goal of having 168 participants enter the randomized trial, with  
405 the expectation that 150 participants will complete the 6-month randomized trial. A maximum  
406 of 225 individuals may be enrolled into screening for the study in order to achieve this goal.

407 Study participants will be recruited from 7 clinical centers in the United States without regard to  
408 gender, race, or ethnicity. There is no restriction on the number of participants to be enrolled by  
409 each site toward the overall recruitment goal.

410 A study goal will be to have the following minimum numbers of participants complete the trial in  
411 the specified subgroups at the time of enrollment:

- 412 • At least 50 participants with HbA1c  $\geq 7.5\%$  and 50 participants with HbA1c  $< 7.5\%$
- 413 • At least 50 participants in the age range 14 to  $< 26$  and 50 participants  $\geq 26$  years old
- 414 • At least 30 participants who are on multiple daily injections (MDI) rather than pump
- 415 • At least 30 participants who are CGM-naïve (defined as not using a CGM in the prior 14  
416 days)

417

#### 2.1.1 Informed Consent and Authorization Procedures

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

421 For potential study participants  $\geq 18$  years old, the study protocol will be discussed with the  
422 potential study participant by study staff. The potential study participant will be given the  
423 Informed Consent Form to read. Potential study participants will be encouraged to discuss the  
424 study with family members and their personal physicians(s) before deciding whether to  
425 participate in the study.

426 For potential participants under 18 years of age, a parent/legal guardian (referred to subsequently  
427 as “parent”) will be provided with the Informed Consent Form to read and will be given the  
428 opportunity to ask questions. Potential participants meeting the IRB’s minimum age of assent  
429 will be given a Child Assent Form to read and discuss with his/her parents and study personnel.  
430 If the parent and child agree to participate, the Informed Consent Form and Child Assent Form  
431 will be signed. A copy of the consent form will be provided to the participant and his/her parent  
432 and another copy will be added to the participant’s study record.

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

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

439 **2.2 Participant Inclusion Criteria**

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

- 442 1. Clinical diagnosis, based on investigator assessment, of type 1 diabetes for at least one year  
443 and using insulin for at least 1 year
- 444 2. Familiarity and use of a carbohydrate ratio for meal boluses.
- 445 3. Age  $\geq 14.0$  years old
- 446 4. For females, not currently known to be pregnant  
447 *If female and sexually active, must agree to use a form of contraception to prevent pregnancy*  
448 *while a participant in the study. A negative serum or urine pregnancy test will be required*  
449 *for all females of child-bearing potential. Participants who become pregnant will be*  
450 *discontinued from the study. Also, participants who during the study develop and express*  
451 *the intention to become pregnant within the timespan of the study will be discontinued.*
- 452 5. For participants <18 years old, living with one or more parent/legal guardian knowledgeable  
453 about emergency procedures for severe hypoglycemia and able to contact the participant in  
454 case of an emergency.
- 455 6. Willingness to suspend use of any personal CGM for the duration of the clinical trial once the  
456 study CGM is in use
- 457 7. Willingness to use a regular insulin pump during the study with no automatic insulin  
458 adjustment based on glucose level when assigned to participate in an SAP group
- 459 8. Investigator has confidence that the participant can successfully operate all study devices and  
460 is capable of adhering to the protocol
- 461 9. Willingness to switch to lispro (Humalog) or aspart (Novolog) if not using already, and to  
462 use no other insulin besides lispro (Humalog) or aspart (Novolog) during the study.
- 463 10. Total daily insulin dose (TDD) at least 10 U/day
- 464 11. Willingness not to start any new non-insulin glucose-lowering agent during the course of the  
465 trial (see section 2.3)

466 **2.3 Participant Exclusion Criteria**

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

- 469 1. Concurrent use of any non-insulin glucose-lowering agent other than metformin (including  
470 GLP-1 agonists, Symlin, DPP-4 inhibitors, SGLT-2 inhibitors, sulfonylureas).
- 471 2. Hemophilia or any other bleeding disorder
- 472 3. A condition, which in the opinion of the investigator or designee, would put the participant or  
473 study at risk

- 474 4. Participation in another pharmaceutical or device trial at the time of enrollment or during the  
475 study
- 476 5. Employed by, or having immediate family members employed by Tandem Diabetes Care,  
477 Inc. or TypeZero Technologies, LLC, or having a direct supervisor at place of employment  
478 who is also directly involved in conducting the clinical trial (as a study investigator,  
479 coordinator, etc.); or having a first-degree relative who is directly involved in conducting the  
480 clinical trial

481 **2.4 Screening Procedures**

482 After informed consent has been signed, a potential participant will be evaluated for study  
483 eligibility through the elicitation of a medical history, performance of a physical examination  
484 by study personnel and local laboratory testing if needed to screen for exclusionary medical  
485 conditions.

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

488 **2.4.1 Data Collection and Testing**

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

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

- 494 • Inclusion and exclusion criteria assessed
- 495 • Demographics (date of birth, sex, race and ethnicity)
- 496 • Contact information (retained at the site and not entered into study database)
- 497 • Medical history
- 498 • Concomitant medications
- 499 • Physical examination to include:
- 500     ◆ Weight, height
- 501     ◆ Vital signs including measurement of blood pressure and pulse

- 502 • Blood draw for:
- 503     ◆ HbA1c level measured using the DCA2000 or comparable point of care device or local
- 504     lab
- 505     ◆ Measurement performed as part of usual clinical care prior to obtaining informed
- 506     consent for participation in the trial may be used
- 507     ◆ Measurement must be made within two weeks prior to enrollment
- 508 • Urine or serum pregnancy test for all women of child-bearing potential
- 509 Screening procedures will last approximately 1-2 hours.

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## Chapter 3: Run-In Phase

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### 3.1 Run-in Phase Overview

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This phase may begin immediately after enrollment is complete or may be deferred for a maximum of 28 days. The purpose of this run-in phase is to 1) assess compliance with study procedures, 2) to introduce the study CGM to study participants without current use of a CGM and 3) to introduce an insulin pump to participants who have not previously used an insulin pump.

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Participants who do not currently use an insulin pump and a Dexcom G4, G5, or G6 CGM with readings captured on at least 11 out of the previous 14 days at the time of enrollment will be required to participate in the run-in phase. Participants will use the study CGM for a minimum of 11 days with a goal of at least 14 days during the run-in phase. Participants who are on MDI at enrollment will receive a study pump to use and will receive training as detailed below. All participants will receive training on the study CGM as detailed below. This will be an unblinded use of the study CGM.

524

#### Initiation of CGM

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The participant will be provided with sensors and instructed to use the study CGM on a daily basis. Training will be provided to participants not experienced with CGM use as to how to use the CGM in real-time to make management decisions and how to review the data after an upload for retrospective review. Participants using a personal CGM prior to the study will discontinue the personal CGM beginning in this period.

530

531

The participant will be observed placing the sensor. The study CGM user's guide will be provided for the participant to take home.

532

#### Initiation of Pump

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Pump-naïve participants who have not used a CGM in the 14 days prior to enrollment will first complete a CGM-only Run-in period of approximately 14 days prior to initiating study pump use.

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Participants who are pump-naïve will be provided with a study pump similar to the pump used with the closed-loop system, but with the closed-loop control feature either absent or deactivated, and will be instructed to use the pump on a daily basis. An initial basal insulin profile will be customized on a per-participant basis. Total daily insulin dose will be reduced by approximately 20% as a general rule, with a recommended method outlined in a separate procedures manual. Further adjustments to total daily dose (TDD) and intraday basal rate profile may be made during the course of the run-in period.

543

Participants will complete training on the study pump as detailed below.

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- The participant will be fully instructed on the study insulin pump. A qualified system trainer will conduct the training and in particular discuss differences from their home pump in important aspects such as calculation of insulin on board (IOB) and correction boluses.

547 Additional topics are not limited to but may include: infusion site initiation,  
548 cartridge/priming procedures, setting up the pump, charging the pump, navigation  
549 through menus, bolus procedures including stopping a bolus, etc.

550 • The study team will assist the participant in study pump infusion site initiation and will start  
551 the participant on the study pump. The study pump will be programmed with the  
552 participant's usual basal rates and pump parameters. The participant's personal pump will be  
553 removed.

554 • The participant will be supervised with the study pump during at least one meal or snack  
555 bolus to ensure participant understanding of the pump features.

556 • The participant will be encouraged to review the literature provided with the pump and  
557 infusion sets after the training is completed.

### 558 **Blood Glucose and Ketone Testing**

559 Participants will receive supplies for blood glucose and ketone testing.

#### 560 • Blood glucose testing

561 ♦ Participants will be provided with a study blood glucose meter, test strips, and standard  
562 control solution to perform quality control (QC) testing at home per manufacturer  
563 guidelines.

564 ♦ All study blood glucose meters will be QC tested with at least two different  
565 concentrations of control solution if available during all office visits. A tested meter  
566 will not be used in a study if it does not read within the target range at each  
567 concentration per manufacturer labeling. The participant will be instructed to contact  
568 study staff for a replacement of the meter, test strips, and control solution if a meter  
569 fails QC testing at home.

570 ♦ Participants will be reminded to use the study blood glucose meter for all fingerstick  
571 BGs during the study.

572 ♦ Participants will be given guidelines for treatment of low or high blood glucose.

#### 573 • Blood ketone testing

574 ♦ Participants will be provided with a study blood ketone meter, test strips, and standard  
575 control solution to perform QC testing at home per manufacturer guidelines.

576 ♦ All study blood ketone meters will be QC tested with at least two different  
577 concentrations of control solution if available during all office visits. A tested meter  
578 will not be used in a study if it does not read within the target range at each  
579 concentration per manufacturer labeling. The participant will be instructed to contact  
580 study staff for a replacement of the meter, test strips, and control solution if a meter  
581 fails QC testing at home.

