Open, Single Arm, Prospective, Multicenter Study of an Investigational Extended Wear Insulin Infusion Set During Home Use in People with Type 1 Diabetes

Protocol Identifying Number: 150-1261-00
IDE Sponsor: Capillary Biomedical

Version Number: v.5.0
08 February 2024

CONFIDENTIAL

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VERSION HISTORY

VERSION NUMBER	AUTHOR	APPROVER	EFFECTIVE DATE	REVISION DESCRIPTION
1.0	John Lum	Alayne Lehman	20 Aug 2021	Original
2.0	John Lum	Alayne Lehman	28 Oct 2021	Major revisions include: • Addressed FDA questions during IDE review • Revised language in primary efficacy endpoint • Revised inclusion criteria • Revised sample size • Revised statistical methods • Added background information • Added infusion set removal guidelines
3.0	Alayne Lehman	Alayne Lehman	09 Jan 2023	Major revisions include: • Addressed FDA questions during IDE review • Revised language in secondary/exploratory endpoints • Revised exclusion criteria • Added background information • Revised hyperglycemia management and infusion set guidelines
4.0*	John Lum	Alayne Lehman	05 Sep 2023	• Added version history table • Removed requirement to provide digital photographs of infusion sets/sites • Updated schedule of study visits and procedures in Table 1 • Added background information in Chapter 1 • Updated hyperglycemia management and infusion set guidelines language in Section 1.4 • Removed insulin reimbursement per IRB request in Section 7.1 • Revised key secondary endpoints in Sections 1.3.3 and 8.4.4 • Fixed clerical errors, typos, formatting throughout protocol
5.0	Alayne Lehman, John Lum	Alayne Lehman	08 Feb 2024	• Added Dexcom G7 CGM support to the protocol to allow participants to use either Dexcom G6 or Dexcom G7 in the study • Reworded “serum ketone” as “blood ketone” in eligibility criteria for consistency with “blood glucose” • Added clarification that insulin aspart and insulin lispro along with name brand Humalog and Novolog are permitted in this clinical trial. • Changed required time to be on baseline insulin from 3 months to 1 month • Clarified the screening assessment of Control-IQ adherence will be based on Subject’s personal t:connect data • Added wording to hyperglycemic/ketoic reportable event to include “the participant contacted the site and

VERSION NUMBER	AUTHOR	APPROVER	EFFECTIVE DATE	REVISION DESCRIPTION
				received guidance on how to manage the acute hyperglycemia/ketosis event unrelated to the infusion set

*Version in effect at study initiation

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ADE	Adverse Device Effect
AE	Adverse Event
AP	Artificial Pancreas
BG	Blood Glucose
BGM	Blood Glucose Meter
BMI	Body Mass Index
CA	California
CEC	Clinical Events Committee
CI	Confidence Interval
CFR	Code of Federal Regulations
CO2	Carbon Dioxide
CRF	Case Report Form
CGM	Continuous Glucose Monitor
CSII	Continuous Subcutaneous Insulin Infusion
CT	Computed Tomography
DCCT	Diabetes Control and Complications Trial
DKA	Diabetic Ketoacidosis
DOI	Day of Insertion
DPP-4	Dipeptidyl peptidase-4
e.g.	exempli gratia (for example)
eCRF	electronic Case Report Form
et al.	et alia (and others)
etc.	et cetera (and so forth)
FDA	Food and Drug Administration
FL	Florida
GEE	Generalized Estimated Equations
GLP-1	Glucagon-like peptide-1
HbA1c	Glycated Hemoglobin
i.e.	id est (that is)
ICF	Informed Consent Form
ICH	International Conference of Harmonization
IFU	Instructions For Use
ID	Identification
IIS	Insulin Infusion Set
Inc	Incorporated

ABBREVIATION	DEFINITION
IRB	Institutional Review Board
JCHR	Jaeb Center Health Research
JDRF	Juvenile Diabetes Research Foundation
MedDRA	Medical Dictionary for Regulatory Activities
mg/dL	milligrams per deciliter
Micro-CT	micro computed tomography
mmol/L	millimoles per liter
MRI	Magnetic Resonance Imaging
NGSP	National Glycohemoglobin Standardization Program
p	probability
PD	Pharmacodynamic
pH	power of Hydrogen
PI	Principal Investigator
PK	Pharmacokinetic
QA	Quality Assurance
QC	Quality Control
RBM	Risk Based Monitoring
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SC	Subcutaneous
SD	Standard deviation
SGLT-2	Sodium-glucose cotransporter-2
SOP	Standard Operating Procedures
T1D	Type 1 Diabetes
UADE	Unanticipated Adverse Device Effect
WOCBP	Women of Childbearing Potential

SITE PRINCIPAL INVESTIGATOR STATEMENT OF COMPLIANCE

Protocol Title: Open, Single Arm, Prospective, Multicenter Study of an Investigational Extended Wear Insulin Infusion Set During Home Use in People with Type 1 Diabetes

Protocol Version/Date: v5.0 / 08 February 2024

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

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

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

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

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

Investigator's Name _____

Site Name/Number _____

PROTOCOL SUMMARY

Title	Open, Single-Arm, Prospective, Multicenter Study of an Investigational Extended Wear Insulin Infusion Set During Home Use in People with Type 1 Diabetes
Précis	Prospective evaluation of the SteadiSet insulin infusion set with 12 wear periods of up to 7 days each in adults with type 1 diabetes (T1D) using Tandem pump with t:slim X2 Control-IQ
Investigational Device	SteadiSet
Objectives	Primary Objective: ◆ The evaluation of SteadiSet device function as evidenced by the absence of device failure due to uncontrolled hyperglycemia with or without ketosis Secondary Objectives: ◆ Characterization of safety endpoints, glycemic control and insulin dosing while using the SteadiSet device
Study Design	Prospective, Multi Center, Single Arm study
Number of Sites	Up to 20 sites in the United States
Endpoint	**Primary Efficacy Endpoint:** Percentage of successfully inserted SteadiSet infusion sets (i.e., not removed within 8 hours of insertion) that are not withdrawn from use prior to 7 days (168 hours) due to either (1), (2), or (3): 1. Blood Glucose value ≥250 mg/dL with ketones >1.0 mmol/L, in the absence of illness or other physiological stress. 2. Blood Glucose value ≥250 mg/dL for at least 60 minutes duration, 3 hours or more following a snack or meal event AND failure to respond to up to 2 adequate corrective boluses delivered by the pump with a fall of at least 50 mg/dL. 3. Investigator advises the infusion set should be replaced to assure subject's safety See Section 1.4 Subject Hyperglycemia Management and Infusion Set Removal Guidelines for additional details. A Clinical Events Committee (CEC) will adjudicate primary and secondary clinical endpoint events based on review of all available information that is relevant to determine whether protocol-defined endpoint events have occurred during the study. See Section 8.4.1 Clinical Events Committee for additional details. **Safety Endpoints:** The incidence, severity, and relationship to the investigational device of all reported adverse events (serious and non-serious including diabetic ketoacidosis (DKA) and severe hypoglycemia) from day of insertion through day of device removal for each wear period. **Key Secondary Endpoint:** Proportion (%) of SteadiSet infusion sets withdrawn from use at any time following insertion prior to 7 days (168 hours) as evidenced by one or more of the following device failure modes. NOTE: infusion set removals prior to 168 hours due to miscalculation of date and/or time, along with other removals that cannot be ascribed to the investigational device performance, are excluded from this proportion calculation. 1. Infusion set failure as defined in the Primary Endpoint (including any such removals occurring during the first 8 hours following set insertion) 2. Evidence of infusion set site infection defined as requiring treatment or at the investigator's judgment 3. Cannula dislodgement from subcutaneous (SC) space (with or without liquid leakage at the cannula insertion site) a. Leakage at the cannula insertion site may or may not be deemed by the investigator to constitute infusion set failure following consultation with the study subject

	b. Accidental removal events (e.g., tubing caught on doorknob) are excluded from this proportion calculation 4. Occurrence of a non-resolvable pump occlusion alarm 5. Other device malfunction (e.g., inability to pierce skin, bending, or other malformation that might impact insulin infusion, securement failure) 6. Presence of pain of sufficient severity to prompt early removal of infusion set 7. Any other event that can be ascribed to the investigational device performance that results in failure of insulin delivery **Other Secondary Endpoints:** 1. Standard glucose control metrics obtained from CGM, including hyper- and hypoglycemic episodes, time in range, mean 24-hour glucose, and other measures 2. Total daily insulin dose, basal dose, bolus dose, and bolus basal ratio overall and by day of infusion set wear 3. Subject tolerability levels for the infusion set insertion as assessed by a pain scale of 0 to 100 with zero being no pain and 100 being significant pain 4. Hyperglycemia trends in days 1-3 versus after day 3 5. Infusion set performance (including set failures as defined above and also glucose metrics, insulin doses, pump occlusion alarms and hyperglycemia trends) in subjects who use low doses (e.g., <25 units/day) of insulin and in subjects who experience frequent stops and start of pump use **Exploratory Endpoint:** 1. HbA1c change from baseline to the end of study participation.
Eligibility Criteria	**Inclusion Criteria:** 1. Age 18 to 80 years old inclusive 2. Generally in good health, as determined by the investigator 3. Living in the United States with no plans to move outside the United States during the study 4. Diagnosis of T1D for at least 12 months 5. Minimum of 6 months of insulin pump experience and at least 3 months of current experience with a Tandem pump 6. Using Tandem t:slim X2 insulin pump with Control-IQ technology for a minimum of 1 month at the time of enrollment 7. Minimum of 14 days of Control-IQ data immediately preceding screening that demonstrate pump use compliance, including at least 85% of time with Control-IQ technology active 8. HbA1c <9.0% in the last 6 months. 9. Willing to implement and adhere to pump alert/alarm settings on a study-provided pump as instructed during the study 10. Willing to wear each investigational infusion set for up to 7 days during each of the 12 consecutive wear periods in the study 11. Willing to perform blood ketone and blood glucose (fingerstick) measurements as directed using provided ketone and blood glucose meters and strips 12. Access to internet for required periodic uploads of study device data 13. BMI in the range 18–35 kg/m^2, both inclusive 14. Currently using one of the following insulins with no expectation of a need to change insulin type during the study: a. Humalog™ (insulin lispro) b. NovoLog™ (insulin aspart) 15. Using Humalog™ insulin lispro or NovoLog™ insulin aspart for a minimum of 1 month at the time of enrollment

