Study Title	Randomized Crossover Euglycemic Clamp Study in Adult Patients with Type 1 Diabetes to Assess Pharmacokinetics and Pharmacodynamics of Subcutaneously Infused Insulin Using an Investigational Extended Wear Continuous Subcutaneous Insulin Infusion Cannula Compared to a Commercial Infusion Set
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Principal Investigator:
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Sponsor: Capillary Biomedical, Inc.

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
1.3 Table 2 5.6 6.1.1.4 6.1.1.5	Clarify procedure; added one time rescreen for A1C and C-peptide	Align to Study Center procedure; Capillary Biomedical's standard procedure has been to allow for a single rescreen attempt for key labs (e.g. A1C and c-peptide).

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STATEMENT OF COMPLIANCE

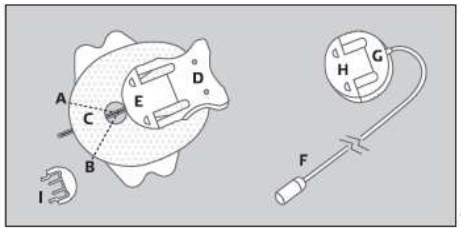
The trial will be conducted in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the NIH National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Terms and Conditions of Award. The Principal Investigator (PI) will assure that no deviation from, or changes to the protocol will take place without prior agreement from the abbreviated Investigational Device Exemption (IDE) sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form will be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Table 1: Study Synopsis

Study Title:	Randomized Crossover Euglycemic Clamp Study in Adult Patients with Type 1 Diabetes to Assess Pharmacokinetics and Pharmacodynamics of Subcutaneously Infused Insulin Using an Investigational Extended Wear Continuous Subcutaneous Insulin Infusion Cannula Compared to a Commercial Infusion Set
Short Title:	PK/PD of an Extended Wear Infusion Set for CSII in T1DM Patients ("**PEXIS**")
Device Description:	The Capillary Biomedical, Inc. (CapBio) Achilles infusion set is a sterile, non-pyrogenic, single use device for continuous subcutaneous insulin infusion (CSII). Achilles infusion sets are designed to be used with commercially available infusion pumps (e.g., Medtronic Paradigm). The use of the Achilles infusion set is identical to the commercially available MiniMed Silhouette control device. The investigational Achilles infusion set and control Silhouette devices differ only in the materials (coil-reinforced soft polymer vs Teflon) and construction (one distal and three side ports vs single distal port, respectively) of the indwelling cannula. Each infusion set has two basic components: the infusion set body with an indwelling cannula and a tubing set for connection to the infusion pump reservoir. The Achilles infusion set body is provided individually packaged in a sterile pouch. The infusion set body is then connected to the tubing set from a commercially available infusion set with the proprietary pump reservoir connector (e.g., Medtronic Paradigm) for use with specific infusion pumps.
Device Illustration:	 CONTENTS A. Needle guard B. Soft cannula C. Adhesive tape D. Introducer needle E. Cannula housing F. Tubing G. Connector needle H. Circular protective cap I. Disconnect cover See document 710-1021-00 *Achilles Infusion Set, Instruction For Clinical Use.*
Indication/ Intended Use	The Achilles Infusion Set is intended for the subcutaneous (SC) infusion of medication, including insulin, from an external infusion pump.
Study Description:	This study has been designed as a prospectively enrolled, randomized sequence, 2-way crossover study of device performance, tolerability and safety of the investigational Achilles infusion set or commercial infusion set during two 7-day home use periods with 4 in-clinic euglycemic clamp sessions during each of the 7-day periods. After a wash-out period, patients will cross over into the investigational or control group, respectively.