582 ♦ Participants will be instructed to perform blood ketone testing as described in  
583 section 6.2.4

584 ♦ Participants will be given guidelines for treatment of elevated blood ketones

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

587 **Assessment of Successful Completion of the Run-in Phase**

588 Enrolled participants will return approximately 14 days after the initiation of the run-in phase  
 589 to assess progress or successful completion of the phase. If needed, one or more interim visits or  
 590 phone contacts may occur to assist the participant with any system use issues. Visit procedures  
 591 will include the following:

- 592 • Assessment of compliance with the use of the CGM (and study pump if applicable)
- 593 • Assessment of skin reaction in areas where a CGM sensor was worn
- 594 • Assessment of eligibility to continue to the RCT phase of the study

595 The CGM data (and pump data if applicable) will be downloaded and reviewed. CGM-naïve  
 596 MDI participants who have completed an initial CGM-only use period without any safety issues  
 597 will be transitioned to a study pump as described above and will begin home use of CGM use  
 598 with study pump for approximately 14 days before returning to the clinic for another progress  
 599 assessment. MDI participants will be contacted by study staff within approximately 24hrs, 72hrs,  
 600 and 1 week after pump initiation to answer any questions related to device use prior to the 2  
 601 week visit. All subjects may have unlimited contact with the study team as needed.

602 To enter the randomized trial, participants must have obtained CGM readings on at least 11 out  
 603 of the previous 14 days, and pump-naïve patients must have successfully used the study pump  
 604 each day. If a participant fails to meet these criteria, or if it is determined that the participant will  
 605 benefit from additional time with equipment training, the run-in period may be extended at the  
 606 discretion of the investigator. One or two additional periods may occur, each a minimum of 11  
 607 days with a goal of at least 14 days, with another clinic visit to assess results after each period  
 608 using the same criteria as above. The run-in duration will therefore vary from approximately  
 609 2 to 8 weeks, depending on the participant. Additional visits and phone contacts for further  
 610 training are at investigator discretion.

611 An assessment of CGM and pump knowledge will be made and the participant must demonstrate  
 612 sufficient competency to proceed to the RCT. The trainer and participant will review the  
 613 individual items listed on the pump training checklist to ensure competency.

614 Participants who are unable to meet the CGM or study pump compliance requirements will be  
 615 withdrawn from the study, as will participants who no longer meet all of the inclusion and  
 616 exclusion criteria.

617 If the participant is eligible to continue in the study, study staff will follow the procedure for  
 618 insulin pump optimization described below in section 3.2.

619 **3.2 Optimization of Insulin Pump Settings**

620 Data-driven optimization of pump settings will occur at the following times:

- 621 • Prior to Randomization:
  - 622 ♦ At the Run-in Review Visit
- 623 • Following Randomization:

- 624           ♦ At the 2-, 13-, and 26-week visits for all study participants (both the CLC and SAP  
625           Group).
- 626           ♦ If the study participant contacts the study physician due to concerns about their pump  
627           settings due to recurring hypo- or hyperglycemia.

628           Data will be obtained from CGM and/or pump downloads at the visit. Adjustments to pump  
629           settings (basal rates, correction factor, insulin-to-carbohydrate ratio, etc.) will be made in  
630           response to major trends observed in the CGM data, with flexibility for clinicians to adhere to  
631           guidelines and practices established at each individual practice rather than a fixed set of  
632           heuristics for all sites.

633

## Chapter 4: Randomization Visit

634

### 4.1 Randomization Visit

635 The visit may occur on the same day as the Screening or Run-in Review Visit, or on a  
636 subsequent day. If deferred, the randomization visit should occur no more than 14 days after  
637 screening (if Run-in skipped) or successful completion of the run-in phase.

638 A urine pregnancy test will be repeated for all females of child-bearing potential if this visit is  
639 not on the same day as the Screening Visit.

640

#### 4.1.1 HbA1c

641 HbA1c will be measured using DCA Vantage or similar point-of-care (POC) device or local lab  
642 if this visit is not on the same day as the Screening Visit. A blood sample also will be drawn to  
643 send to the central laboratory for baseline HbA1c determination to be used in outcome analyses.

644

#### 4.1.2 Baseline C-Peptide Assessment

645 A blood sample will be drawn to send to the central laboratory for a random, non-fasting  
646 C-peptide determination to characterize baseline residual insulin production. In conjunction,  
647 blood glucose may be measured using the study blood glucose meter or a blood sample may be  
648 drawn to send to the central laboratory for a blood glucose assessment.

649

#### 4.1.3 Randomization

650 Eligible participants will be randomly assigned to one of two treatment groups in a 2:1 ratio:

651 1. CLC Closed-Loop Group

652 2. SAP Group

653 The participant's randomization group assignment is determined by completing a Randomization  
654 Visit case report form on the study website. The randomization list will use a permuted block  
655 design, stratified by clinical center.

656 *The participant will be included in the data analysis regardless of whether or not the protocol*  
657 *for the assigned randomization group is followed. Thus, the investigator must not randomize a*  
658 *participant until he/she is convinced that the participant/parent will accept assignment to either*  
659 *of the two groups.*

660 *It was decided that it was more important to stratify randomization by site than by factors such*  
661 *as baseline time in range, HbA1c, or device use since these factors will be easier to adjust for in*  
662 *analysis than will site in view of the relatively small number at each site.*

663

#### 4.1.4 Questionnaires

664 Participants will complete a set of baseline questionnaires, described in section 7.2, prior to  
665 randomization. Participants assigned to the CLC group also will complete the Technology  
666 Expectation Survey after randomization.

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## **Chapter 5: Randomized Trial Procedures**

### **5.1 Procedures for the CLC Group**

#### **5.1.1 Study System Training**

Participants assigned to the CLC group will receive study system training. These training sessions can occur on the same day or extend to up to one additional day if needed within 1-7 days from randomization; participants will not take the study system home until training has been completed.

For participants <18 years old, the parent/guardian will be trained on severe hypoglycemia emergency procedures including removal of the study pump and administration of glucagon. The parent/guardian will be asked to attend any/all of the other training procedures.

#### **Study System Training and Initiation**

##### **Study System Training**

Participants 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.

CGM training will include:

- The participant will be instructed and supervised on how to insert the sensor and transmitter.
- The participant will learn how to calibrate the CGM unit
- The participant will learn how to access the CGM trace via the t:slim X2 with Control-IQ user interface
  - Participants will be asked to perform fingerstick blood glucose measurements in accordance with the labeling of the study CGM device

Pump training will include:

- The participant will be fully instructed on the study insulin pump. A qualified system trainer 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 participant in study pump infusion site initiation and will start the participant on the study pump. The study pump will be programmed with the participant's usual basal rates and pump parameters. The participant's personal pump will be removed.
- The participant will be supervised with the study pump during at least one meal or snack bolus to ensure participant understanding of the pump features.

- 701 • The participant will be encouraged to review the literature provided with the pump and  
702 infusion sets after the training is completed.

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

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

712 **System Initiation**

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

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

723 For participants <18 years of age, the participant's parent/legal guardian will be required to  
724 attend the training procedures.

725 Participants will be provided with sufficient supplies to last until the subsequent visit.

726 Participants will be provided with contact information and will be asked to call the study  
727 clinical staff for any health related issues and for technical issues with t:slim X2 with  
728 Control-IQ. Participants may use the study pump without Control-IQ activated and study  
729 CGM during periods of component disconnections or technical difficulties. Participants will  
730 also receive study staff contact information to ask any questions they may have during the study.

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

736 Upon completion of the t:slim X2 with Control-IQ training, study staff will document, using a  
737 checklist, that the participant is familiar with the function/feature and/or capable of performing  
738 each of the tasks specified.

739 Participants will be provided Hypoglycemia, Hyperglycemia and Ketone Guidelines (section 6.2)  
740 for when their glucose levels are >300 mg/dL for more than two hours or >400 mg/dL at any  
741 time or <70 mg/dL or ketones >0.6 mmol/L.

#### 742 **5.1.2 Home Use of the Study System**

743 After training on the study system has been completed, participants will proceed with home use  
744 (meaning free-living use at work, home, etc.) of the t:slim X2 with Control-IQ technology  
745 system.

746 Participants may use available manufacturer-provided software and features of the study CGM  
747 related to mobile data access or remote monitoring, but will be instructed not to use any third-  
748 party components for this purpose.

#### 749 **5.1.3 Study Device Download**

750 Participants will be instructed to download the study device prior to each phone visit or on at  
751 least every 4 week basis throughout the remainder of the study.

#### 752 **5.1.4 1-Week Phone Contact**

753 Study staff will perform a phone call with the participant within 7 ( $\pm$ 1) days following  
754 randomization.

755 The following will occur:

- 756 • Assessment of compliance with study device use by review of any available device data
- 757 • Assessment of adverse events, adverse device effects, and device issues
- 758 • Study staff will answer any questions related to device use

759 Participants will then complete an additional week of home use with the study system.  
760 Participants will return to clinic 14 ( $\pm$ 3) days from the date of randomization.

#### 761 **5.1.5 2-Week Visit (Training Review and Insulin Pump Optimization)**

762 The participant will be offered review training to address any questions on the use of the study  
763 device including meal bolus strategies and strategies related to pump use and exercise.

764 The following will occur:

- 765 • Assessment of compliance with study device use by review of any available device data
- 766 • Assessment of adverse events, adverse device effects, and device issues
- 767 • Study staff will answer any questions related to device use and follow the procedure for  
768 insulin pump optimization described in section 3.2 using the study CGM available data from  
769 the previous two weeks.
- 770 • The study blood glucose meter and study ketone meter will be downloaded and QC tested  
771 with at least two different concentrations of control solution if available.

## 772 **5.2 Procedures for the SAP Group**

773 Participants in the SAP group will use an insulin pump with no automated insulin delivery in  
774 conjunction with the study CGM, study blood glucose meter and study ketone meter. Participants  
775 not already using an insulin pump with no automated insulin delivery at enrollment will be  
776 provided with a study pump to use. Study pump training and/or study CGM training will be  
777 provided if the participant is initiating use of these devices at this point.

778 Participants may use available manufacturer-provided software and features of the study CGM  
779 related to mobile data access or remote monitoring, but will be instructed not to use any third-  
780 party components for this purpose.