	16. Willing to change insulin cartridge every 48-72 hours, as recommended by patient's healthcare provider during the study 17. Has routine access to a smart phone e.g., ability to receive text messages 18. Has the ability to understand and comply with protocol procedures and to provide informed consent (i.e., English proficient in both verbal and written communication) **Exclusion Criteria:** 1. Concurrent use of any non-insulin glucose-lowering agent, other than metformin (for example, GLP-1 agonists, Symlin, DPP-4 inhibitors, SGLT-2 inhibitors, sulfonylureas) 2. Female subject is pregnant, planning to become pregnant, or not using adequate method of contraception 3. Episodes of severe hypoglycemia in the last 6 months resulting in: a. Medical Assistance (i.e., paramedics, hospital evaluation or hospitalization) b. Loss of consciousness c. Seizures 4. One or more episodes of diabetic ketoacidosis (DKA) in the last 6 months requiring hospitalization 5. Currently on a ketogenic or low-carbohydrate diet of less than 60 grams of carbohydrates per day, or intending to begin one during the study period 6. Known cardiovascular disease considered to be clinically relevant by the investigator 7. Known history of any of the following conditions: a. Cushing's Disease b. Pancreatic islet cell tumor c. Insulinoma d. Lipodystrophy e. Extensive lipohypertrophy, as assessed by the investigator 8. Currently undergoing treatment with: a. Systemic oral or intravenous corticosteroids (current or within the last 8 weeks from screening), b. Thyroid hormones, unless use has been stable during the past 3 months 9. Significant history of any of the following, that in the opinion of the investigator would compromise safety or successful study participation: a. Alcoholism b. Drug abuse 10. Significant acute or chronic illness, that in the opinion of the investigator might interfere with safety or integrity of study results 11. Current participation in another clinical drug or device study 12. Immediate family member (spouse, biological or legal guardian, child, sibling, parent) who is a study site personnel directly affiliated with this study or who is an employee of Capillary Biomedical
Sample Size	Up to 300 with the goal of completing approximately 120 Subjects for each insulin type (Humalog and Novolog)
Treatment Groups	All subjects use the SteadiSet insulin infusion set for 12 wear periods of up to 7 days each.
Subject Duration	Up to 14 weeks for each subject to complete the study
Study Duration (planned)	8 months from first enrollment until last subject visit

Protocol Overview/Synopsis	Subjects with T1D and experience using a Tandem t:slim X2 pump with Control-IQ technology will be evaluated for study participation. Following screening, eligible subjects will enter the active phase of the study and receive the SteadiSet infusion set and a study-provided Control-IQ pump for use during the study. Subjects will wear the SteadiSet infusion set with the study pump for up to 7 days for each of 12 consecutive wear periods.
Statistical Methods and Sample Size Documentation	Kaplan-Meier estimates will be reported along with a curve used to estimate the proportion of infusion sets that meet the primary and secondary endpoint definitions. A point estimate and two-sided 95% confidence interval for the 7-day survival rate will be calculated with a bootstrap to account for the correlated data from having each subject wear multiple infusion sets. A corresponding p-value will be given for the null hypothesis that the true survival probability is 75%. If the true success probability is 83% and we conservatively estimate the within-subject correlation to be as high as 0.4, then a sample size of 120 patients per insulin type with 12 infusion set wears per subject would give 87% power for a two-sided test at alpha = 0.05 to reject the null hypothesis that the success rate is 75%. Nine wears per subject, N=120 subjects would give 86% power.

SCHEMATIC OF STUDY DESIGN

Figure 1. Study Schematic. Note timing of study visits/calls at 2 weeks and 6 weeks will be with respect to initiation of Set #1 and likely will not correspond exactly with removal of Set #2 and Set #6, respectively. See Section 3.5 for additional visit and contact schedule details.

Table 1-1. Schedule of Study Visits and Procedures

	Screening/ Baseline Visit	Day 0 - Initiation of Study Infusion Set	3 Days	2 Weeks	6 Weeks	Final Visit	Unsched. Call/Visit
Visit Window	N/A	≤14 days	(-1 to +3 days)	(± 4 days)	(± 7 days)	(+ 7 days from final wear period)	N/A
Informed Consent (enrollment)	X						
Eligibility Criteria	X[1]						
Medical History including baseline medications	X						
Survey Usability, Satisfaction & Preference[2]	X			X		X	
Height and Weight to Calculate BMI	X						
Pregnancy Test (Urine) for WOCBP[3]	X						
Central Lab HbA1c		X				X	
Subject Training for SteadiSet		X					
Upload Ketone and Glucose Meters				X	X	X	
Insertion of 1st SteadiSet by Subject		X					
Pain Assessment		Infusion Set Insertion					
Dispense SteadiSets & other study supplies	X						
Upload Insulin Pump Data	X		At time of each infusion set removal and study visit				X
Adverse Event Assessment		X	X	X	X	X	X
Reportable Medication Changes			X	X	X	X	X
Collect all used & unused infusion sets						X	

[1]Confirm eligibility if the screening and initiation visits are not completed on the same day.
[2]There are 2 different SUS scales. The 1st assess the Subject's opinion of their commercial infusion set and should be completed before insertion of the study device. The next two are surveys assess the Subject's opinion of the study device after use. Site to send the appropriate link to Subject to complete each assessment.
[3]Pregnancy test should be completed at Day 0 before insertion of investigational product.

Chapter 1: Background Information

1.1 Introduction

Type 1 diabetes (T1D) causes autoimmune pancreatic beta cell destruction and lifelong dependency on exogenous insulin, typically delivered via either multiple daily injections or via an infusion set with a subcutaneous catheter (continuous subcutaneous insulin infusion, or CSII).

1.1.1 Statement of the Problem

Insulin infusion sets fail early and fail often. Research from Stanford University found that most infusion set failures are due to cannula kinking or a clogged insulin port[3], Table 1-1. Additional literature on infusion set failures, which is indicative of a high failure rate with currently available infusion sets, is provided in Appendix A, Relevant Literature on Infusion Sets.

Table 1-1. Infusion Set Failure Rate by Duration of Use

DAY(S) OF USE	FAILURE RATE
Day 1	> 15%
Day 3	> 25%
Day 7	> 65%

This high failure rate prevents wider adoption of insulin pump therapy that could improve current patient outcomes and expand pump access to more users.

Results from pre-clinical animal and bench studies of the Capillary Biomedical infusion set design (see Section 1.1.2) have shown a lower rate of cannula kinking (2.1% vs 32.5% for straight Teflon cannulas, $p<0.001$) and improved infusion set functionality for extended use periods beyond 72 hours (In-Vivo Study of the Tissue Trauma Caused by a New, Kink-Resistant Insulin Infusion Set Compared to a Commercial Control over Two Weeks of Wear Time [unpublished data, 2021]).

Currently, a change of insulin infusion sets is recommended every 72 hours for commercially available Teflon insulin infusion sets and every 48 hours for steel cannulas.[1,7] Based on clinical experience and recently published data, there is evidence that cannula wear time might be extended in some patients without worsening of glucose control. [1,3,8,9] Other patients report a worsening of glycemic control over time, which prompts them to change the infusion set prior to the recommended 3-day period.[1,3] An ideal IIS would provide high reliability while leveraging the on/off insulin pharmacokinetics (PK) and pharmacodynamics (PD) of modern rapid-acting insulin analogs over an extended period (>3 days). An optimized IIS would also enhance the safety and performance of a closed-loop artificial pancreas (AP) system,[10] perhaps with CGM and insulin infusion combined in one device, capable of a 7+ day wear-time.[11-13]

1.1.2 Preclinical Testing of the Capillary Biomedical Infusion Cannula

Between 2016 and 2018, Capillary Biomedical, Inc. (CapBio) and the Jefferson Artificial Pancreas Center (JAPC, Thomas Jefferson University, Philadelphia, PA) performed preclinical studies in 18 swine funded by JDRF. The JAPC research team iteratively tested multiple generations of cannulas developed by CapBio to identify the optimum cannula design that eventually became the *Achilles Infusion Set*. The Achilles prototype was well tolerated by all animals (n=3) with no signs of inflammation or infection. The JAPC was able to show the improved CapBio cannula design successfully prevented kinking (0% versus 57% kink rate in Silhouette commercial angled cannulas, $p<0.001$). As measured in micro-CT,

the surface-area-to-volume ratio of a bolus of insulin/x-ray contrast agent was significantly greater than that of a bolus delivered through a commercial catheter (+16.5%, $p<0.05$), suggesting better delivery of insulin into the adjacent tissue and vasculature/lymphatics. The JAPC furthermore evaluated tissue response to Achilles cannulas by means of histopathological staining. The inflammatory layer (thrombus, inflammatory cells, collagen, debris, proteins, etc.) was consistently thinner around CapBio cannulas compared with the commercial Silhouette over 8 days of wear time ($p<0.001$). The overall area of inflamed tissue surrounding the CapBio cannula was significantly larger around Silhouette control catheters compared to the Achilles cannula between 4 and 8 days of wear time ($p=0.003$). A publication of a head-to-head comparison of the Achilles infusion set and a commercial infusion set with a 90° cannula is currently in preparation. The methods have been published in 2019 together with results showing significantly better tissue response when using angled cannulas.[14]

1.1.3 Human Use of the Capillary Biomedical Infusion Cannula

Feasibility Study

This was a prospective non-randomized home use feasibility study of the manually inserted Achilles device (previous version of the SteadiSet) performance, usability, tolerability and safety in patients with T1D. Twenty-one subjects were enrolled at St. Vincent's Hospital, Melbourne, Australia, under principal investigator Prof. David O'Neal. The study was composed of 3 periods with each period initiated at the CRU and followed by a home-use phase of up to 7 days. A run-in period (Week 1) was followed by two test periods (Week 2 and Week 3) in which subjects discontinued the use of their routine IIS and managed their BG solely using the Achilles infusion set and their insulin pump. Week 2 and Week 3 were considered complete when an Achilles infusion set failure occurred, or the subject wore the Achilles for the total 7-day wear period. Twenty subjects completed the study and a total of 41 infusion sets were inserted in Week 2 and Week 3. The overall 7-day survival rate for the infusion sets was 88% (36/41). Proportional time spent with glucose <3.9 mmol/L did not increase while wearing the Achilles infusion set.

A total of 23 adverse events were reported from 15 (75%) of subjects. The most common adverse events included: hyperglycemia (35%) and infusion/insertion site reactions (35%). There were no serious or unanticipated adverse events from this investigation. Overall, the Achilles infusion set was safe and well tolerated for and extended wear time. Results published Kastner JR, Venkatesh N, Brown K, Muchmore DB, Ekinci E, Fourlanos S, Joseph JI, Shafeeq M, Shi L, Strange P, Strasma PJ, O'Neal DN. Feasibility study of a prototype extended-wear insulin infusion set in adults with type 1 diabetes. Diabetes Obes Metab. 2022 Jun;24(6):1143-1149. doi: 10.1111/dom.14685. Epub 2022 Mar 18. PMID: 35257468.