Hypothesis:	We hypothesize that the rate of decline or slope (s) of natural logarithm of the area under the glucose infusion rate curve $AUC_{0\text{-}300(GIR)}$ over wear time (=4 clamp experiments) will be less using the investigational Achilles infusion set compared to the commercial control. Statistical hypotheses: • Null Hypothesis: There is no difference in the population mean rates of decline for the Achilles and control infusion sets, as measured by the slope (s) contrast for the $\ln(AUC_{0\text{-}300(GIR)})$ assessed over study days DOI (day 0), day 3, day 5, and day 7. $H_0: s_{control} = s_{Achilles}$ • Alternative Hypothesis: The rate of decline (slope coefficient s) for the Achilles infusion set is less that the corresponding rate for control. $H_A: s_{control} < s_{Achilles}$
Primary Objective	To assess the reliability of delivery using the investigational Achilles infusion set by evaluating the rate of decline of the glucose lowering effect of insulin from DOI through day 7 (8^{th} calendar day of wear) compared to the commercially available control.
Primary Endpoint	Rate of decline (s) over wear time (DOI, day 3, day 5, day 7) of the natural logarithm of the area under the glucose infusion rate curve [$\ln(AUC_{0\text{-}300(GIR)})$]
Secondary Objective 1:	To assess pharmacodynamic (PD) parameters within and across treatments following subcutaneous insulin delivery using Achilles vs Teflon control set on DOI and days 3, 5 and 7 post insertion.
Secondary Endpoints 1:	Mean differences (within treatments over time and between treatments at specified time points) in: • Time-to-Maximum Glucose Infusion Rate (GIR) ($t_{max(GIR)}$) • Time to half-maximal GIR, both early and late ($t_{50(GIR),early}$ & $t_{50(GIR),late}$) • Onset of action as measured by a drop of blood glucose (BG) by 5 mg/dL • Duration of insulin action (calculated the same as MRT for PK) • GIR_{max} • Area under the GIR curve ($AUC_{0\text{-}t(GIR)}$), both absolute and as a percentage of total $AUC_{0\text{-}\infty}$ and Coefficient of Variation (CV) of $AUC_{0\text{-}t(GIR)}$, where t = 5, 10, 15, 20, 30, 45, 60, 90, 120, 150, 180, 210, 240, and 300 min Other PD parameters may also be calculated.

Secondary Objective 2:	To assess pharmacokinetic (PK) parameters within and across treatments following subcutaneous delivery using Achilles vs Teflon control set on DOI and days 3, 5, and 7 post insertion.
Secondary Endpoints 2:	Mean differences (within treatments over time and between treatments at specified time points) in: • Early exposure ($AUC_{0\text{-}60min}$) • Mean-residence time (MRT) of insulin • Maximum Insulin concentration (C_{max}) • Time-to-Maximum Insulin Concentration (t_{max}) • Time-to-50% Maximum Insulin Concentration [$t_{50,early}$ & $t_{50,late}$], both early (i.e. before C_{max}) and late (i.e. after C_{max}) • $AUC_{(0\text{-}t)}$ (both absolute and as a percentage of $AUC_{(0\text{-}300)}$) and Coefficient of Variability (CV) $AUC_{(0\text{-}t)}$ where t = 3, 6, 9, 12 ,15, 20, 25, 30, 35, 40, 45, 50, 60, 70, 80, 90, 105, 120, 150, 180, 210, 240 and 300 min Other PK parameters may also be calculated.
Secondary Objective 3:	To assess continuous glucose monitoring (CGM) data, comparing data within and across treatments.
Secondary Endpoints 3:	• Mean daily time in range (70-180 mg/dL), DOI through Day 7 inclusive • Mean daily time in target (70-140 mg/dL), DOI through Day 7 inclusive • Mean and median daily glucose, DOI through Day 7 inclusive • Glucose variability (%CV), DOI through Day 7 inclusive • Mean daily time ≤70 mg/dL, <54 mg/dL, DOI through Day 7 inclusive • Mean daily time >140 mg/dL, >180 mg/dL, >240 mg/dL, DOI through Day 7 inclusive • Other CGM metrics may also be calculated
Secondary Objective 4:	To assess performance of investigational infusion set on DOI through 7 for each treatment
Secondary Endpoints 4:	• Proportion of investigational CSII sets that did not fail on each day of use. • Mean difference across treatments in time to device failure • Mean difference across treatment in incidence of pump bolus occlusion alarms • Mean difference across treatment in incidence of pump basal occlusion alarms

Safety Objectives:	To assess Achilles infusion set safety and tolerability from DOI through day 7 for each treatment
Safety Endpoints:	• The occurrence hyperglycemia (glucose >250 mg/dL) not responsive to a pump bolus dose where response to the bolus is defined as a fall of at least 50 mg/dL in blood glucose within one hour, • The occurrence of hyperglycemia (glucose >250 mg/dL) after prolonged fasting (e.g. overnight or more than 5 hours following a meal), not associated with acute intercurrent illness, but with a concurrent ketone level ≥0.6 mmol/L. • Localized infection or inflammation of greater than 1.0 cm in diameter at the infusion site • Occurrence of an insulin pump occlusion alarm signal • Cannula dislodgement from subcutaneous space, • Cannula malfunction (inability to pierce skin, bending, kinking, fluid leakage or other malfunction that might impact insulin infusion) • Mean visual analog scores (VAS) scores (0-100 mm) from Day of insertion through Day 7 of use • Mean difference of VAS scores (0-100mm) of CSII investigational sets and CSII control sets • Descriptive statistics of per subject term, severity, adverse device effects, and frequency of adverse events for each treatment • Descriptive statistics of per subject incidence of unanticipated adverse device effects
Study Population:	Up to 30 adult participants, with the goal of having approximately 24 completers, may be enrolled, ages 18–70, diagnosed with Type 1 diabetes mellitus (T1DM) who have ≥6 months experience using rapid-acting insulin analog delivered via Medtronic MiniMed insulin pump and infusion sets. Only Medtronic pump models 530 and higher may be used. Study participants will be drawn from existing T1DM patient populations meeting the study eligibility at each study center and from referral practices.
Phase:	Phase 1b
Description of Sites /Facilities Enrolling Participants:	This study will be conducted at no more than 5 centers in the United States. Each site will be qualified to conduct insulin treatment studies per a standardized euglycemic clamp protocol.