### 781 **5.2.1 Study Device Data Download**

782 Participants will be instructed to upload data from the study CGM using commercially available  
783 software prior to the 1-week phone contact and prior to the 2-week clinic visit for clinician  
784 review. Participants will be provided with any software and hardware needed to perform these  
785 data uploads.

### 786 **5.2.2 1-Week Phone Contact**

787 Study staff will perform a phone call with the participant within 7 ( $\pm 1$ ) days following  
788 randomization.

789 The following will occur:

- 790 • Assessment of compliance with study device use by review of any available device data
- 791 • Assessment of adverse events, adverse device effects, and device issues
- 792 • Study staff will answer any questions related to device use

793 The participant will continue on SAP for a second week, then return to the clinic 14 ( $\pm 3$ ) days  
794 from the date of randomization.

### 795 **5.2.3 2-Week Visit (Training Review and Insulin Pump Optimization)**

796 The participant will be offered review training on the use of SAP during the remainder of the  
797 study, including meal bolus strategies and strategies related to pump use and exercise.

798 The following will occur:

- 799 • Assessment of compliance with study device use by review of any available device data
- 800 • Assessment of adverse events, adverse device effects, and device issues
- 801 • Study staff will review uploaded CGM data, answer any questions related to device use, and
- 802 follow the procedure for insulin pump optimization described in section 3.2.
- 803 • The study blood glucose meter and study ketone meter will be downloaded and QC tested
- 804 with at least two different concentrations of control solution if available.

805 The participant will be instructed to upload data from the CGM at least once every 4 weeks for  
806 the remainder of the study.

### 807 **5.3 Follow-up Visits and Phone Contacts for Both Groups**

808 The schedule for remaining follow-up visits and phone contacts is the same for both treatment  
809 groups. Study staff will discuss with the participant that periodic contact is required and will  
810 make arrangements with the participant for the contacts. If the participant (or parent/guardian,  
811 for participants less than 18 years old) cannot be reached, the participant's other contact methods  
812 will be utilized, including the emergency contact.

#### 813 **5.3.1 Follow-up Visits**

814 Follow-up visits in clinic will occur at:

- 815 • 6 weeks ( $\pm 1$  week)
- 816 • 13 weeks ( $\pm 1$  week)
- 817 • 26 weeks ( $\pm 1$  week)

#### 818 **5.3.1.1 Procedures at Follow-up Visits**

819 Procedures performed in both groups at each visit, unless otherwise specified below:

- 820 • Assessment of compliance with study device use by review of any available device data
- 821 • Assessment of adverse events, adverse device effects, and device issues
- 822 • Download of device data (study system or personal pump and study CGM, study BG
- 823 meter, study ketone meter)

824 Procedures Specific to the 13- and 26-Week Visit

- 825 • HbA1c determination using the DCA Vantage or similar point of care device
- 826 • Collection of a blood sample to send to the central laboratory for HbA1c determination
- 827 • Completion of questionnaires
- 828 • Weight measurement will be repeated, in addition to height for participants <21 years old
- 829 • Insulin Pump Optimization as described above

830 **5.3.2 Phone Contacts**

831 In addition to the 1-week phone contact described above for the respective treatment groups, the  
832 following phone contacts will be made:

- 833 • 4 weeks ( $\pm 3$  days)
- 834 • 9 weeks ( $\pm 3$  days)
- 835 • 17 weeks ( $\pm 3$  days)
- 836 • 21 weeks ( $\pm 3$  days)

837 At each phone contact the following procedures are performed in both treatment groups:

- 838 • Review of available CGM and/or system data to identify any safety issues associated with  
839 insulin pump settings and current diabetes management approach
- 840 • Assessment of adverse events, adverse device effects, and device issues

841 Additional phone contacts may be performed as needed.

842 **5.4 Early Termination Visit (If Applicable)**

843 Participants will be asked to come for an end of study visit in the event of withdrawal or early  
844 termination.

845 **5.5 Unscheduled Visits**

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

848 **5.6 Participant Access to Study Device at Study Closure**

849 Participant will return all investigational study devices and supplies (insulin pump, CGM and  
850 related supplies) at study closure. Participant may keep the study ketone meter and study  
851 glucometer if these devices are not marked for investigational use only.

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## **Chapter 6: Study Devices**

### **6.1 Description of the Investigational Device**

#### **6.1.1 Insulin Pump**

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

#### **6.1.2 Continuous Glucose Monitoring**

The study CGM will include Dexcom G6 transmitter and sensors when using the Tandem t:slim X2 with Control-IQ technology. This may not be an FDA-approved device system at the start of the study, but may become approved during the course of the study. The CGM sensor will be replaced at least once every 10 days.

#### **6.1.3 Blood Glucose Meter and Strips**

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

#### **6.1.4 Ketone Meter and Strips**

Blood ketone levels will be measured using the Abbott Precision Xtra meter and strips in accordance with the manufacturer’s labeling. The blood glucose meter component of the Precision Xtra device will not be used.

#### **6.1.5 Study Device Accountability Procedures**

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

#### **6.1.6 Blood Glucose Meter Testing**

- Participants will be provided with instructions to perform QC testing per manufacturer guidelines.
- All study blood glucose meters will be QC tested with at least two different concentrations of control solution if available during all office visits. 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. The participant will be instructed to contact study staff for a replacement of the meter, test strips, and control solution if a meter fails QC testing at home.
- Participants will be reminded to use the study blood glucose meter for all fingerstick blood glucose measurements.
- Participants will be asked to perform fingerstick blood glucose measurements in accordance with the labelling of the study CGM device.

#### **6.1.7 Blood Ketone Testing**

- Participants to perform QC testing at home per manufacturer guidelines.
- All study blood ketone meters will be QC tested with at least two different concentrations of control solution if available during all office visits. A tested meter will not be used in a study

887 if it does not read within the target range at each concentration per manufacturer labeling.  
888 The participant will be instructed to contact study staff for a replacement of the meter, test  
889 strips, and control solution if a meter fails QC testing at home.

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

## 892 **6.2 Safety Measures**

### 893 **6.2.1 CGM Calibration**

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

### 896 **6.2.2 System Failure**

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

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

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

### 907 **6.2.3 Hypoglycemia Threshold Alert and Safety Protocol**

908 During the course of the study, participants will be permitted to change the CGM low glucose  
909 threshold alert setting on their device or mobile app, but will be instructed to choose a value no  
910 less than 60 mg/dL.

911 The t:slim X2 with Control-IQ system will issue a predictive hypoglycemia alert (Control-IQ  
912 Low Alert) when the system predicts BG <70 mg/dL within the next 15 minutes (<80 mg/dL  
913 when exercise mode is activated).

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

### 918 **6.2.4 Hyperglycemia Threshold Alert and Safety Protocol**

919 During the course of the study, participants will be permitted to change the CGM high glucose  
920 threshold alert setting on their device or mobile app, but will be instructed to choose a value no  
921 greater than 300 mg/dL.

922 The t:slim X2 with Control-IQ system will issue a predictive hyperglycemia alert (Control-IQ  
923 High Alert) when the system has increased insulin delivery, but detects a CGM value above 200  
924 mg/dL and does not predict the value will decrease in the next 30 minutes.

925 If the participant receives a Control-IQ High Alert, a message appears on the UI that is  
926 accompanied by vibration followed by vibrations and/or sound if not acknowledged by the user  
927 in 5 minutes. This alert remains on the screen until acknowledged by the user. The user is  
928 prompted to check the site for occlusion and test blood glucose.

929 If a participant's CGM reading is  $>300$  mg/dL for over 2 hours or  $\geq 400$  mg/dL at any point, the  
930 participant will be instructed to take the following steps:

- 931 • Perform a blood glucose meter check.
- 932 • If the blood glucose is  $>300$  mg/dL, check for blood ketones with the study ketone meter.
- 933 • If the ketone level is  $>0.6$  mmol/L, take correction insulin, change insulin (pump) infusion  
934 site and contact study staff.
- 935 • If a participant administers correction insulin via insulin syringe, participants will be  
936 instructed to turn Control-IQ off for approximately four hours.

937

## Chapter 7: Testing Procedures and Questionnaires

938

### 7.1 Laboratory Testing

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1. HbA1c:

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- Performed locally at the Screening visit, Randomization visit, 13-week visit, and 26-week visit. The Screening visit test may be skipped if a local test result is already available within the prior 2 weeks.

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- A blood sample will be obtained and sent to central lab at the Randomization visit, 13-week visit, and 26-week visit.

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2. Urine Pregnancy:

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- Performed locally for females of child-bearing potential at the Screening visit, Randomization visit, and 13-week visit. This will also be done anytime pregnancy is suspected.

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### 7.2 Questionnaires

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Questionnaires are completed at the Randomization Visit, Week 13 Visit, and Week 26 Visit.

951

The questionnaires are described briefly below. The procedures for administration are described in the study procedures manual.

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953

The following questionnaires will be completed at the randomization visit:

954

- Diabetes Specific Personality Questionnaire

955

- Clarke’s Hypoglycemia Awareness Scale

956

- Fear of Hypoglycemia Survey (HFS-II)

957

- Hyperglycemia Avoidance Scale

958

- Hypoglycemia Confidence Scale

959

- Diabetes Distress Scale

960

- INSPIRE Survey

961

- Technology Expectations Survey (*Closed-Loop participants only at randomization; SAP group will complete this survey at week 26 prior to starting closed-loop control*)

962

963

The following questionnaires will be completed at the Week 13 and Week 26 Visits:

964

- Clarke’s Hypoglycemia Awareness Scale

965

- Fear of Hypoglycemia Survey (HFS-II)

966

- Hyperglycemia Avoidance Scale

967

- Hypoglycemia Confidence Scale

968

- Diabetes Distress Scale

- 969 • INSPIRE Survey
- 970 • Technology Acceptance Survey (*Closed-Loop participants only*)
- 971 • System Usability Scale (SUS) (*Closed-Loop participants only*)

972 **Diabetes Specific Personality Questionnaire**

973 The Diabetes Specific Personality Questionnaire (26) is based on the original Six Factor  
974 Personality Questionnaire (27), a well-validated measure that was adapted for the diabetes-  
975 specific version of the questionnaire. The SFPQ is a measure of six personality dimensions  
976 each consisting of three facet scales, measured by 108 Likert items. The SFPQ facet scales are  
977 organized in terms of six factor scales.