PK/PD Study 150-1022-00

This was a prospective, single center, randomized sequence, 2-way crossover study to assess the Achilles device's performance, survivability, consistency, efficacy, and safety over an extended wear time of up to 7 days. Pharmacokinetic (PK) and pharmacodynamic (PD) profiles of a bolus of rapid-acting insulin were measured on 4 separate days of IIS wear time during 2 separate wear periods. Following a wash-out period, subjects crossed over into the investigational or control group, respectively. Seven subjects enrolled and six subjects completed the study at the Advanced Metabolic Care + Research (AMCR) endocrinology center in Escondido, CA, USA under principal investigator Dr. Timothy Bailey. No serious or unanticipated adverse events were reported from this investigation. The study was terminated early by the sponsor after randomization of 7 subjects, and the final study report is complete. The pharmacokinetic results of the study confirm and extend previous studies that have shown that insulin exposure is accelerated as wear time increases over 7 days of infusion set use. Further, the results of this small study are supportive of the conclusion that the Achilles IIS reliably delivers insulin and facilitates maintenance of satisfactory glucose control over 7 days. Given the progressive acceleration of insulin exposure over the 7-day wear period, it may be that the deployment of an automated insulin delivery

system may help to automatically match insulin delivery to insulin requirements across infusion set wear time. Results published in a brief report: Kastner JR et.al Progressive acceleration of insulin exposure over 7 days of infusion set wear. Diabetes Technol Ther. 2202 Dec 20.doi:10.89/dia 2022.0323.

Pilot Study 150-1139-00

This study was designed as a controlled, random-sequence, single-center study of device performance, tolerability, and safety of the SteadiSet infusion set compared to a commercially available Teflon control device during four home use periods of up to 14 days each (AABB vs. BBAA). The primary endpoint of this study was the duration (days) of successful insulin delivery through the SteadiSet before removal due to normal use, or an infusion set failure.

Thirteen subjects were enrolled with 12 subjects completing the study at the Medical University of Graz, Austria under principal investigator Dr. Julia Mader. There were no unexpected or serious adverse events. Results published: Kastner, Jasmine R., PhD. et. al. Current insulin infusion set failure criteria may be too stringent for real-life settings and may skew infusion set failure outcomes in extended-wear infusion set studies. Diabetes, Obesity and Metabolism 08 December 2022, https://doi.org/10.1111/dom.14935.

1.2 Objective and Rationale

The objective of this prospective, multi center, single-arm study is to assess the efficacy, safety, and tolerability of using the SteadiSet infusion set for insulin delivery when each set is used continuously for up to 7 days in adults with T1D, to provide data for regulatory submission.

The rationale for the study is based on the aforementioned literature that has documented that high failure rate with currently available infusion sets and the promising preliminary data indicating that the SteadiSet infusion set may fail less frequently and function longer.

1.3 Endpoints

1.3.1 Primary Efficacy Endpoint

Percentage of successfully inserted SteadiSet infusion sets (i.e., not removed within 8 hours of insertion) that are not withdrawn from use prior to 7 days (168 hours) due to either (1), (2), or (3):

1. Blood Glucose value ≥250 mg/dL with ketones >1.0 mmol/L, in the absence of illness or other physiological stress.
2. Blood Glucose value ≥250 mg/dL for at least 60 minutes duration, 3 hours or more following a snack or meal event AND failure to respond to up to 2 adequate corrective boluses delivered by the pump with a fall of at least 50 mg/dL.
3. Investigator advises the infusion set should be replaced to assure subject's safety

1.3.2 Safety Endpoints

The incidence, severity, and relationship to the investigational device of all reported adverse events (serious and non-serious including DKA and severe hypoglycemia) from day of insertion through day of device removal for each wear period.

1.3.3 Key Secondary Endpoint

Proportion (%) of SteadiSet infusion sets withdrawn from use at any time following insertion prior to 7 days (168 hours) as evidenced by one or more of the following device failure modes. NOTE: infusion set removals prior to 168 hours due to miscalculation of date and/or time, along with other removals that cannot be ascribed to the investigational device performance, are excluded from this proportion calculation.

1. Infusion set failure as defined in the Primary Endpoint (including any such removals occurring during the first 8 hours following set insertion)
2. Evidence of infusion set site infection defined as requiring treatment or at the investigator's judgment
3. Cannula dislodgement from subcutaneous (SC) space (with or without liquid leakage at the cannula insertion site)
    a. Leakage at the cannula insertion site may or may not be deemed by the investigator to constitute infusion set failure following consultation with the study subject
    b. Accidental removal events (e.g., tubing caught on doorknob) are excluded from this proportion calculation
4. Occurrence of a non-resolvable pump occlusion alarm
5. Other device malfunction (e.g., inability to pierce skin, bending, or other malformation that might impact insulin infusion, securement failure)
6. Presence of pain of sufficient severity to prompt early removal of infusion set
7. Any other event that can be ascribed to the investigational device performance that results in failure of insulin delivery

1.3.4 Other Secondary Endpoints

1. Standard glucose control metrics obtained from CGM, including hyper- and hypoglycemic episodes, time in range, mean 24-hour glucose, and other measures
2. Total daily insulin dose, basal dose, bolus dose, and bolus basal ratio, overall, and by day of infusion set wear
3. Subject tolerability levels for the infusion set insertion as assessed by a pain scale of 0 to 100 with zero being no pain and 100 being significant pain
4. Hyperglycemia trends in days 1-3 versus after day 3
5. Infusion set performance (including set failures as defined above and also glucose metrics, insulin doses, pump occlusion alarms and hyperglycemia trends) in subjects who use low doses (e.g., <25 units/day) of insulin and in subjects who experience frequent stops and start of pump use

1.3.5 Exploratory Endpoint

1. HbA1c change from baseline to the end of study participation.

1.4 Subject Hyperglycemia Management and Infusion Set Removal Guidelines

1. If, in the absence of illness or other physiological stress, blood glucose is ≥250 mg/dL and ketones are >1.0 mmol/L, then infusion set failure is established.*
    - Ketones are to be measured any time the blood glucose value is ≥250 mg/dL
    - If ketones are elevated the subject should test ketones hourly until ketones fall below 0.6 mmol/L.

2. If the CGM glucose value is ≥250 mg/dL for 60 minutes or longer, 3 hours or more following a snack or meal event AND ketones measure ≤1.0 mmol/L then attempts to correct the hyperglycemia are to occur as follows:
    - Confirm the blood glucose value is ≥250 mg/dL with a fingerstick BG value.
    - If this fingerstick BG value is <250 mg/dL the subject will be instructed to continue to follow CGM readings.

- If confirmatory fingerstick BG value is ≥250 mg/dL then an initial manual correction bolus delivered by the pump is to be given using the fingerstick BG value.
- 60 minutes from the initial correction bolus (not the time of an auto bolus) will start the hourly testing schedule for fingerstick BGs and ketones. If the repeat ketone level after the initial correction bolus is ≤1.0 mmol/L, and the glucose has not fallen by 50 mg/dL then a second correction bolus should be administered using the same procedures described above. (*The manual correction bolus dose given from the Bolus Calculator the subject administers will take into consideration the estimated residual Insulin on Board*)
    - If a repeat fingerstick BG value shows failure to respond to the second correction bolus within an additional hour with a fall of 50 mg/dL from the fingerstick BG prior to initial correction bolus *and there has been no intervening snack or meal event,* then the infusion set failure is established.*
    - If the fingerstick BG has responded to the second correction bolus with a fall of at least 50 mg/dL from the fingerstick BG prior to the initial correction bolous AND the fingerstick BG is still ≥250 mg/dL then fingerstick BGs and ketone levels should be rechecked hourly until the fingerstick BG level falls below 250 mg/dL.
    - If fingerstick BG does not fall below 250 mg/dL within six (6) hours from initial hyperglycemic event (i.e., 9 hours after a meal event) infusion set failure is established*.
    - If the ketone level measures >1.0 mmol/L at any of these hourly rechecks, then the infusion set is deemed to have failed.*

*If the above scenarios occur prior to 174 hours of infusion set wear, the subject is required to contact the study site to confirm set failure prior to removing the infusion set and provide information to the study site regarding circumstances around the event.

If study personnel are not available the subject should remove and replace the infusion set. If this happens, the subject will need to contact the study site at their earliest convenience to provide the study personnel with detailed information regarding the events surrounding the infusion set removal.

When the study site personnel have been contacted (either during the infusion set change procedure or afterwards), they will conduct a structured interview and document the relevant information in the eCRF.

If infusion is still functioning satisfactorily after 174 hours, then subject may take up to 18 additional hours to replace the set. In no case should the set be worn beyond 192 hours of use.

1.5 Potential Risks and Benefits of the Investigational Device System

Risks and benefits are detailed below. Loss of confidentiality is a potential risk; however, data are handled securely to minimize this risk. Hypoglycemia and hyperglycemia are always a risk in subjects with type 1 diabetes and insulin treatment, and subjects will be monitored for this.

The SteadiSet device has been analyzed for possible hazards using the methods in ISO 14971:2012 Medical Devices, Application of Risk Management to Medical Devices. Capillary Biomedical Inc. considers SteadiSet to be adequately safe to justify its use in clinical trials based on the benefits compared to overall risk.

1.5.1 Known Potential Risks

1.5.1.1 Risk of Hypoglycemia

As with any person having type 1 diabetes and using insulin, there is always a risk of hypoglycemia. The frequency of hypoglycemia should be no more than it would be as part of daily living. Symptoms of hypoglycemia can include sweating, jitteriness, and not feeling well. Severe hypoglycemia is possible with loss of consciousness or seizures. Recurrent hypoglycemia may reduce hypoglycemia awareness. A CGM functioning poorly and significantly over-reading glucose values could lead to inappropriate insulin delivery.

1.5.1.2 Risk of Hyperglycemia

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

1.5.1.3 Insulin Infusion Risks

The study infusion set is inserted under the skin. Infection can occur very infrequently, but, if an infection was to occur, oral and/or topical antibiotics can be used to treat the infection.

Examples of possible infusion site reactions include: localized pain, bleeding, bruising, induration, infection, itching/pruritus, purulence, reddening (erythema), swelling, and other non-specified irritation.

Infusion set failure may occur, leading to hyperglycemia or ketosis. The risk for infusion set failure may be increased in this study because sets are worn for an extended period. Examples of insulin infusion failure modes include: clogs, accidental removal, insulin leak from site, insulin leak from set or tubing, adhesive failure, cannula insertion failure (not all holes below epidermis), incomplete tubing prime, incomplete cannula prime, air bubbles in tubing, inadequate insulin pump/cartridge/infusion set connection, and cannula inserted too deep.

1.5.1.4 Risks of Use of Insulin Pump with Automated Insulin Delivery

CGM sensor readings higher or lower than the actual blood glucose level increases the risk for hypoglycemia and hyperglycemia with use of automated insulin delivery systems.

Algorithm or other device malfunctions could produce a suspension of insulin delivery or over-delivery of insulin which increases risk for hyperglycemia and hypoglycemia.

1.5.1.5 Fingerstick Risks

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

1.5.1.6 CGM Subcutaneous Catheter Risks

Use of CGM has a low risk for developing a local skin infection at the site of the sensor needle placement. There may be bleeding where the catheter is put in and bleeding under the skin causes a bruise (1 in 10 risk).

On rare occasions, the sensor may break and leave a small portion of the sensor under the skin that may cause redness, swelling or pain at the insertion site.

1.5.1.7 Risks Associated with Device Reuse

In this study, device components (CGM, BG meter, or ketone meter) will not be reused between different subjects.

1.5.1.8 Rapid-Acting Insulin Analog Adverse Reactions

Study subjects must be current users of rapid-acting insulin analogs at the time of enrollment (i.e., completion of consent documentation). Therefore, the risk of adverse reactions to commercially available rapid-acting insulin used during the study should be very low, but development of the following conditions is possible: anaphylaxis, antibody production, hypokalemia, lipodystrophy, peripheral edema, renal or hepatic impairment, and weight gain.

1.5.1.9 Questionnaire-Associated Risks

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

1.5.1.10 Other Risks

Some subjects may develop skin irritation or allergic reactions to the adhesives used to secure the CGM, or to secure the insulin infusion sets for the continuous subcutaneous insulin infusion.

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

There may be other risks that are unknown at this time and new risks that may be identified during the study.

The infusion set has not been tested with radiation therapy or an MRI procedure. The infusion set should be removed before radiation therapy or an MRI procedure.

1.5.2 Known Potential Benefits

Study participation may not provide any immediate benefit to study subjects. However, results of this research may result in the following potential benefits to the study subjects or to future patients with diabetes:

- Development of an extended wear insulin infusion set
- Reduction in the number of required infusion set insertions and number of infusion sites
- Reduction in infusion site (skin/tissue) reactions
- Improved glucose control (e.g., more stable insulin kinetics)

- Improved Continuous Subcutaneous Insulin Infusion (CSII) and insulin pump therapy options
- Reduced environmental waste

1.5.3 Risk Assessment

It is the assessment of the investigators that this protocol falls under DHHS 45 CFR 46.406 and 21 CFR 50.53 as a clinical investigation involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition.

1.6 General Considerations

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

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

Chapter 2: Study Enrollment and Screening

2.1 Subject Recruitment and Enrollment

Enrollment will proceed with the goal of 240 subjects (120 each on insulins lispro and aspart) completing the main study phase involving use of the study infusion set. A maximum of 300 individuals may be consented for screening to achieve this goal. Subjects who complete at least six wear periods will be considered as completers. Subjects who have signed consent and started the screening process may be permitted to continue into the trial, if eligible, even if the goal of 240 completers has been reached.

Study subjects will be recruited from up to 20 clinical centers in the United States. All eligible subjects will be included without regard to gender, race, or ethnicity. Each site may contribute a maximum of 25 subjects toward the target of 240 who complete the main study phase. If the enrollment of one insulin type reaches its enrollment goal, that insulin cohort may be closed and only subjects using the insulin in the other insulin cohort would then be eligible for study enrollment.

2.1.1 Informed Consent and Authorization Procedures

Potential eligibility may be assessed as part of a routine-care examination or via interaction with the potential subject following a direct inquiry (e.g., resulting from IRB-approved recruiting materials) or a referral from another source. Before completing any procedures or collecting any data that are not part of usual care, electronic informed consent will be obtained.

The potential study subject will be provided with the Informed Consent Form to read and will be given the opportunity to ask questions either in-person, via phone/videoconference, or by mail or email. If the potential subject is interested in the study, the investigator will schedule a virtual or in-person visit to discuss the study, and if the potential subject agrees to participate, that individual will electronically sign the Informed Consent Form through the JCHR study website, and the enrolling investigator will also electronically sign the document. A copy of the electronically signed consent form can be printed by the subject and another copy will be printed by the site to add to the subject's study record.

As part of the informed consent process, the subject will be asked to sign an authorization for release of personal information. This may be done electronically with the consent, or on paper if the site requires their own process. The investigator, or his or her designee, will review the study-specific information that will be collected and to whom that information will be disclosed. After speaking with the subject, questions will be answered about the details regarding authorization.

A subject is considered enrolled when the informed consent form has been electronically signed by all parties and HIPAA authorization has been provided. No study procedures may be performed before the completion of the informed consent documentation.

2.2 Subject Inclusion Criteria

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

1. Age 18 to 80 years old inclusive
2. Generally, in good health, as determined by the investigator
3. Living in the United States with no plans to move outside the United States during the study
4. Diagnosis of T1D for at least 12 months
5. Minimum of 6 months of insulin pump experience and at least 3 months of current experience with a Tandem pump

6. Using Tandem t:slim X2 insulin pump with Control-IQ technology for a minimum of 1 month at the time of enrollment
7. Minimum of 14 days of Control-IQ data immediately preceding screening that demonstrate pump use compliance, including at least 85% of time with Control-IQ technology active
8. HbA1c <9.0% in the last 6 months
9. Willing to implement and adhere to pump alert/alarm settings on a study-provided pump as instructed during the study
10. Willing to wear each investigational infusion set for up to 7 days during each of the 12 consecutive wear periods in the study
11. Willing to perform blood ketone and blood glucose (fingerstick) measurements as directed using provided ketone and blood glucose meters and strips
12. Access to internet for required periodic uploads of study device data
13. BMI in the range 18–35 kg/m2, both inclusive
14. Currently using one of the following insulins with no expectation of a need to change insulin type during the study:
    a. Humalog™ (insulin lispro)
    b. NovoLog™ (insulin aspart)
15. Using Humalog™ insulin lispro or NovoLog™ insulin aspart for a minimum of 1 month at the time of enrollment
16. Willing to change insulin cartridge every 48-72 hours, as recommended by patient's healthcare provider during the study
17. Has routine access to a smart phone e.g., ability to receive text messages
18. Has the ability to understand and comply with protocol procedures and to provide informed consent (i.e., English proficient in both verbal and written communication)

2.3 Subject Exclusion Criteria

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

1. Concurrent use of any non-insulin glucose-lowering agent, other than metformin (for example, GLP-1 agonists, Symlin, DPP-4 inhibitors, SGLT-2 inhibitors, sulfonylureas)
2. Female subject is pregnant, planning to become pregnant, or not using adequate method of contraception
3. Episodes of severe hypoglycemia in the last 6 months resulting in:
    a. Medical Assistance (i.e., paramedics, hospital evaluation or hospitalization)
    b. Loss of consciousness
    c. Seizures
4. One or more episodes of diabetic ketoacidosis (DKA) in the last 6 months requiring hospitalization
5. Currently on a ketogenic or low-carbohydrate diet of less than 60 grams of carbohydrates per day, or intending to begin one during the study period

6. Known cardiovascular disease considered to be clinically relevant by the investigator
7. Known history of any of the following conditions:
    a. Cushing's Disease
    b. Pancreatic islet cell tumor
    c. Insulinoma
    d. Lipodystrophy
    e. Extensive lipohypertrophy, as assessed by the investigator
8. Currently undergoing treatment with:
    a. Systemic oral or intravenous corticosteroids (current or within the last 8 weeks from screening),
    b. Thyroid hormones, unless use has been stable during the past 3 months
9. Significant history of any of the following, that in the opinion of the investigator would compromise safety or successful study participation:
    a. Alcoholism
    b. Drug abuse
10. Significant acute or chronic illness, that in the opinion of the investigator might interfere with safety or integrity of study results
11. Current participation in another clinical drug or device study
12. Immediate family member (spouse, biological or legal guardian, child, sibling, parent) who is a study site personnel directly affiliated with this study or who is an employee of Capillary Biomedical

2.4 Eligibility Assessment and Baseline Data Collection

Potential subjects will be evaluated for study eligibility through the elicitation of a medical history and local laboratory testing as needed in the judgment of the investigator (as part of usual care).

The screening visit and subsequent scheduled study visits may be conducted virtually via videoconference at the discretion of the study investigator, for example due to institutional restrictions or the subject or investigator's preference for a remote visit. Study staff will discuss the feasibility of conducting virtual visits with each subject and provide support as needed to ensure adequate access. The initial screening visit must be completed within 30 days of subject enrollment (i.e., completion of consent documentation).

2.5 Historical Information

A history will be elicited from the subject and extracted from available medical records with respect to the subject's diabetes history, current diabetes management, other past and current medical problems, past and current medications, and drug allergies.

When evaluating subjects not already being treated at the enrolling clinic, information will be solicited from the subject's primary diabetes provider, for example, via a phone call or videoconference between the enrolling investigator and the current provider.

2.6 Screening Testing and Procedures

At the Screening Visit the following procedures will be performed/information will be elicited:

- Assessment of eligibility
- Demographics (date of birth, gender, race, and ethnicity)
- Contact information (retained at the site and provided to Coordinating Center to allow automated text or email messages during study)
- Medical history as described above in Section 2.4
- Substance use history (drinking, smoking, and drug habits)
- Current medications
- Measurement of height/weight
  - If the visit is conducted virtually, a verbal report of the subject's weight and verbal report of height will be acceptable.
- Urine pregnancy test for all women who have reached menarche and are premenopausal and are not surgically sterile.
  - If the visit is conducted virtually, a negative urine pregnancy test result from a test kit sent to the subject may be confirmed via teleconference.
- Determination of adherence to Control-IQ use in the 14 days prior to screening based on data from the subject's personal t:connect account.
  - Subjects must have had Control-IQ technology active at least 85% of the time during the 14 days before screening to be eligible to continue in the study.
- Verification HbA1c is <9.0% in the last 6 months.
- Completion of the Usability, Satisfaction & Preference Survey (study web site link sent to subject) to evaluate subject's experience with the insertion and daily wear of their current infusion set before exposure to the study infusion set.
- Subject demonstrates proficiency in following study procedures.

Screening procedures will last approximately 2 hours.

2.7 Screen Failures

Individuals who do not initially meet study eligibility requirements, such as required Control-IQ adherence or estimated HbA1c value, may be rescreened once while study enrollment is still open.