978 Administration time is approximately 15 minutes.

979 **Clarke's Hypoglycemia Awareness Scale**

980 The scale (28) comprises eight questions characterizing the participant's exposure to episodes  
981 of moderate and severe hypoglycemia. It also examines the glycemic threshold for, and  
982 symptomatic responses to hypoglycemia. A score of four or more on a scale of 0 to 7 implies  
983 impaired awareness of hypoglycemia.

984 Administration time is approximately 5 minutes.

985 **Hypoglycemia Fear Survey (HFS-II)/Low Blood Sugar Survey**

986 The Hypoglycemia Fear Survey-II (29) was developed to measure behaviors and worries related  
987 to fear of hypoglycemia in adults with type 1 diabetes. It is composed of 2 subscales, the  
988 Behavior (HFS-B) and Worry (HFS-W). HFS-B items describe behaviors in which patients may  
989 engage to avoid hypoglycemic episodes and/or their negative consequences (e.g., keeping blood  
990 glucose levels above 150 mg/dL, making sure other people are around, and limiting exercise or  
991 physical activity). HFS-W items describe specific concerns that patients may have about their  
992 hypoglycemic episodes (e.g., being alone, episodes occurring during sleep, or having an  
993 accident).

994 Administration time is approximately 10 minutes.

995 **Hyperglycemia Avoidance Survey (HAS)/High Blood Sugar Survey**

996 The HAS (30) reliably quantifies affective and behavioral aspects of hyperglycemia avoidance  
997 and is used to assess the extent of potentially problematic avoidant attitudes and behaviors  
998 regarding hyperglycemia in people with Type 1 diabetes (T1D).

999 Administration time is approximately 10 minutes.

1000 **Hypoglycemia Confidence Scale**

1001 The HCS (31) is a 9-item self-report scale that examines the degree to which people with  
1002 diabetes feel able, secure, and comfortable regarding their ability to stay safe from  
1003 hypoglycemic-related problems. It has been validated for use in adults with type 1 diabetes and  
1004 insulin-using type 2 diabetes.

1005 Administration time is approximately 5 minutes.

1006 **Diabetes Distress Scale**

1007 The Diabetes Distress Scale (32) is a measure of diabetes-related emotional distress and consists  
1008 of a scale of 28 items. These include 7 items from each of four domains central to diabetes-  
1009 related emotional distress. Patients rate the degree to which each item is currently problematic  
1010 for them on a 6-point Likert scale, from 1 (no problem) to 6 (serious problem).

1011 Administration time is approximately 10 minutes.

1012 **Technology Expectation and Technology Acceptance Surveys**

1013 The Technology Expectation and Technology Acceptance Surveys were developed for a Bionic  
1014 Pancreas camp study (33). The 38 items in the Questionnaire were based on interviews  
1015 conducted with individuals who had participated in previous Bionic Pancreas trials about their  
1016 experience regarding the Bionic Pancreas. It was subsequently adapted to assess these same  
1017 measures for the inControl closed-loop system. It assesses both positive and negative  
1018 experiences with inControl, including blood glucose management, device burden, and overall  
1019 satisfaction. Items were rated on a 5-point scale.

1020 Administration time is approximately 10 minutes.

1021 **INSPIRE Survey**

1022 The INSPIRE (Inulin Delivery Systems: Perceptions, Ideas, Reflections and Expectations)  
1023 survey was developed to assess various aspects of a user's experience regarding automated  
1024 insulin delivery for both patients and family members. The surveys include various topics  
1025 important to patients with type 1 diabetes and their family members based upon >200 hours  
1026 of qualitative interviews and focus groups. The adult survey includes 31 items; the adolescent  
1027 survey includes 28 items; and the parent survey includes 30 items. Response options for all  
1028 surveys include a 5-point Likert scale from strongly agree to strongly disagree, along with an  
1029 N/A option.

1030 Administration time is approximately 5 minutes.

1031 **System Usability Scale (SUS)**

1032 The System Usability Scale (SUS) is a 10-item questionnaire that measures the overall  
1033 usability of a system. It is a valid and reliable measure of the perceived usability of a system  
1034 and is technology-agnostic. The questionnaire presents statements with five response options  
1035 (anchoring the options from strongly disagree to strongly agree) and asks users to rate their  
1036 agreement to the statements. User scores are transformed into a composite score, from 0 to 100,  
1037 and this score is taken as an overall measure of the system's usability; higher scores indicate  
1038 better perceived usability.

1039 Administration time is approximately 5 minutes.

1040 **Chapter 8: Adverse Events, Device Issues, and Stopping Rules**

1041 **8.1 Adverse Events**

1042 **8.1.1 Definitions**

1043 Adverse Event (AE): Any untoward medical occurrence in a study participant, irrespective of the  
 1044 relationship between the adverse event and the device(s) under investigation (see section 8.1.2  
 1045 for reportable adverse events for this protocol).

1046 Serious Adverse Event (SAE): Any untoward medical occurrence that:

- 1047 • Results in death.
- 1048 • Is life-threatening; (a non-life-threatening event which, had it been more severe, might have  
 1049 become life-threatening, is not necessarily considered a serious adverse event).
- 1050 • Requires inpatient hospitalization or prolongation of existing hospitalization.
- 1051 • Results in persistent or significant disability/incapacity or substantial disruption of the ability  
 1052 to conduct normal life functions (sight threatening).
- 1053 • Is a congenital anomaly or birth defect.
- 1054 • Is considered a significant medical event by the investigator based on medical judgment (e.g.,  
 1055 may jeopardize the participant or may require medical/surgical intervention to prevent one of  
 1056 the outcomes listed above).

1057 Unanticipated Adverse Device Effect (UADE): Any serious adverse effect on health or safety or  
 1058 any life-threatening problem or death caused by, or associated with, a device, if that effect,  
 1059 problem, or death was not previously identified in nature, severity, or degree of incidence in the  
 1060 investigational plan or application (including a supplementary plan or application), or any other  
 1061 unanticipated serious problem associated with a device that relates to the rights, safety, or  
 1062 welfare of participants (21 CFR 812.3(s)).

1063 Adverse Device Effect (ADE): Any untoward medical occurrence in a study participant which  
 1064 the device may have caused or to which the device may have contributed (Note that an Adverse  
 1065 Event Form is to be completed in addition to a Device Deficiency or Issue Form).

1066 Device Complaints and Malfunctions: A device complication or complaint is something that  
 1067 happens to a device or related to device performance, whereas an adverse event happens to a  
 1068 participant. A device complaint may occur independently from an AE, or along with an AE.  
 1069 An AE may occur without a device complaint or there may be an AE related to a device  
 1070 complaint. A device malfunction is any failure of a device to meet its performance specifications  
 1071 or otherwise perform as intended. Performance specifications include all claims made in the  
 1072 labeling for the device. The intended performance of a device refers to the intended use for  
 1073 which the device is labeled or marketed. (21 CFR 803.3). Note: for reporting purposes, sites  
 1074 will not be asked to distinguish between device complaints and malfunctions.

1075 **8.1.2 Reportable Adverse Events**

1076 For this protocol, a reportable adverse event includes any untoward medical occurrence that  
1077 meets one of the following criteria:

- 1078 1. A serious adverse event
- 1079 2. An Adverse Device Effect as defined in section 8.1.1, unless excluded from reporting in  
1080 section 8.2
- 1081 3. An Adverse Event occurring in association with a study procedure
- 1082 4. Hypoglycemia meeting the definition of severe hypoglycemia as defined below
- 1083 5. Diabetic ketoacidosis (DKA) as defined below or in the absence of DKA, a hyperglycemic or  
1084 ketosis event meeting the criteria defined below

1085 Hypoglycemia and hyperglycemia not meeting the criteria below will not be recorded as adverse  
1086 events unless associated with an Adverse Device Effect. Skin reactions from sensor placement  
1087 are only reportable if severe and/or required treatment.

1088 Pregnancy occurring during the study will be recorded.

1089 **8.1.2.1 Hypoglycemic Events**

1090 Hypoglycemia not associated with an Adverse Device Effect is only reportable as an adverse  
1091 event when the following definition for severe hypoglycemia is met: the event required  
1092 assistance of another person due to altered consciousness, and required another person to actively  
1093 administer carbohydrate, glucagon, or other resuscitative actions. This means that the participant  
1094 was impaired cognitively to the point that he/she was unable to treat himself/herself, was unable  
1095 to verbalize his/ her needs, was incoherent, disoriented, and/or combative, or experienced seizure  
1096 or coma. These episodes may be associated with sufficient neuroglycopenia to induce seizure or  
1097 coma. If plasma glucose measurements are not available during such an event, neurological  
1098 recovery attributable to the restoration of plasma glucose to normal is considered sufficient  
1099 evidence that the event was induced by a low plasma glucose concentration.

1100 **8.1.2.2 Hyperglycemic Events/Diabetic Ketoacidosis**

1101 Hyperglycemia not associated with an Adverse Device Effect is only reportable as an adverse  
1102 event when one of the following 4 criteria is met:

- 1103 • the event involved DKA, as defined by the Diabetes Control and Complications Trial  
1104 (DCCT) and described below
- 1105 • evaluation or treatment was obtained at a health care provider facility for an acute event  
1106 involving hyperglycemia or ketosis
- 1107 • blood ketone level  $\geq 1.0$  mmol/L and communication occurred with a health care provider  
1108 at the time of the event
- 1109 • blood ketone level  $\geq 3.0$  mmol/L, even if there was no communication with a health care  
1110 provider

1111 Hyperglycemic events are classified as DKA if the following are present:

- 1112 • Symptoms such as polyuria, polydipsia, nausea, or vomiting;
- 1113 • Serum ketones >1.5 mmol/L or large/moderate urine ketones;
- 1114 • Either arterial blood pH <7.30 or venous pH <7.24 or serum bicarbonate <15; and
- 1115 • Treatment provided in a health care facility

1116 All reportable Adverse Events—whether volunteered by the participant, discovered by study  
1117 personnel during questioning, or detected through physical examination, laboratory test, or other  
1118 means—will be reported on an adverse event form online. Each adverse event form is reviewed  
1119 by the Medical Monitor to verify the coding and the reporting that is required.