Chapter 3: Main Study

3.1 Study Infusion Set Initiation Visit

This visit may be concurrent with the Screening Visit or may be completed within 14 days of completion of the Screening visit. Study site will verify subjects received all study supplies.

Study supplies, including study Control-IQ insulin pump, SteadiSet infusion sets, BG and ketone meters, and ancillary supplies, will be provided to the subject either in-person at the clinic or via delivery by other means (personal delivery, overnight shipment, etc).

Before dispensing, BG and ketone meters will be QC tested with control solution to verify readings are within the target range per manufacturer labeling.

Study subjects will be provided with a Tandem t:slimX2 with Control-IQ insulin pump to use in the study instead of their personal insulin pump. The study pump will be programmed by the Study Site with criteria outlined in Section 3.2 as well as subject's personnel profile settings. Subjects will continue to use their personal Dexcom G6 or G7 CGM system. Subjects may switch between G6 and G7 sensors during the course of the study and will be instructed to only do so at the time of insertion of a new study infusion set.

The Tandem t:connect mobile app will not work with the study insulin pumps. Subjects will upload study insulin pump data via USB cable. Subjects may use available manufacturer-provided software and features of their personal CGM related to mobile data access or remote monitoring.

3.1.1 Baseline HbA1c Determination

A capillary blood sample will be obtained for baseline HbA1c determination. For remote subject's capillary collection, supplies will be provided to the subject within 3 days of the Study Infusion Set Initiation Visit. Collection of HbA1c may occur either in-person at the clinic, or via delivery by other means (personal delivery, overnight shipment, etc.).

3.1.2 Study Infusion Set Training and Initiation

Subjects will be trained (in-person or via videoconference) on how to insert the SteadiSet infusion set. The initial insertion will be observed either in person or on video during a virtual visit.

Subjects who are unable to insert the SteadiSet within 3 attempts will be dropped from study participation.

Points of training will include the following:

- Subjects will be advised to avoid inserting the SteadiSet device in places that may cause pressure—e.g., under a belt or snug waist band.
- Subjects will be advised to closely monitor their CGM for the first 8 hours following the insertion of each SteadiSet. If CGM is uncorrectable per the hyperglycemic management guidelines, the subject will be instructed to call the study center for guidance.
- Subjects will be given guidelines with detailed procedures on what to do if prolonged elevated CGM glucose or other signs that infusion set failure might have occurred (Section 3.2).
- Subjects will be instructed to contact the study site before removing an infusion set that has been worn for less than 7 full days.
- Subjects will be instructed to retain all parts of the used infusion set and label and return to the clinic.

- Subjects will be instructed to insert a new sequential infusion set following removal of each prior set until 12 infusion sets have been used. Sets that fail in the first 8 hours of use will be replaced and will not count toward the target of 12 infusion sets worn.
- Subjects will be instructed to change the insulin cartridge every 48-72 hours, as recommended by their healthcare provider.
- Subjects will be instructed to change their insulin cartridge and infusion set independent of each other and follow instructions in the Participant Guidebook and IFU. Subjects will be instructed to contact study site if there is concern about infusion set failure.
- Subjects will be required to upload insulin pump data (which includes both insulin dosing and CGM data). This will be performed remotely for virtual visits or in clinic for face-to-face visits. Ketone and BG meters will be uploaded during face-to-face visits.
- Subjects who have only virtual visits will be provided with three ketone and BG meters each, and will be instructed to mail the meters to the study site at week 2, week 6 and final visits.

3.2 Hyperglycemia Management Guidelines

The study pump's Control-IQ High Alert, which cannot be disabled, will alert the subject when there is a CGM reading >200 mg/dL and no prediction the CGM will decrease in the next 30 minutes.

The study pump's optional CGM High Alert will be configured by study staff with a threshold of 250 mg/dL and a Repeat setting of 60 minutes, so the alert recurs every 60 minutes as long as the hyperglycemia persists. High BG reminder should be set to OFF.

The pump will have the "out of range" alert set for 20 minutes (shortest possible setting) to reduce risk of missing data. The pump "low insulin alert" will be set at ≥ 20 units to reduce risk of running the pump on an empty cartridge. It is recommended to set the Auto Off Alert to OFF. Site Reminder alert may be set to ON to remind subjects to change their cartridge but not their infusion set.

Subjects will be instructed not to modify the alert settings configured by study staff that are described above.

Subjects will receive training on how to address Occlusion alarm #1 (resolvable alarm) and Occlusion alarm #2 (non-resolvable alarm) requires infusion set change.

Study subjects will be provided a written Hyperglycemia Management Guidelines that will specify the steps to take in case of prolonged hyperglycemia, testing of blood glucose, ketones, and correction boluses.

3.3 Hypoglycemia Management

Hypoglycemia will be managed by the Study subjects as they would as part of their usual diabetes management. Hypoglycemia alarms may be set at the discretion of the study subject.

3.4 Daily Text

Subjects will receive a daily reminder text indicating the target date and time of infusion set removal. The daily text will provide a link to a questionnaire for the subject to complete with each infusion set insertion and removal providing specifics about all infusion set changes.

3.5 Follow-up Visit and Contact Schedule

Subjects will have the following scheduled follow-up visits and phone contacts as follows:

Table 3-1 Follow-up Visit and Contact Schedule

TIMING	CONTACT TYPE	TARGET/ ALLOWABLE WINDOW (AROUND TARGET DAY/WEEK)
3 Days	Phone	-1 to +3 days
2 Weeks	Clinic/Virtual	± 4 days
6 Weeks	Clinic/Virtual	± 7 days
Final Visit (completion of 12th wear period or termination)	Clinic/Virtual	+ 7 days

The Final Visit will occur after the subject has completed the 12th set wear period. The maximum time point will be approximately 12 weeks but generally will be less. The visit should occur within 7 days following the 12th wear period or the last study infusion set worn.

Additional contacts will occur when a subject experiences an infusion set failure prior to 7 days of use or when a subject has concerns about hyperglycemia or any other aspect of the study. Additional visits can occur as needed.

3.5.1 Procedures at Study Visits

3.5.1.1 Day 3

- Assessment of compliance with guidelines for SteadiSet device use
- Assessment of adverse events, adverse device effects, and device issues
- Review key aspects of study protocol regarding infusion set failure

3.5.1.2 Week 2

Procedures are identical to those above for the 3-Day visit with the addition of:

- Completion of the Usability, Satisfaction & Preference Survey (study web site link sent to subject) to evaluate subject's experience with the insertion and daily wear of the SteadiSet infusion set.
- Upload Ketone and BG meters

3.5.1.3 Week 6

Procedures are identical to those above for the 3-Day visit, with the addition of:

- Upload Ketone and BG meters

3.5.1.4 Final Visit

The following will occur.

- Upload Ketone and BG meters
- Assessment of adverse events, adverse device effects, and device issues

- Completion of the Usability, Satisfaction & Preference Survey (study web site link sent to subject) to evaluate subject's experience with the insertion and daily wear of the SteadiSet infusion set.
- A capillary blood sample will be obtained for end-of-study HbA1c determination. Capillary collection supplies will be provided to the subject as described above, before the Final Visit so that sample collection can occur during the Final Visit.
- Collection of all used and unused (as applicable) SteadiSet devices, ancillary supplies and study pump.

3.5.2 Study Completion

Subjects will have completed all study protocol requirements at the end of the 12th wear period (Wear Period 12) regardless of actual total days of SteadiSet infusion set wear. Subject will return to using their personal pump and routine insulin infusion sets at the completion of their participation in the study.

3.5.3 Early Study Discontinuation

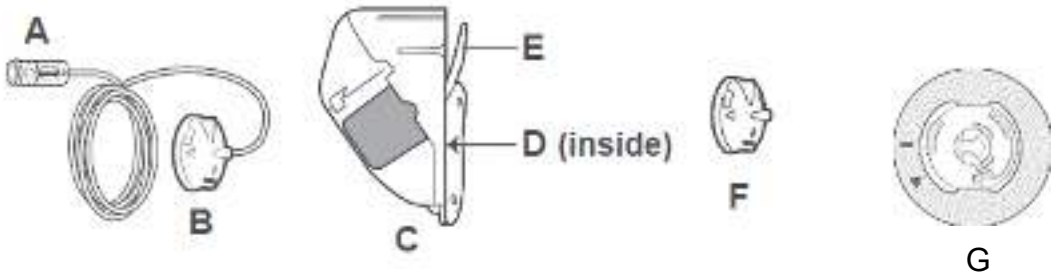
Subjects who discontinue the study prior to the 12th infusion set wear period either by choice or by investigator decision, will be asked to complete the end of study visit as outlined in Final Visit Section 3.5.1.4.

Chapter 4: Study Devices

4.1 Description of the Investigational Device: SteadiSet Infusion Set

The Capillary Biomedical, Inc. (CapBio) SteadiSet Infusion Set (SteadiSet device) is a sterile single use device for continuous subcutaneous insulin infusion (CSII). SteadiSet Infusion Sets are designed to be used with commercially available infusion pumps by direct connection; this will limit pump use to only Tandem t:slim X2 insulin pumps. The investigational SteadiSet Infusion Set contains a coil reinforced soft polymer indwelling cannula with one distal and three proximal holes. This cannula is deployed into subcutaneous tissue via an integrated single use insertion device (inserter). Figure 2 The SteadiSet consists of an (A) insertion mechanism, hub holding the cannula in place, and (B) pump-specific tubing set. For this study only the longest tubing (43 inch) will be used. The SteadiSet Infusion Set, with cannula, insertion mechanism, and tubing, is individually packaged and sterilized in a vacuum formed cup with a Tyvek™ lid.

Figure 2. Components of the SteadiSet Infusion Set



A. Cartridge connector
B. Set connector
C. Inserter
D. Set with cannula (inside inserter)
E. Paper liner
F. Disconnect cover
G. Set

For this clinical trial subjects will be exposed to the device for 12 consecutive wear periods of up to 7 days each. Devices will be returned to the study site at the end of study participation, defined as after 12 wear periods or end of their study participation regardless of the number of wear periods.

4.2 Insulin Pump

Subjects will be provided with a Tandem t:slim X2 pump with Control-IQ technology and insulin cartridges that will be the same as the commercially-available device. These pumps will be returned at conclusion of study participation.

4.3 Insulin Cartridges

Insulin cartridges will be provided to subjects.

4.4 Ancillary Supplies

Subjects will be provided with ancillary supplies as requested to be used at their discretion for skin prep and tapes to assist in securing infusion sets. Under taping is prohibited in this study. In addition, subjects may request lancets and alcohol wipes.

4.5 Blood Glucose Meter

A study BG meter will be provided to subjects with test strips.

4.6 Blood Ketone Meter

A study Blood Ketone meter will be provided to subjects with test strips.

4.7 Continuous Glucose Monitor

Subjects will use their personal Dexcom G6 or G7 CGM and personal supplies for measuring glucose and communicating with the Tandem pump.

4.8 Subject Access to Study Devices at Study Closure

Subjects will return the study pump and all used and unused study infusion sets. Subjects may keep the ancillary supplies, BG and ketone meters once confirmation all data has been uploaded into study database.

Chapter 5: Testing Procedures and Questionnaires

5.1 Laboratory Testing

5.1.1 HbA1c

Performed at the Day 0 Visit and Final Visit.

Blood samples will be sent to the central laboratory for sample analysis using an NGSP approved method.

5.1.2 Urine Pregnancy

Urine pregnancy testing will be performed locally at clinical sites for females of child-bearing potential at the Screening visit and anytime pregnancy is suspected or performed at home with a urine pregnancy kit sent to the subject if visits are virtual. Pregnancy test results will be reported to the study center per the clinical site's standard procedures.

5.2 Questionnaires

5.2.1 Screening Visit

Study personnel will ask subjects to complete a Usability, Satisfaction & Preference Survey with multiple-choice questions and optional comment areas about their experience with their current insulin infusion set during their Screening Visit. The survey takes approximately 5 to 10 minutes to complete.

5.2.2 Week 2 Visit

Study personnel will ask subjects to complete a Usability, Satisfaction & Preference Survey with multiple-choice questions and optional comment areas about their experience with the SteadiSet infusion set following their first two Wear Periods. The survey should take approximately 5 to 10 minutes to complete.

5.2.3 Final Visit

Study personnel will ask subjects to complete a Usability, Satisfaction & Preference Survey with multiple-choice questions and optional comment areas about their experience with the SteadiSet infusion set following their final Wear Period. The survey should take approximately 5 to 10 minutes to complete.

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

6.1 Unanticipated Problems

Site investigators will promptly report to the Coordinating Center on an eCRF all unanticipated problems meeting the criteria below. Sites overseen by the JCHR IRB must report Unanticipated Problems to the IRB within seven (7) calendar days of recognition. Sites using other IRBs will follow their reporting guidelines. All Serious and Unanticipated Adverse Events must be reported to the Coordinating Center within 24 hours of learning of the events. For this protocol, an unanticipated problem is an incident, experience, or outcome that meets all of the following criteria:

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

The Coordinating Center will also report to the IRB all unanticipated problems not directly involving a specific site such as such as unanticipated problems that occur study-wide or at another participating entity such as a pharmacy or laboratory. These instances must be reported to the JCHR IRB within seven (7) calendar days of recognition. The Director of the Human Research Protection Program (HRPP) will report to the appropriate regulatory authorities if the IRB determines that the event indeed meets the criteria of an Unanticipated Problem requiring additional reporting to fulfill the reporting obligations of the HRPP.

6.2 Adverse Events

6.2.1 Definitions

Adverse Event (AE): Any untoward medical occurrence (including laboratory findings) associated with study procedures, the use of a device, biologic, or drug in humans, including any comparator used, whether or not the event is considered related (i.e., irrespective of the relationship between the adverse event and the device(s) under investigation).

Serious Adverse Event (SAE): Any untoward medical occurrence that results in any of the following outcomes:

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

An important medical event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, may jeopardize the patient or

subject and may require medical and/or surgical intervention to prevent one of the outcomes listed in this definition. Note: If either the Sponsor or investigator believes the event is serious, the event must be considered serious and evaluated by the Sponsor for expedited reporting. See 21 CFR 812.3(s) for more information.

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

Adverse Device Effect (ADE): Any untoward medical occurrence in a study subject which the device may have caused or to which the device may have contributed. This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device; any event resulting from use error or from intentional misuse of the investigational medical device. (Note that an Adverse Event Form is to be completed in addition to a Device Deficiency or Issue Form, unless excluded from reporting as defined in Section 6.2).

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

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

6.2.2 Reportable Adverse Events

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

1. A SAE
2. An ADE as defined in Section 6.2.1, unless excluded from reporting in Section 6.3
3. An AE as defined in Section 6.2.1 occurring in association with a study procedure
4. An AE as defined in Section 6.2.1 not related to a device issue which leads to temporary or permanent discontinuation of a study device
5. An AE as defined in Section 6.2.1 that affects the subject's ability to complete any study procedures
6. An AE as defined in Section 6.2.1 for which a visit is made to a hospital emergency department
7. Hypoglycemia meeting the reporting criteria defined in Section 6.2.3
8. Diabetic ketoacidosis (DKA) as defined below; or in the absence of DKA, hyperglycemia or ketosis event meeting the reporting criteria in Section 6.2.4

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

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

6.2.3 Hypoglycemic Events

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

A hypoglycemic event occurred meeting the following definition of severe hypoglycemia:

- The event required assistance of another person due to altered consciousness, and required another person to actively administer carbohydrate, glucagon, or other resuscitative actions. This means that the subject was impaired cognitively to the point that he/she was unable to treat himself/herself, was unable to verbalize his/ her needs, was incoherent, disoriented, and/or combative, or experienced seizure or loss of consciousness. These episodes may be associated with sufficient neuroglycopenia to induce seizure or loss of consciousness. If glucose measurements are not available during such an event, neurological recovery attributable to the restoration of glucose to normal is considered sufficient evidence that the event was induced by a low glucose concentration.
- Evaluation or treatment was obtained at a health care provider facility for an acute event involving hypoglycemia, or the subject contacted the site and received guidance following the occurrence of an acute event involving hypoglycemia.

When a severe hypoglycemia event occurs (as defined above), a Hypoglycemia Form should be completed in addition to the Adverse Event Form. Severe hypoglycemia events should be considered to be serious adverse events with respect to reporting requirements. When a severe hypoglycemia event occurs during use of a study device, it generally will be considered unrelated to the device if the device functioned as intended and there does not appear to be a flaw in how the device is intended to function.

6.2.4 Hyperglycemic/Ketotic Events

Hyperglycemia with or without ketosis that is associated with an infusion set failure will be reported on a protocol-specific CRF and not reported separately as an AE unless criteria for an SAE are met.

Hyperglycemia not associated with an infusion set failure or other Adverse Device Effect is only reportable as an adverse event when one of the following criteria is met:

- The event involved DKA, as defined by the Diabetes Control and Complications Trial (DCCT) and described below
- Evaluation or treatment was obtained at a health care provider facility for an acute event involving hyperglycemia or ketosis, or the participant contacted the site and received guidance on how to manage the acute hyperglycemia/ketosis event unrelated to the infusion set
- Blood ketone level >1.5 mmol/L

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

- Symptoms such as polyuria, polydipsia, nausea, or vomiting;

- Serum ketones >1.5 mmol/L or large/moderate urine ketones;
- Either arterial blood pH <7.30 or venous pH <7.24 or serum bicarbonate (or CO2) <15; and
- Treatment provided in a health care facility.

When a hyperglycemia/ketotic event qualifies as a SAE as defined in Section 6.2.1, a Hyperglycemia/DKA Form should be completed in addition to the Adverse Event Form. Events meeting DKA criteria should be considered as serious adverse events with respect to reporting requirements. Hyperglycemia events not meeting criteria for DKA generally will not be considered as serious adverse events unless one of the SAE criteria in Section 6.2.1 is met.

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

6.2.5 Relationship of Adverse Event to Study Investigational Device

The study investigator will assess the relationship of any adverse event to be related or unrelated by determining if there is a reasonable possibility that the adverse event may have been caused by the study device. The Medical Monitor also will make this assessment, which may or may not agree with that of the study investigator.

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

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

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

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

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

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

Where these relatedness categories are used, events determined to be Possibly Related, Probably Related, or Definitely Related will be considered to meet the reasonable possibility causality standard for relatedness and necessitate reporting as required (see 21 CFR 812.3(s) for more information).

6.2.6 Severity (Intensity) of Adverse Events

The severity (intensity) of an adverse event will be rated on a three-point scale: (1) mild, (2) moderate, or (3) severe. A severity assessment is a clinical determination of the intensity of an event. Thus, a severe

adverse event is not necessarily serious. For example, itching for several days may be rated as severe, but may not be clinically serious.

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

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

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

6.2.7 Expectedness

For a serious adverse event that is considered possibly related to study device, the Medical Monitor will classify the event as unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described in the protocol or the Clinical Investigator Brochure.

6.2.8 Coding of Adverse Events

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

6.2.9 Outcome of Adverse Events

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

RECOVERED/RESOLVED (COMPLETE RECOVERY) – The subject recovered from the AE/SAE without sequelae. Record the AE/SAE stop date.

RECOVERED/RESOLVED WITH SEQUELAE – AE/SAE where the subject recuperated but retained pathological conditions resulting from the prior disease or injury. Record the AE/SAE stop date.

FATAL – A fatal outcome is defined as the SAE that resulted in death. Only the event that was the cause of death should be reported as fatal. AEs/SAEs that were ongoing at the time of death; however, were not the cause of death, will be recorded as "resolved" at the time of death.

ONGOING (NOT RECOVERED/NOT RESOLVED) – An ongoing AE/SAE is defined as an ongoing event with an undetermined outcome.

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

ONGOING (MEDICALLY STABLE) – AE/SAE is ongoing, but medically stable. For example, a chronic condition where no further change is expected.

If any reported adverse events are ongoing when a subject completes the study (or withdraws), adverse events classified as UADEs or related SAEs will be followed until they are either resolved, or have no

prospect of improvement or change, even after the subject has completed all applicable study visits/contacts. For all other adverse events, data collection will end at the time the subject completes the study. Note: Subjects should continue to receive appropriate medical care for an adverse event after their participation in the study ends.

If a Subject is lost to follow up and Subject outcome cannot be determined, outcome classification will be the last known outcome.

6.3 Reportable Device Issues

Infusion set failures will be reported on a protocol-specific CRF and not reported separately as a Device Issue.

All UADEs and ADEs as defined in Section 6.2.1 will be reported on both a device issue form and AE form, except for skin reactions from CGM sensor placement or pump infusion set placement that do not require pharmacologic treatment.

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

- Battery lifespan deficiency due to inadequate charging or extensive wireless communication
- Intermittent device component disconnections/communication failures not requiring system replacement or workaround/resolution not specified in user guide/manual.
- Device issues clearly addressed in the user guide manual that do not require additional troubleshooting

6.4 Timing of Event Reporting

SAEs possibly related to a study device or study participation and UADEs must be reported by the investigator to the Coordinating Center within twenty-four (24) hours of the site becoming aware of the event. This can occur via phone or email, or by completion of the online serious adverse event form and device issue form if applicable. If the form is not initially completed, it should be competed as soon as possible after there is sufficient information to evaluate the event. All other reportable ADEs and other reportable AEs should be submitted by completion on the online form within seven (7) days of the site becoming aware of the event.