### 1120 **8.1.3 Relationship of Adverse Event to Study Device**

1121 The study investigator will assess the relationship of any adverse event to be related or unrelated  
1122 by determining if there is a reasonable possibility that the adverse event may have been caused  
1123 by the study device.

1124 To ensure consistency of adverse event causality assessments, investigators should apply the  
1125 following general guideline when determining whether an adverse event is related:

#### 1126 Yes

1127 There is a plausible temporal relationship between the onset of the adverse event and the study  
1128 intervention, and the adverse event cannot be readily explained by the participant’s clinical state,  
1129 intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern  
1130 of response to the study intervention; and/or the adverse event abates or resolves upon  
1131 discontinuation of the study intervention or dose reduction and, if applicable, reappears upon  
1132 re-challenge.

#### 1133 No

1134 Evidence exists that the adverse event has an etiology other than the study intervention (e.g.,  
1135 preexisting medical condition, underlying disease, intercurrent illness, or concomitant  
1136 medication); and/or the adverse event has no plausible temporal relationship to study  
1137 intervention.

### 1138 **8.1.4 Intensity of Adverse Event**

1139 The intensity of an adverse event will be rated on a three point scale: (1) mild, (2) moderate, or  
1140 (3) severe. It is emphasized that the term severe is a measure of intensity: thus a severe adverse  
1141 event is not necessarily serious. For example, itching for several days may be rated as severe,  
1142 but may not be clinically serious.

- 1143 • MILD: Usually transient, requires no special treatment, and does not interfere with the  
1144 participant’s daily activities.

- 1145 • MODERATE: Usually causes a low level of inconvenience or concern to the participant and  
1146 may interfere with daily activities, but is usually ameliorated by simple therapeutic measures.
- 1147 • SEVERE: Interrupts a participant's usual daily activities and generally requires systemic  
1148 drug therapy or other treatment.

1149 **8.1.5 Coding of Adverse Events**

1150 Adverse events will be coded using the MedDRA dictionary. The Medical Monitor will review  
 1151 the investigator’s assessment of causality and may agree or disagree. Both the investigator’s and  
 1152 Medical Monitor’s assessments will be recorded. The Medical Monitor will have the final say in  
 1153 determining the causality.

1154 Adverse events that continue after the participant’s discontinuation or completion of the study  
 1155 will be followed until their medical outcome is determined or until no further change in the  
 1156 condition is expected.

1157 **8.1.6 Outcome of Adverse Event**

1158 The outcome of each reportable adverse event will be classified by the investigator as follows:

- 1159 • RECOVERED/RESOLVED – The participant recovered from the AE/SAE without sequelae.  
 1160 Record the AE/SAE stop date.
- 1161 • RECOVERED/RESOLVED WITH SEQUELAE – The event persisted and had stabilized  
 1162 without change in the event anticipated. Record the AE/SAE stop date.
- 1163 • FATAL – A fatal outcome is defined as the SAE that resulted in death. Only the event that  
 1164 was the cause of death should be reported as fatal. AEs/SAEs that were ongoing at the time  
 1165 of death; however, were not the cause of death, will be recorded as “resolved” at the time of  
 1166 death.
- 1167 • NOT RECOVERED/NOT RESOLVED (ONGOING) – An ongoing AE/SAE is defined as  
 1168 the event was ongoing with an undetermined outcome.
  - 1169 ♦ An ongoing outcome will require follow-up by the site in order to determine the final  
 1170 outcome of the AE/SAE.
  - 1171 ♦ The outcome of an ongoing event at the time of death that was not the cause of death,  
 1172 will be updated and recorded as “resolved” with the date of death recorded as the stop  
 1173 date.
- 1174 • UNKNOWN – An unknown outcome is defined as an inability to access the participant or  
 1175 the participant’s records to determine the outcome (for example, a participant that was lost to  
 1176 follow-up).

1177 All clinically significant abnormalities of clinical laboratory measurements or adverse events  
 1178 occurring during the study and continuing at study termination should be followed by the  
 1179 participant’s physician and evaluated with additional tests (if necessary) until diagnosis of the  
 1180 underlying cause, or resolution. Follow-up information should be recorded on source  
 1181 documents.

1182 If any reported adverse events are present when a participant completes the study, or if a  
 1183 participant is withdrawn from the study due to an adverse event, the participant will be contacted  
 1184 for re-evaluation within 2 weeks. If the adverse event has not resolved, additional follow-up will  
 1185 be performed as appropriate. Every effort should be made by the Investigator or delegate to  
 1186 contact the participant until the adverse event has resolved or stabilized.

1187 **8.2 Reportable Device Issues**

1188 All UADEs, ADEs, device complaints, and device malfunctions will be reported irrespective of  
1189 whether an adverse event occurred, except in the following circumstances.

1190 The following device issues are anticipated and will not be reported on a Device Issue Form but  
1191 will reported as an Adverse Event if the criteria for AE reporting described above are met:

- 1192 • Component disconnections
- 1193 • CGM sensors lasting fewer than the number of days expected per CGM labeling
- 1194 • CGM tape adherence issues
- 1195 • Pump infusion set occlusion not leading to ketosis
- 1196 • Battery lifespan deficiency due to inadequate charging or extensive wireless communication
- 1197 • Intermittent device component disconnections/communication failures not leading to system  
1198 replacement
- 1199 • Device issues clearly addressed in the user guide manual that do not require additional  
1200 troubleshooting
- 1201 • Skin reactions from CGM sensor placement or pump infusion set placement that do not meet  
1202 criteria for AE reporting

1203 **8.3 Pregnancy Reporting**

1204 If pregnancy occurs, the participant will be discontinued from the study. The occurrence of  
1205 pregnancy will be reported on an AE Form.

1206 **8.4 Timing of Event Reporting**

1207 SAEs and UADEs must be reported to the Coordinating Center within 24 hours via completion  
1208 of the online serious adverse event form.

1209 Other reportable adverse events, device malfunctions (with or without an adverse event), and  
1210 device complaints should be reported promptly by completion of an electronic case report form,  
1211 but there is no formal required reporting period.

1212 The Coordinating Center will notify all participating investigators of any adverse event that is  
1213 serious, related, and unexpected. Notification will be made within 10 days after the Coordinating  
1214 Center becomes aware of the event.

1215 Each principal investigator is responsible for reporting serious study-related adverse events and  
1216 abiding by any other reporting requirements specific to his/her Institutional Review Board or  
1217 Ethics Committee.

1218 Upon receipt of a UADE report, the Sponsor will investigate the UADE and if indicated, report  
1219 the results of the investigation to the sites' IRBs, and the FDA within 10 working days of the  
1220 Sponsor becoming aware of the UADE per 21CFR 812.46(b) (2). The Medical Monitor must  
1221 determine if the UADE presents an unreasonable risk to participants. If so, the Medical Monitor

1222 must ensure that all investigations, or parts of investigations presenting that risk, are terminated  
1223 as soon as possible but no later than 5 working days after the Medical Monitor makes this  
1224 determination and no later than 15 working days after first receipt notice of the UADE.

1225 In the case of a device system component malfunction (e.g. pump, CGM, control algorithm),  
1226 information will be forwarded to the responsible company by the site personnel, to be handled  
1227 by its complaint management system.

## 1228 **8.5 Stopping Criteria**

### 1229 **8.5.1 Participant Discontinuation of Study Device**

1230 Rules for discontinuing study device use are described below.

- 1231 • The investigator believes it is unsafe for the participant to continue on the intervention. This  
1232 could be due to the development of a new medical condition or worsening of an existing  
1233 condition; or participant behavior contrary to the indications for use of the device that  
1234 imposes on the participant's safety
- 1235 • The participant requests that the treatment be stopped
- 1236 • Participant pregnancy
- 1237 • Two distinct episodes of DKA
- 1238 • Two distinct severe hypoglycemia events as defined in section 8.1.2.1

1239 If pregnancy occurs, the participant will be discontinued from the study entirely. Otherwise, even  
1240 if the study device system is discontinued, the participant will be encouraged to remain in the  
1241 study through the final study visit.

### 1242 **8.5.2 Criteria for Suspending or Stopping Overall Study**

1243 In the case of an unanticipated system malfunction resulting in a severe hypoglycemia or severe  
1244 hyperglycemia event (as defined in section 8.1.2.2), use of the study device system will be  
1245 suspended while the problem is diagnosed.

1246 In addition, study activities could be similarly suspended if the manufacturer of any constituent  
1247 study device requires stoppage of device use for safety reasons (e.g. product recall). The  
1248 affected study activities may resume if the underlying problem can be corrected by a protocol or  
1249 system modification that will not invalidate the results obtained prior to suspension. The study  
1250 Medical Monitor will review all adverse events and adverse device events that are reported  
1251 during the study and will review compiled safety data at periodic intervals (generally timed to  
1252 the review of compiled safety data by the DSMB). The Medical Monitor may request suspension  
1253 of study activities or stoppage of the study if deemed necessary based on the totality of safety  
1254 data available.

1255 **8.6 Independent Safety Oversight**

1256 A Data and Safety Monitoring Board (DSMB) will review compiled safety data at periodic  
1257 intervals (typically every 6 months). In addition, the DSMB will review all DKA and severe  
1258 hypoglycemia irrespective of relatedness to study device use, and all serious events (including  
1259 UADEs) related to study device use at the time of occurrence. The DSMB also will be informed  
1260 of any ADEs not meeting criteria for a UADE if the Medical Monitor requests the DSMB  
1261 review. The DSMB can request modifications to the study protocol or suspension or outright  
1262 stoppage of the study if deemed necessary based on the totality of safety data available. Details  
1263 regarding DSMB review will be documented in a separate DSMB document.