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

Each principal investigator is responsible for reporting serious study-related adverse events and abiding by any other reporting requirements specific to his/her Institutional Review Board or Ethics Committee. Where the JCHR IRB is the overseeing IRB, sites must report all serious, related adverse events within seven calendar days.

Upon receipt of a qualifying event, the Sponsor will investigate the event to determine if a UADE has occurred, and if indicated, report the results of the investigation to all overseeing IRBs, and the FDA within ten (10) working days of the Sponsor becoming aware of the UADE per 21CFR 812.46(b) (2). The Sponsor in conjunction with the Medical Monitor must determine if the UADE presents an unreasonable risk to subjects. If so, the Sponsor must ensure that all investigations, or parts of investigations presenting that risk, are terminated as soon as possible but no later than five (5) working days after the Sponsor makes this determination and no later than fifteen (15) working days after first receipt notice of the

UADE. The investigator(s) may then be required to provide approval or acknowledgment of receipt of that notification and must submit to their overseeing IRB as required.

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

6.5 Safety Oversight

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

The Clinical Study Director will be informed of all cases of severe hypoglycemia and DKA and the Medical Monitor's assessment of relationship to the study device; and informed of all reported device issues.

6.6 Stopping Criteria

6.6.1 Subject Discontinuation of Study Device

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

In the absence of a device malfunction, use of the SteadiSet by a subject will be discontinued if any of the following occur:

- The investigator believes it is unsafe for the subject to continue on the intervention. This could be due to the development of a new medical condition or worsening of an existing condition; or subject behavior contrary to the indications for use of the device that imposes on the subject's safety
- The subject requests that the treatment be stopped
- Subject pregnancy
- Two distinct episodes of DKA as defined in Section 6.2.4
- Two distinct severe hypoglycemia events as defined in Section 6.2.3
- One episode of DKA as defined in Section 6.2.4 and one severe hypoglycemia event as defined in Section 6.2.3

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

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

6.6.2 Criteria for Suspending or Stopping Overall Study

In addition to the suspension of device use due to a UADE as described in Section 6.6.1, study activities could be similarly suspended if the manufacturer of any constituent study device requires stoppage of device use for safety reasons (e.g., product recall). The affected study activities may resume if the underlying problem can be corrected by a protocol or system modification that will not invalidate the results obtained prior to suspension.

Chapter 7: Miscellaneous Considerations

7.1 Drugs Used as Part of the Protocol

Subjects will use their personal insulin, either insulin lispro (Humalog) or insulin aspart (NovoLog), throughout their study participation.

In the event a subject's insulin changes from Humalog to NovoLog, or vice versa, it will be noted in the case report form and analysed accordingly.

7.2 Collection of Medical Conditions and Medications

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

Medical Conditions during the study: In addition to conditions meeting the reporting requirements for an adverse event or device issue as described above, the following medical conditions should also be reported: (1) new diagnosis of a chronic disease (i.e., not present at the time of enrollment), and (2) any medical condition that could affect the subject's ability to carry out any aspect of the protocol or could affect an outcome assessment. New conditions or worsening of a previous medical condition should be reported as adverse events.

Medications: All medications for the treatment of pre-existing conditions at screening and/or adverse events, or other medications that could impact blood glucose, should be recorded.

7.3 Prohibited Medications, Devices, Treatments, and Procedures

Treatment with any insulin other than insulin lispro and insulin aspart and treatment with any non-insulin glucose lowering agent besides metformin is not permitted.

The insulin pump and CGM device must be removed before magnetic resonance imaging (MRI), computed tomography (CT) or diathermy treatment. Subjects may continue in the trial after temporarily discontinuing use if requiring one of the above.

Subjects will be discontinued from the study if systemic corticosteroids are used for more than 7-sequential days.

Under taping of the infusion set is prohibited. Over taping is acceptable per Subject's preference.

7.4 Pregnancy Reporting

If pregnancy occurs, the subject will be discontinued from the study. The occurrence of pregnancy will be reported to the Coordinating Center within seven days and to the JCHR IRB on the Unanticipated Problem form within seven (7) calendar days.

7.5 Subject Compensation

Subject compensation will be specified in the informed consent form.

7.6 Subject Withdrawal

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

7.7 Confidentiality

For security and confidentiality purposes, subjects 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 subject information may also be provided to research sites involved in the study.

Chapter 8: Statistical Considerations

8.1 Statistical and Analytical Plans

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

8.2 Statistical Hypotheses

A 95% confidence interval (95% CI) for the 7-day survival rate (i.e., primary efficacy endpoint as defined in Section 8.4.2 below) will be calculated.

The null/alternative hypotheses are:

a. *Null Hypothesis*: The success rate is 75%.

b. *Alternative Hypothesis*: The success rate is different from 75% (two-sided).

8.3 Power

Assuming (1) n=120 subjects completing the study for each insulin type, (2) a null hypothesis stating that the success rate is 75%, (3) a true success rate of 83%, (4) 12 wear periods per subject (5) within-subject correlation of at most 0.4, and (6) two-sided type 1 error rate of 5% we will have statistical power of 87%. Note that with only 9 wear periods per subject we would still have 86% power.

8.4 Outcome Measures

8.4.1 Clinical Events Committee

Clinical Primary and Secondary Endpoint events will be adjudicated by the Clinical Events Committee (CEC). The CEC will be made up of the Medical Monitor, Lead Investigator and one independent diabetes expert.

The CEC will adjudicate endpoint events based on review of all available information that is relevant to determining whether protocol-defined clinical endpoint events have occurred during the study as outlined in the CEC Charter. Operational details will be defined in a separate Clinical Events Committee SOP document.

8.4.2 Primary Efficacy Endpoint

Percentage of successfully-inserted SteadiSet infusion sets (i.e., not removed within 8 hours of insertion) that are not withdrawn from use prior to 7 days (168 hours) due to either (1), (2), or (3):

1. Blood Glucose value ≥250 mg/dL with ketones >1.0 mmol/L, in the absence of illness or other physiological stress.
2. Blood Glucose value ≥250 mg/dL for at least 60 minutes duration, 3 hours or more following a snack or meal event AND failure to respond to up to 2 adequate corrective boluses delivered by the pump with a fall of at least 50 mg/dL. In the absence of BGM testing immediately prior to or following a corrective bolus then CGM values will be used for the primary endpoint analyses.
3. Investigator advises the infusion set should be replaced to assure subject's safety.

8.4.3 Safety Endpoints

The incidence, severity, and relationship to the investigational device of all reported adverse events (serious and non-serious including DKA and severe hypoglycemia) from day of insertion through day of device removal for each wear period.

8.4.4 Key Secondary Endpoint

Proportion (%) of SteadiSet infusion sets withdrawn from use at any time following insertion prior to 7 days (168 hours) as evidenced by one or more of the following device failure modes. NOTE: infusion set removals prior to 168 hours due to miscalculation of date and/or time, along with other removals that cannot be ascribed to the investigational device performance, are excluded from this proportion calculation.

1. Infusion set failure as defined in the Primary Endpoint (including any such removals occurring during the first 8 hours following set insertion)
2. Evidence of infusion set site infection defined as requiring treatment or at the investigator's judgment
3. Cannula dislodgement from subcutaneous (SC) space (with or without liquid leakage at the cannula insertion site)
    a. Leakage at the cannula insertion site may or may not be deemed by the investigator to constitute infusion set failure following consultation with the study subject
    b. Accidental removal events (e.g., tubing caught on doorknob) are excluded from this proportion calculation
4. Occurrence of a non-resolvable pump occlusion alarm,
5. Other device malfunction (e.g., inability to pierce skin, bending, or other malformation that might impact insulin infusion, securement failure)
6. Presence of pain of sufficient severity to prompt early removal of infusion set
7. Any other event that can be ascribed to the investigational device performance that results in failure of insulin delivery

8.4.5 Other Secondary Endpoints

1. Standard glucose control measures obtained from CGM, including observed hyper- and hypoglycemic episodes, time in range, mean 24-hour glucose, and other measures
2. Total daily insulin dose, basal dose, bolus dose, and bolus basal ratio, overall, and by day of infusion set wear.
3. Subject tolerability levels for the infusion set insertion as assessed by a pain scale of 0 to 100 with zero being no pain and 100 being significant pain
4. Hyperglycemia trends in days 1-3 versus after day 3
5. Infusion set performance (including set failures as defined above and also glucose metrics, insulin doses, pump occlusion alarms and hyperglycemia trends) in subjects who use low doses (e.g., <25 units/day) of insulin and in subjects who experience frequent stops and start of pump use

8.4.6 Exploratory Endpoint

1. HbA1c change from baseline to the end of study participation.

8.5 Analysis Datasets and Sensitivity Analyses

1. Only wears of the investigational infusion set will be included in the analysis (i.e., any wear of a personal infusion set will be excluded)
2. All subjects with at least one wear of the investigational infusion set and all such wears will be included in the primary and secondary efficacy analyses. Subjects who complete at least six wear periods will be considered as "completers."
3. Since this is not a randomized trial, the intention-to-treat principle does not apply.
4. All reported adverse events will be included in the safety analyses.

8.6 Analysis of the Primary Efficacy Endpoint(s)

Analysis will be done separately for each insulin type (Humalog and Novolog).

Kaplan-Meier estimates will be reported along with a curve used to estimate the proportion of infusion sets that last at least 7 days. Any infusion sets that are removed prior to day 7 without meeting the stated failure criteria will be treated as a censored observation.

A two-sided 95% confidence interval (95% CI) for the 7-day survival rate will be calculated with a bootstrap to account for the correlated data from having each subject wear multiple infusion sets. A corresponding p-value will be given for the null hypothesis that the true survival probability is 75%.

8.7 Analysis of the Secondary and Exploratory Endpoints

If results from the primary analysis are comparable for Humalog and Novolog, then the data will be pooled for secondary analyses. Otherwise, separate analyses will be done by insulin type. Percentage of SteadiSet infusion sets not withdrawn from use prior to 7 days (168 hours) as evidenced by the absence of device failure, and as defined above, will be analyzed using the same statistical methods as described above for the primary efficacy endpoint.

A paired t-test will be used to compare the central lab HbA1c values measured at the final study visit versus the Day 0 value. A two-sided 95% CI will be given for the mean difference. Only subjects with a central lab value at both times will be included in this analysis. Similar pre- post comparisons will be done with selected CGM metrics. These will include data from the final 14 days of the study compared with the baseline CGM data.