1264 **8.7 Risks**

1265 The potential risks associated with use of the study device are described in section 1.3.

1266 Additional risks are minor and/or infrequent and include:

- 1267 • Pain, bruising, redness, or infection from blood draws
- 1268 • Loss of confidentiality
- 1269 • Stress from completing quality of life questionnaires

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## **Chapter 9: Miscellaneous Considerations**

### **9.1 Drugs Used as Part of the Protocol**

Participants will use either lispro or aspart insulin prescribed by their personal physician.

### **9.2 Prohibited Medications, Treatments, and Procedures**

Participants using glulisine at the time of enrollment will be asked to contact their personal physician to change their prescribed personal insulin to lispro or aspart for the duration of the trial.

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

The investigational study devices (t:slim X2 insulin pump, study CGM systems) must be removed before Magnetic Resonance Imaging (MRI), Computed Tomography (CT) or diathermy treatment. Participants may continue in the trial after temporarily discontinuing use if requiring one of the treatments above.

### **9.3 Participant Compensation**

Participant compensation will be specified in the informed consent form.

A maximum of \$375 will be paid for completing the entire study. Participants will be paid \$100 for completing 13- and 26-week visits and \$50 for each separate scheduled visit that requires traveling to the research site. No additional payments will be provided for unplanned visits to the research site.

- Screening Visit: \$25
- Run-in Visit/Randomization Visit: \$50
- 2-week Visit: \$50
- 6-week Visit: \$50
- 13-week Visit: \$100
- 26-week Visit: \$100

### **9.4 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.

### **9.5 Confidentiality**

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

1304 study. De-identified participant information may also be provided to Tandem for system  
1305 evaluation purposes.

1306

## Chapter 10: Statistical Consideration

1307

### 10.1 Statistical and Analytical Plans

1308 The approach to sample size and statistical analyses are summarized below. A detailed statistical  
1309 analysis plan will be written and finalized prior to the first tabulation of data by treatment group  
1310 (ie, for DSMB review). The analysis plan synopsis in this chapter contains the framework of the  
1311 anticipated final analysis plan.

1312

### 10.2 Statistical Hypotheses

1313 The primary outcome for this study (6-month randomized trial) is CGM-measured % in range  
1314 70-180 mg/dL.

1315 The hypotheses for the primary outcome are:

1316 a. *Null Hypothesis*: There is no difference in mean CGM-measured % in range 70-180  
1317 mg/dL over 6 months between SAP and CLC

1318 b. *Alternative Hypothesis*: The mean CGM-measured % in range 70-180 mg/dL over 6  
1319 months is different for SAP and CLC.

1320

### 10.3 Sample Size

1321 Sample size has been computed for the primary outcome (CGM-measured % in range 70-180  
1322 mg/dL). Data from the CGM arm of the JDRF CGM RCT from participants meeting the  
1323 eligibility criteria for the current trial were used to project the distribution of % in range 70-180  
1324 mg/dL as measured by CGM for the SAP group in the proposed study.

1325 The total minimum sample size was computed to be 123 for the following assumptions: (1) 2:1  
1326 [CLC:SAP] randomization, (2) 90% power, (3) a 7.5% absolute increase in % in range 70-180  
1327 mg/dL, (4) an effective SD of 12%, (5) and 2-sided type 1 error of 5%.

1328 The total sample size has been increased to 168 to account for dropouts and to increase the  
1329 number of participants who will be exposed to the CLC system for an enhanced safety and  
1330 feasibility assessment.

1331

### 10.4 Outcome Measures

1332

#### 10.4.1 Primary Efficacy Endpoint

1333 • CGM-measured % in range 70-180 mg/dL

1334 **10.4.2 Secondary Efficacy Endpoints**

1335 **10.4.2.1 Secondary Efficacy Endpoints Included in Hierarchical Analysis**

1336 The following secondary endpoints will be tested in a hierarchical fashion as described in  
1337 section 10.7.1.

- 1338 • CGM-measured % above 180 mg/dL
- 1339 • CGM-measured mean glucose
- 1340 • HbA1c at 26 weeks
- 1341 • CGM-measured % below 70 mg/dL
- 1342 • CGM-measured % below 54 mg/dL

1343 **10.4.2.2 Other Secondary Efficacy Endpoints**

1344 The following endpoints are considered exploratory. Type 1 error for these endpoints will be  
1345 controlled using the false discovery rate (FDR) instead of the familywise error rate (FWER). See  
1346 section 10.15 below.

1347 CGM-Measured:

- 1348 • % in range 70-140 mg/dL
- 1349 • glucose variability measured with the coefficient of variation (CV)
- 1350 • glucose variability measured with the standard deviation (SD)
- 1351 • % <60 mg/dL
- 1352 • low blood glucose index
- 1353 • hypoglycemia events (defined as at least 15 consecutive minutes <70 mg/dL)
- 1354 • % >250 mg/dL
- 1355 • % >300 mg/dL
- 1356 • high blood glucose index

1357 HbA1c:

- 1358 • HbA1c <7.0% at 26 weeks
- 1359 • HbA1c <7.5% at 26 weeks
- 1360 • HbA1c improvement from baseline to 26 weeks >0.5%
- 1361 • HbA1c improvement from baseline to 26 weeks >1.0%
- 1362 • HbA1c relative improvement from baseline to 26 weeks >10%
- 1363 • HbA1c improvement from baseline to 26 weeks >1.0% or HbA1c <7.0% at 26 weeks

1364 Questionnaires:

- 1365 • Fear of Hypoglycemia Survey (HFS-II) – total score and 3 subscales:

- 1366     ◆ Behavior (avoid)  
 1367     ◆ Behavior (maintain high BG)  
 1368     ◆ Worry

- 1369 • Hyperglycemia Avoidance Scale – total score and 4 subscales:

- 1370     ◆ Immediate action  
 1371     ◆ Worry  
 1372     ◆ Low BG preference  
 1373     ◆ Avoid extremes

- 1374 • Diabetes Distress Scale – total score and 4 subscales:

- 1375     ◆ Emotional burden  
 1376     ◆ Physician-related distress  
 1377     ◆ Regimen-related distress  
 1378     ◆ Interpersonal distress

- 1379 • Hypoglycemia Confidence Scale – total score

- 1380 • Clarke Hypoglycemia Awareness Scores

- 1381 • INSPIRE survey scores

- 1382 • System Usability Scale (SUS)

1383

1384 Other:

- 1385 • Insulin

- 1386     ◆ Total daily insulin (units/kg)

- 1387     ◆ Basal: bolus insulin ratio

- 1388 • Weight and Body Mass Index (BMI)

1389                   **10.4.2.3 Safety Analyses**

1390 All randomized participants will be included in these analyses and the circumstances of all  
 1391 reportable cases of the following will be summarized and tabulated by treatment group:

- 1392 • Severe hypoglycemia

- 1393 • Diabetic ketoacidosis

- 1394 • Other serious adverse events and serious adverse device events

- 1395 • Unanticipated adverse device effects

1396 **10.4.3 CGM Metrics Calculations**

1397 Randomization is preceded by two weeks of CGM run-in, which will be used in the calculation  
1398 of baseline CGM metrics.

1399 CGM data starting from randomization visit through the 6 month visit will be included in the  
1400 calculation of each CGM metric. Percentages in range 70-180 mg/dL (and all other CGM-based  
1401 metrics) will be calculated giving equal weight to each CGM point for each participant.

1402 **10.5 Analysis Datasets and Sensitivity Analyses**

1403 All analyses comparing the CLC arm with SAP arm will follow the intention-to-treat (ITT)  
1404 principle with each participant analyzed according to the treatment assigned by randomization.  
1405 All randomized participants will be included in the primary and secondary hierarchical analyses.

1406 Safety outcomes will be reported for all enrolled participants, irrespective of whether the  
1407 participants was randomized or the study was completed.

1408 **10.5.1 Per Protocol Analyses**

1409 If more than 5% of participants have fewer than 168 hours of post-randomization CGM data,  
1410 the primary and secondary hierarchical analyses will be replicated excluding such participants.

1411 The primary and secondary hierarchical analyses will be replicated only with participants from  
1412 CLC group who used the system in CL mode for >80% overall and with participants from SAP  
1413 group who used the sensor for >80% overall.

1414 **10.5.2 Other Sensitivity Analyses**

1415 Confounding

1416 The primary analysis described below will include a pre-specified list of covariates. As an  
1417 additional sensitivity analysis, any baseline demographic or clinical characteristics observed to  
1418 be imbalanced between treatment groups will be added as covariates to the analyses of the  
1419 primary and secondary hierarchical metrics. The determination of a meaningful baseline  
1420 imbalance will be based on clinical judgement and not a p-value.

1421 Exclude First 2 Weeks of CGM Data

1422 As noted above in Section 10.4.3, calculation of CGM metrics will include all available post-  
1423 randomization CGM data. As a sensitivity analysis, each of the primary and secondary  
1424 hierarchical CGM metrics listed in 10.4.1 and 10.4.2.1 will be recalculated excluding the first  
1425 two weeks of CGM data following the randomization visit. A parallel set of analyses will be  
1426 done on these recalculated metrics.

1427 Missing Data

1428 It is worth emphasizing that any statistical method for handling missing data makes a number of  
 1429 untestable assumptions. The goal will be to minimize the amount of missing data in this study so  
 1430 that results and conclusions will not be sensitive to which statistical method is used. To that end,  
 1431 sensitivity analyses will be performed to explore whether results are similar for primary and  
 1432 secondary hierarchical analysis when using different methods. The following methods will be  
 1433 applied:

- 1434 • Direct likelihood (primary analysis described below)
- 1435 • Rubin’s multiple imputation
- 1436 • Available cases only

1437

1438 **10.6 Analysis of the Primary Efficacy Endpoint**

1439 Summary statistics (mean ± SD or median (quartiles)) will be reported for the CGM-measured %  
 1440 in range 70-180 mg/dL and for differences from pre-randomization by treatment group.

1441 Changes from run-in pre-randomization CGM wear to the 6-month post-randomization period in  
 1442 CGM-measured % in range 70-180 mg/dL between two treatment arms will be compared using a  
 1443 linear mixed effects regression model while adjusting for baseline CGM-measured % in range  
 1444 70-180 mg/dL, age, prior CGM and pump use, and clinical center (random effect). Missing data  
 1445 will be handled using direct likelihood. Residual values will be examined for an approximate  
 1446 normal distribution. If residuals are highly skewed even after the transformation, then a  
 1447 transformation or robust statistical method (e.g., non-parametric or MM estimation) will be used  
 1448 instead. It is expected that the residual values for CGM-measured % in range 70-180 mg/dL will  
 1449 follow an approximate normal distribution.

1450 **10.7 Analysis of the Secondary Endpoints**

1451 Point estimated and confidence intervals for the treatment arm differences will be presented for  
 1452 all secondary metrics. The models will adjust for the corresponding baseline metric, age, prior  
 1453 CGM and pump use, and clinical center (random effect).

1454 **10.7.1 Hierarchical Analyses**

1455 To preserve the overall type 1 error for selected key secondary endpoints, a hierarchical testing  
 1456 procedure will be used. If the primary analysis for time in range described above results in a  
 1457 statistically significant result ( $p < 0.05$ ), then testing (similar with the model described above  
 1458 for the primary outcome) will proceed to the next outcome metric in the following order:

- 1459 • CGM-measured % in range 70-180 mg/dL (primary outcome)
- 1460 • CGM-measured % above 180 mg/dL
- 1461 • CGM-measured mean glucose
- 1462 • HbA1c at 26 weeks
- 1463 • CGM-measured % below 70 mg/dL
- 1464 • CGM-measured % below 54 mg/dL

1465 This process continues iteratively moving to the next variable down on the list until a non-  
1466 significant result ( $p \geq 0.05$ ) is observed, or all six variables have been tested. If a non-significant  
1467 result is encountered, then formal statistical hypothesis testing is terminated and any variables  
1468 below on the list are not formally tested and analysis of these variables become exploratory.

1469 For example, in the hypothetical scenario depicted in the table below, the first four outcome  
1470 variables have a significant result so testing continues to the fifth variable (CGM % below 70  
1471 mg/dL). The result is not significant for that fifth variable ( $p = 0.06$ ) so testing stops. No formal  
1472 hypothesis test is conducted for the sixth variable on the list in this example scenario.

1473

**Table 3. Example Hierarchical Test Results**

HIERARCHICAL ORDER	OUTCOME VARIABLE	TREATMENT ARM P-VALUE	SIGNIFICANT?	ACTION
1 <sup>st</sup>	CGM % 70-180 mg/dL (primary outcome)	0.001	Yes	Test next variable
2 <sup>nd</sup>	CGM % above 180 mg/dL	0.02	Yes	Test next variable
3 <sup>rd</sup>	CGM mean glucose	0.007	Yes	Test next variable
4 <sup>th</sup>	HbA1c at 26 weeks	0.03	Yes	Test next variable
5 <sup>th</sup>	CGM % below 70 mg/dL	0.06	No	Stop formal testing
6 <sup>th</sup>	CGM % below 54 mg/dL	Not tested	Unknown	N/A

1474 Regardless of the results of the hierarchical testing, summary statistics appropriate to the  
 1475 distribution will be tabulated by treatment arm for each hierarchical outcome. A 95% confidence  
 1476 interval for the treatment arm difference will also be calculated for all four hierarchical outcomes  
 1477 listed above. However, a confidence interval that excludes zero will not be considered a  
 1478 statistically significant result if an outcome variable higher on the hierarchical list failed reach  
 1479 statistical significance.

1480 **10.7.2 Other Endpoint Analyses**

1481 CGM-Measured Outcomes

1482 The analyses for the secondary CGM-measured outcomes will parallel those mentioned above  
 1483 for the primary outcome.

1484 HbA1c

1485 Summary statistics (mean ± SD) will be reported for the central lab HbA1c at 26-weeks and for  
 1486 differences from pre-randomization by treatment group.

1487 Change in HbA1c from baseline to 26 weeks will be compared between the two treatment arms  
 1488 using a linear model while adjusting for baseline HbA1c, age, prior CGM and pump use, and  
 1489 clinical center (random factor).

1490 Missing data will be handled using direct likelihood in a regression model including all available  
 1491 central laboratory HbA1c measurements at baseline and 26 weeks visits. When available, the  
 1492 local HbA1c measurement will be included in the regression model as an auxiliary variable.

1493 For the binary HbA1c outcomes listed above, risk-adjusted percentages by treatment group will  
 1494 be computed from a logistic regression model. The logistic regression will adjust for the same  
 1495 factors mentioned above for the analysis with HbA1c as a continuous factor (i.e., baseline  
 1496 HbA1c, age, prior CGM and pump use, and clinical site as a random effect).

1497 Questionnaires and Other Outcomes

1498 For questionnaires administered to both randomization groups, comparisons will be made using  
 1499 similar linear models as described above for the primary outcomes. Separate models will be run  
 1500 for the total score and each of the subscales listed above.

1501 Similarly, for insulin, weight, and BMI metrics comparisons will be made using similar linear  
 1502 models as described above for the primary HbA1c analysis.

1503 **10.8 Safety Analyses**

1504 All randomized participants will be included in these analyses and all their post-randomization  
 1505 safety events will be reported.

1506 The circumstances of all reportable cases of the following will be summarized and tabulated by  
 1507 treatment group:

- 1508 • Severe hypoglycemia (as defined in section 8.1)
- 1509 • Diabetic ketoacidosis (as defined in section 8.1)
- 1510 • Ketone events defined as day with ketone level >1.0 mmol/L
- 1511 • CGM-measured hypoglycemic events ( $\geq 15$  minutes with glucose concentration <54 mg/dL)
- 1512 • CGM-measured hyperglycemic events ( $\geq 15$  minutes with glucose concentration >300  
 1513 mg/dL)
- 1514 • BG-measured hypoglycemic events (one BG record <54 mg/dL)
- 1515 • BG-measured hyperglycemic events (one BG record >350 mg/dL)
- 1516 • Worsening of HbA1c from baseline to 26 weeks by >0.5%
- 1517 • Other serious adverse events (SAE) and serious adverse device events (SADE)
- 1518 • Adverse device effects (ADE)
- 1519 • Unanticipated adverse device effects (UADE)

1520 For the following outcomes, mean  $\pm$  SD or summary statistics appropriate to the distribution will  
 1521 be tabulated by treatment group:

- 1522 • Number of SH events and SH event rate per 100 person-years
- 1523 • Number of DKA events and DKA event rate per 100 person-years
- 1524 • Any adverse event' rate per 100 person-years

1525 If enough events, the numbers will be compared between the two treatment arms using a robust  
1526 Poisson regression. The regression will adjust for the participant-reported number of events prior  
1527 to the start of the study and site as random effect. The amount of follow up will be included as an  
1528 offset covariate to compare the rates.

1529 Comparison of safety outcomes between the two treatment groups only include those  
1530 events occurring on or after randomization until the 26 week visit.

1531 Any pre-randomization adverse events will be tabulated separately and will include participants  
1532 who were never randomized.

### 1533 **10.9 Intervention Adherence**

1534 The following tabulations and analyses will be performed by treatment group to assess  
1535 intervention adherence for the study:

- 1536 • Sensor use – hours of use and percent time of use
- 1537 • The daily frequency of downloaded BGM use

1538 For CLC arm only, the following will be tabulated to assess adherence:

- 1539 • % time in different operational modes per week - overall and by month

### 1540 **10.10 Adherence and Retention Analyses**

1541 The following tabulations and analyses will be performed by treatment group to assess protocol  
1542 adherence for the study:

- 1543 • Number of protocol and procedural deviations per participant along with the number and  
1544 percentage of participants with each number of deviations
- 1545 • Number of protocol and procedural deviations by severity with brief descriptions listed
- 1546 • Flow chart accounting for all participants at all scheduled visits and phone contacts post  
1547 treatment initiation to assess visit and phone completion rates
- 1548 • Number of and reasons for unscheduled visits and phone calls
- 1549 • Number of participants who stopped treatment and reasons

### 1550 **10.11 Baseline Descriptive Statistics**

1551 Baseline demographic and clinical characteristics of the cohort of all randomized participants  
1552 will be summarized in a table using summary statistics appropriate to the distribution of each  
1553 variable. Descriptive statistics will be displayed overall and by treatment group.

1554 Will include:

- 1555 • Age
- 1556 • HbA1c
- 1557 • Gender
- 1558 • Race/ethnicity
- 1559 • Income, education, and/or insurance status
- 1560 • Insulin method before enrollment (pump vs. MDI)
- 1561 • CGM use before enrollment
- 1562 • Diabetes duration
- 1563 • BMI
- 1564 • C-peptide
- 1565 • Scores for diabetes specific personality, quality of life, hypoglycemia awareness and fear
- 1566 questionnaires

1567 **10.12 Device Issues**

1568 The following tabulations and analyses will be performed by treatment group to assess device  
1569 issues:

- 1570 • Device malfunctions requiring study team contact and other reported device issues
- 1571 • Sensor performance metrics (difference, absolute relative difference, and International  
1572 Organization for Standardization criteria) – if applicable, by sensor version.
- 1573 • % time CGM data available - overall and by month

1574 The following tabulations will be performed for the CLC arm only:

- 1575 • Performance metrics, describing the Control-IQ system and its components like:
  - 1576 ♦ % time CGM data were available to the Control-IQ system – overall and by month
  - 1577 ♦ % time in different operational modes per week - overall and by month
  - 1578 ♦ Rate of different failure events and alarms per 24 hours recorded by the Control-IQ
  - 1579 system – overall and by month
- 1580 • Technology Expectations Survey score at baseline and Technology Acceptance Survey score
- 1581 at 26 weeks

1582 **10.13 Planned Interim Analyses**

1583 No interim efficacy analysis is planned.

1584 The DSMB will review safety data at intervals, with no formal stopping rules other than the  
 1585 guidelines provided in the participant-level and study-level stopping criteria (as defined in  
 1586 section 8.5 of the protocol).