Survey and pain assessment results will be tabulated.

The other continuous and binary outcomes will be summarized as appropriate to their distributions (i.e., mean (SD), median (IQR), or n (%)). Plots and 95% CI will be calculated for selected outcomes.

CGM metrics will be calculated over the entire study period (24-hour, daytime, and nighttime) and by study week (24 hour only).

Hyperglycemia Trend in Days 1-3 versus after Day 3

The trend in hyperglycemia in days 1-3 versus after day 3 will be assessed with the CGM metrics % time above 180 mg/dL, % time above 250 mg/dL, and mean glucose. Summary statistics appropriate to their distributions, boxplots will be used to compare data in days 1-3 versus after day 3. Formal comparisons will be done using paired t-tests (or non-parametric analogs if the data are not approximately normally distributed) to account for the correlated data from the same subject.

8.8 Safety Analyses

All enrolled subjects will be included in these analyses and all their safety events up to the end of study will be listed. In particular, any AEs involving hyperglycemia/ketosis will include an assessment whether or not it corresponded to an infusion set failure.

The circumstances of all reportable adverse events as defined in the protocol above will be summarized.

8.9 Baseline Descriptive Statistics

Baseline demographic and clinical characteristics of the cohort of all enrolled subjects with at least one wear will be summarized in a table using summary statistics appropriate to the distribution of each variable. Will include:

- Age
- Gender
- Race/ethnicity
- Diabetes duration
- HbA1c
- BMI
- CGM metrics (including estimated HbA1c)
- Insulin type
- Infusion set type

8.10 Planned Interim Analyses

No formal interim efficacy analyses are planned for this study.

8.11 Multiple Comparison/Multiplicity

Since this is an exploratory and a single arm trial, there will be no formal adjustment for multiple comparisons.

Chapter 9: Data Collection and Monitoring

9.1 Case Report Forms and Other Data Collection

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

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

9.2 Study Records Retention

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

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

9.3 Quality Assurance and Monitoring

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

A risk-based monitoring (RBM) plan will be developed and revised as needed during the study, consistent with the FDA "Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring" (August 2013). Study conduct and monitoring will conform with 21 Code of Federal Regulations (CFR) 812. This plan describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

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

- Qualification assessment, training, and certification for sites and site personnel
- Oversight of Institutional Review Board (IRB) coverage and informed consent procedures
- Central (remote) data monitoring: validation of data entry, data edits/audit trail, protocol review of entered data and edits, statistical monitoring, study closeout

- On-site monitoring (site visits): source data verification, site visit report
- Agent/Device accountability
- Communications with site staff
- Patient retention and visit completion
- Quality control reports
- Management of noncompliance
- Documenting monitoring activities
- Adverse event reporting and monitoring

Coordinating Center representatives or their designees may visit the study facilities at any time in order to maintain current and personal knowledge of the study through review of the records, comparison with source documents, observation and discussion of the conduct and progress of the study. The study site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

9.4 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or procedure requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. A significant (or major) deviation is any deviation that departs from the established materials in such a way that it poses an increase in the risk to subjects, adversely affects the welfare, rights, or safety of the research subjects, or negatively influences the scientific study integrity. As a result of a significant deviation, a corrective and preventive action plan shall be developed by the site and implemented promptly.

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

Chapter 10: Ethics/Protection of Human Subjects

10.1 Ethical Standard

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

10.2 Institutional Review Boards

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

10.3 Informed Consent Process

10.3.1 Consent Procedures and Documentation

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

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

10.3.2 Subject and Data Confidentiality

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

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

The study subject's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, institutional policies, or sponsor requirements.

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

10.3.3 Subject Future Use of Stored Specimens and Data

Data collected for this study will be analyzed and stored at Jaeb. After the study is completed, the de-identified, archived data will be transmitted to and stored at Capillary Biomedical, under the supervision of the Program Manager for use by other researchers including those outside of the study. Permission to transmit data to Jaeb and Capillary Biomedical will be included in the informed consent.

Blood and urine samples will only serve the purpose of identifying whether the subject can be included in the study. Biological samples will be destroyed/discarded after laboratory analysis.

When the study is completed, access to study data and/or samples will be provided through Capillary Biomedical.

Chapter 11: References

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Appendix A: Relevant Literature on Infusion Sets

A.1 Failure Modes and Failure Rates for Current Infusion Sets

The nationwide pediatric surveillance of insulin infusion sets in Germany and Austria reported that 192 (29%) patients had no infusion set issues at all. However, the other 475 (71%) patients reported 1,404 events. The most often reported device adverse event was cannula obstruction (32.9%). A total of 14.2% of the patients reported that they had blood in the insulin infusion cannula; 11.1% had skin with redness and 10.1% reported cannula kinking. 36.2% of the reported complications occurred by day 1 of infusion set usage and 82.4% by the end of day 2.[15]

Pfützner *et al*. performed a prospective randomized controlled crossover clinical trial to investigate the tolerability of 2-day use of commercial insulin infusion sets in comparison to 4-day use in a real-world setting. Twenty-four patients with T1D managed with an insulin pump were studied during two 3-month periods. The number of cannula-related adverse events was 290 with 2-day use versus 495 with 4-day use ($P < .05$). The overall number of treatment related events was 750 with 2-day use versus 934 with 4-day use ($P < .001$). There was no difference in glycemic control between the treatment arms. Treatment satisfaction was higher with 2-day use (very high/high satisfaction: 90.4% versus 4 day-use: 77.3%, $P < .05$). The authors concluded that using an infusion set for a longer than 2-3 days resulted in a clinically relevant increase in treatment-related tolerability problems.[16]

Renard *et al.* performed a prospective, two-period, observational, multicenter study in 45 T1D outpatients. During the initial 1-month period the patients used a Teflon cannula (98% of cases) and crossed over to an investigational insulin infusion set (Accu-Chek FlexLink, Disetronic Medical Systems AG) for a 3-month period. Forty-five initial infusion failures occurred in 14 patients among 507 commercial Teflon cannula insertions (8.9% of cases), whereas 15 failures were seen in nine patients during 488 investigational cannula insertions (3.1% of cases) ($P<0.001$). The overall rate of late cumulative events was 113 of 507 (22%) with the commercial infusion set versus 66 of 488 (14%) using the investigational infusion set ($P<0.001$). The occurrence of pain, skin reaction, or redness at the infusion site was lower using the investigational insulin infusion cannula.[17]

Van Bon *et al.* conducted a multi-center trial of 256 patients on three insulins. Approximately 30% of patients experienced at least 1 perceived set failure during the 13-week study period with each insulin. More than 60% of patients experienced unexpected hyperglycemia during the 13-week study period. These results are similar to experts' experience managing T1D using an insulin pump and currently available infusion sets. Improving the reliability, enhancing the comfort and extending the duration of infusion set use each would be important contributions to continuous subcutaneous insulin infusion therapy.[18]

In a pilot study in 22 patients by Lal *et al.* conducted at Stanford University, the most common reason for infusion set removal was adhesive failure (50%), followed by hyperglycemia unresponsive to a correction bolus (33%), hyperglycemia with elevated ketones (8%), and infection of the insertion site (8%).[9]

A.2 Effect of Wear Time on PK/PD and Test Meal Response

Clausen *et al*. observed progressive acceleration of PK exposure over 4 days of wear time[19], and confirmatory evidence was provided by Swan *et al.*[20], who demonstrated progressive acceleration of PD over 3 days of catheter wear time. This was further confirmed by Vaughn and Muchmore.[21]

Luijf *et al.* tested glucose response to a test challenge and showed substantial declines in glucose response between day 1 and day 3 of catheter wear.[22] This improved glucose response was seen for both patch (tubeless) and conventional insulin pump systems, which was presumably a result of improved early insulin exposure that occurs over the first 3 or so days of catheter wear time.

Simic *et al.* performed a clamp study with 16 subjects assessing a new extended-wear infusion set with an anti-inflammatory coating and Lantern technology (ConvaTec) and found that while insulin absorption decreased over wear time, it was also significantly faster 4 and 7 days after insertion. None of the patients experienced severe hypoglycemia over a period of 7 days. The authors claim that increased rate of absorption my facilitate better postprandial control.[23]

A.3 Experience with Extended Wear (>3 days)

Patel *et al.* performed a randomized crossover clinical trial to compare the performance of Teflon versus stainless steel insulin infusion sets in ambulatory humans for up to 1 week. The subjects used a Quick-Set or a Sure-T CSII cannula until the infusion set failed or was worn for 1 week. After 7 days, both types of infusion sets had a 64% failure rate. Eighty-seven percent of the steel sets and 77% of the Teflon sets were functioning after 3 days (this number includes the 15% that failed on the first day because of kinking), after 5 days 68% of the steel and 59% of the Teflon sets were functioning, after 6 days 53% of the steel and 46% of the Teflon sets were functioning, and at the end of 7 days 32% of the steel and 32% of the Teflon sets were functioning. Overall, 30% failed because of hyperglycemia and a failed correction dose, 13% were removed for pain, 10% were pulled out by accident, 10% had erythema and/or induration of >10 mm, 5% fell out because of loss of adhesion, and 4% were removed for infection. The main predictor of length of wear was the individual subject. There was no increase in hyperglycemia or daily insulin requirements when an infusion set was successfully used for 7 days.[24]

Waldenmaier et al. tested extended wear (≥7 days) of commercial steel and Teflon insulin infusion sets in 40 adult subjects on insulin pump therapy. 66% of 160 inserted infusion sets were used for 7 days with no obvious difference between steel and Teflon infusion sets (mean wear time was 6.2 days). The main reasons for early infusion set replacements were occlusions (19%), adhesive issues (4%), and accidental removal (4%). Comparing glycemic control during day 1-3 and 1-7, there was no difference in mean BG and insulin dose. The authors concluded that infusion set replacement intervals may be individualized beyond the currently labeled maximum use duration.[8]

Lal *et al.* assessed longevity of the previously mentioned ConvaTec infusion set in a pilot study including 22 subjects. 45% of the novel infusion sets lasted 10 days, with a median wear time of 9.1 days. While the mean BG concentration increased significantly over time, the total daily insulin dose did not change throughout 10 days of set wear.[9]

Recently, Medtronic reported an overall wear period success rate of 74.8% at 7 days using an extended wear infusion set (Buckingham et al., poster, American Diabetes Association annual meeting, 2021), leading to device approval by the FDA (510k). There has been no marketing experience reported for this device.

Summarizing these various studies of cannula wear time, it appears that currently marketed infusion sets have limited life span, and room for improvement is present.