1587 **10.14 Subgroup Analyses**

1588 In exploratory analyses, all primary outcomes found significant according to the hierarchical  
 1589 rules outlined in section 10.7.1 will be assessed separately in various subgroups and for  
 1590 continuous variables according to the baseline value as defined below. Tests for interaction  
 1591 with treatment group will be performed and further explored if an interaction will be found in  
 1592 the first place.

1593 Interpretation of subgroup analyses will depend on whether the overall analysis demonstrates a  
 1594 significant treatment group difference. In the absence of such an overall difference and if  
 1595 performed, subgroup analyses will be interpreted with caution. For continuous variables, results  
 1596 will be displayed in subgroups based on cutpoints although the analysis will utilize the variable  
 1597 as continuous, except for age which will be analyzed both as a continuous variable and in two  
 1598 age groups. If there is insufficient sample size in a given subgroup, the cutpoints for continuous  
 1599 measures may be adjusted per the observed distribution of values. Cutpoint selection for display  
 1600 purposes will be made masked to the outcome data.

- 1601 • Baseline HbA1c
- 1602 • Baseline CGM time spent <70 mg/dL
- 1603 • Baseline CGM time spent >180 mg/dL
- 1604 • Baseline CGM time 70-180 mg/dL
- 1605 • Device use before the enrollment: pump/MDI, CGM/no CGM, and combinations of both
- 1606 • Age
- 1607 • Sex
- 1608 • Race
- 1609 • Clinical site

1610 Additional analyses may be performed for subgroups defined based on the following baseline  
 1611 demographic/clinical characteristics.

- 1612 • Body mass index
- 1613 • Income, education, and/or insurance status
- 1614 • Baseline scores for quality of life, hypoglycemia awareness and fear questionnaires
- 1615 • C-peptide level

1616 **10.15 Multiple Comparison/Multiplicity**

1617 Primary Analysis

1618 Since there will be a single comparison for the primary outcome (CGM-measured % 70-180  
1619 mg/dL), no adjustment is needed.

1620 Secondary Hierarchical Analyses

1621 The hierarchical testing procedure described above in section 10.7.1 will be used to control the  
1622 overall type 1 error for the primary outcome plus five key secondary outcomes identified above.

1623 All Other Secondary Analyses

1624 For all above-mentioned secondary analyses, the false discovery rate will be controlled using the  
1625 adaptive Benjamini-Hochberg procedure.

1626 **10.16 Exploratory Analyses**

1627 In addition to the analysis for the CGM-measured endpoints described earlier, separate analyses  
1628 will be conducted for daytime and nighttime.

1629 The CGM-measured analyses will be replicated with only CGM data when the closed-loop was  
1630 active for the CLC group. The CGM data for the SAP group will be the same as mentioned  
1631 above in the CGM Metrics Calculation section.

1632

## Chapter 11: Data Collection and Monitoring

1633

### 11.1 Case Report Forms and Device Data

1634 The main study data are collected through a combination of electronic case report forms  
1635 (CRFs) and electronic device data files obtained from the study software and individual  
1636 hardware components. These electronic device files and electronic CRFs from the study  
1637 website are considered the primary source documentation.

1638 When data are directly collected in electronic case report forms, this will be considered the  
1639 source data. Each participating site will maintain appropriate medical and research records for  
1640 this trial, in compliance with ICH E6 and regulatory and institutional requirements for the  
1641 protection of confidentiality of participants.

1642

### 11.2 Study Records Retention

1643 Study documents should be retained for a minimum of 2 years after the last approval of a  
1644 marketing application in an ICH region and until there are no pending or contemplated marketing  
1645 applications in an ICH region or until at least 2 years have elapsed since the formal  
1646 discontinuation of clinical development of the investigational product. These documents should  
1647 be retained for a longer period, however, if required by local regulations. No records will be  
1648 destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the  
1649 sponsor to inform the investigator when these documents no longer need to be retained.

1650

### 11.3 Quality Assurance and Monitoring

1651 Designated personnel from the Coordinating Center will be responsible for maintaining quality  
1652 assurance (QA) and quality control (QC) systems to ensure that the clinical portion of the trial is  
1653 conducted and data are generated, documented and reported in compliance with the protocol,  
1654 Good Clinical Practice (GCP) and the applicable regulatory requirements. Adverse events will  
1655 be prioritized for monitoring.

1656 A risk-based monitoring (RBM) plan will be developed and revised as needed during the course  
1657 of the study, consistent with the FDA “Guidance for Industry Oversight of Clinical  
1658 Investigations — A Risk-Based Approach to Monitoring” (August 2013). Study conduct and  
1659 monitoring will conform with 21 Code of Federal Regulations (CFR) 812.

1660 The data of most importance for monitoring at the site are participant eligibility and adverse  
1661 events. Therefore, the RBM plan will focus on these areas. As much as possible, remote  
1662 monitoring will be performed in real-time with on-site monitoring performed to evaluate the  
1663 verity and completeness of the key site data. Elements of the RBM may include:

- 1664 • Qualification assessment, training, and certification for sites and site personnel
- 1665 • Oversight of Institutional Review Board (IRB) coverage and informed consent procedures
- 1666 • Central (remote) data monitoring: validation of data entry, data edits/audit trail, protocol  
1667 review of entered data and edits, statistical monitoring, study closeout
- 1668 • On-site monitoring (site visits): source data verification, site visit report

- 1669 • Agent/Device accountability
- 1670 • Communications with site staff
- 1671 • Patient retention and visit completion
- 1672 • Quality control reports
- 1673 • Management of noncompliance
- 1674 • Documenting monitoring activities
- 1675 • Adverse event reporting and monitoring

1676 Coordinating Center representatives or their designees may visit the study facilities at any time  
1677 in order to maintain current and personal knowledge of the study through review of the records,  
1678 comparison with source documents, observation and discussion of the conduct and progress of  
1679 the study.

1680 **11.4 Protocol Deviations**

1681 A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or procedure  
1682 requirements. The noncompliance may be either on the part of the participant, the investigator,  
1683 or the study site staff. As a result of deviations, corrective actions are to be developed by the site  
1684 and implemented promptly.

1685 The site PI/study staff is responsible for knowing and adhering to their IRB requirements.  
1686 Further details about the handling of protocol deviations will be included in the monitoring plan.

1687

## **Chapter 12: Ethics/Protection of Human Participants**

1688

### **12.1 Ethical Standard**

1689 The investigator will ensure that this study is conducted in full conformity with Regulations for  
 1690 the Protection of Human Participants of Research codified in 45 CFR Part 46, 21 CFR Part 50,  
 1691 21 CFR Part 56, and/or the ICH E6.

1692

### **12.2 Institutional Review Boards**

1693 The protocol, informed consent form(s), recruitment materials, and all participant materials will  
 1694 be submitted to the IRB for review and approval. Approval of both the protocol and the consent  
 1695 form must be obtained before any participant is enrolled. Any amendment to the protocol will  
 1696 require review and approval by the IRB before the changes are implemented to the study. All  
 1697 changes to the consent form will be IRB approved; a determination will be made regarding  
 1698 whether previously consented participants need to be re-consented.

1699

### **12.3 Informed Consent Process**

1700

#### **12.3.1 Consent Procedures and Documentation**

1701 Informed consent is a process that is initiated prior to the individual's agreeing to participate in  
 1702 the study and continues throughout the individual's study participation. Extensive discussion of  
 1703 risks and possible benefits of participation will be provided to the participants and their families.  
 1704 Consent forms will be IRB-approved and the participant will be asked to read and review the  
 1705 document. The investigator will explain the research study to the participant and answer any  
 1706 questions that may arise. All participants will receive a verbal explanation in terms suited to  
 1707 their comprehension of the purposes, procedures, and potential risks of the study and of their  
 1708 rights as research participants. Participants will have the opportunity to carefully review the  
 1709 written consent form and ask questions prior to signing.

1710 The participants should have the opportunity to discuss the study with their surrogates or think  
 1711 about it prior to agreeing to participate. The participant will sign the informed consent document  
 1712 prior to any procedures being done specifically for the study. The participants may withdraw  
 1713 consent at any time throughout the course of the trial. A copy of the informed consent document  
 1714 will be given to the participants for their records. The rights and welfare of the participants will  
 1715 be protected by emphasizing to them that the quality of their medical care will not be adversely  
 1716 affected if they decline to participate in this study.

1717

#### **12.3.2 Participant and Data Confidentiality**

1718 The study monitor, other authorized representatives of the sponsor, representatives of the IRB or  
 1719 device company supplying study product may inspect all documents and records required to be  
 1720 maintained by the investigator, including but not limited to, medical records (office, clinic, or  
 1721 hospital) for the participants in this study. The clinical study site will permit access to such  
 1722 records.

1723 The study participant's contact information will be securely stored at each clinical site for  
1724 internal use during the study. At the end of the study, all records will continue to be kept in a  
1725 secure location for as long a period as dictated by local IRB and Institutional regulations.

1726 Study participant research data, which is for purposes of statistical analysis and scientific  
1727 reporting, will be transmitted to and stored at the Jaeb Center for Health Research and the  
1728 University of Virginia Center for Diabetes Technology. This will not include the participant's  
1729 contact or identifying information. Rather, individual participants and their research data will be  
1730 identified by a unique study identification number. The study data entry and study management  
1731 systems used by clinical sites and by Jaeb research staff will be secured and password protected.  
1732 At the end of the study, all study databases will be de-identified and archived at Jaeb Center for  
1733 Health Research and the University of Virginia Center for Diabetes Technology. Permission to  
1734 transmit data will be included in the informed consent.

1735

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