Description of Study Intervention:	Existing patient populations at each study center will be screened for study eligibility within 28 days of planned study enrollment. Participants without prior experience using the Dexcom G6 will be allowed up to 14 days of a run-in period to familiarize themselves with the CGM device. Eligible participants will complete written informed consent and be assigned a unique study ID. Eligible participants will be randomized for Treatment Period A to either the Achilles investigational cannula or a Medtronic Silhouette control cannula using commercially available tubing, insulin lispro, insulin pumps and continuous glucose monitoring (CGM) equipment. After 2±1 week of washout each participant will enter Treatment Period B for a second 7-day period of catheter wear-time using the other infusion set. On Day of Insertion (Day 0), participants will have the investigational Achilles infusion set or the control infusion set inserted by a qualified professional during a clinic visit. Participants will undergo training and be provided written instructions if infusion set change out is required during the 7-day wear period. At the start of the study, participants will be provided with an insulin lispro vial (Humalog®, Eli Lilly and Co., Indianapolis, IN), a 23" tubing set compatible with the Achilles infusion set and Ascencia Contour Next glucose monitor plus test strips. Participants will also wear a study-provided Dexcom G6® (study continuous glucose monitor, to be used in real time mode) for the duration of the study. Participants will manage routine basal/bolus insulin therapy using these supplies and their current insulin pump for two home use wear periods of up to 7 days each. Finally, an Abbott Precision Xtra ketone monitor plus test strips will be provided for use in the event of hyperglycemia >250 mg/dL. Visual inspection and photographic documentation of the Achilles and the comparator infusion set insertion site will be recorded at Day 0. Participants will be asked to conduct daily insertion site visual inspection and report/record site reactions, glycemic intervals and/or the need for infusion set change out (Days +1 to +7). During a 7-day wear period, participants will undergo 4 in clinic euglycemic glucose clamps [Day of Insertion (DOI) and 3, 5, and 7 days later] to assess pharmacokinetics (PK) and pharmacodynamics (PD) of a bolus of lispro insulin (0.15 U/kg) when delivered using an insulin pump. Upon completion of the first wear period (after 7 days or sooner, in the event that infusion set change out has occurred) and a 7-21 day washout period, participants will return to the investigational clinic site and will have a second infusion set inserted by a qualified professional. Sequence of control and investigational infusion set will be randomized. It is expected that infusion set change out may be required prior to the end of the 7 day wear period. If necessary, participants will follow written instructions for change out to a commercial CSII set and return to the study center for visual and photographic evaluation of the insertion site. CGM data will be available to the study site in real time (and will be reviewed at each clinic visit) by using Dexcom Clarity software to access the individual participant's Dexcom cloud account data. Data will be downloaded from the participant's

	blood glucose and ketone monitors at the completion of each treatment period. Participants who require change out of their infusion set during the first 7-day study period will still be eligible to participate in the second study period. End-of-study will occur at the end of the second 7-day study period (or sooner, if infusion set change out is required prior to completion of the second 7-day period).
Study Duration:	Estimated duration of the study is 6–12 months to allow for patient screening and obtaining informed consent from up to 30 potential participants, and 2 treatment periods of up to one week (7 days) each.
Participant Duration:	Patient participation is estimated at 7 weeks (±1 week): • Up to 3 weeks for screening, enrollment/randomization, and 1 week adjustment period with Dexcom G6® study CGM • 1-week Treatment Period 1; • 2-week washout/rest (±1 week); • 1-week Treatment Period 2.
Investigator(s)/ Study Sites:	Timothy S Bailey, MD President & CEO, AMCR Institute 625 W. Citracado Pkwy, # 112 Escondido, CA 92025 Telephone: 760.466.1520 E-mail: tbailey@amcrinstitute.com

1.2 SCHEMA

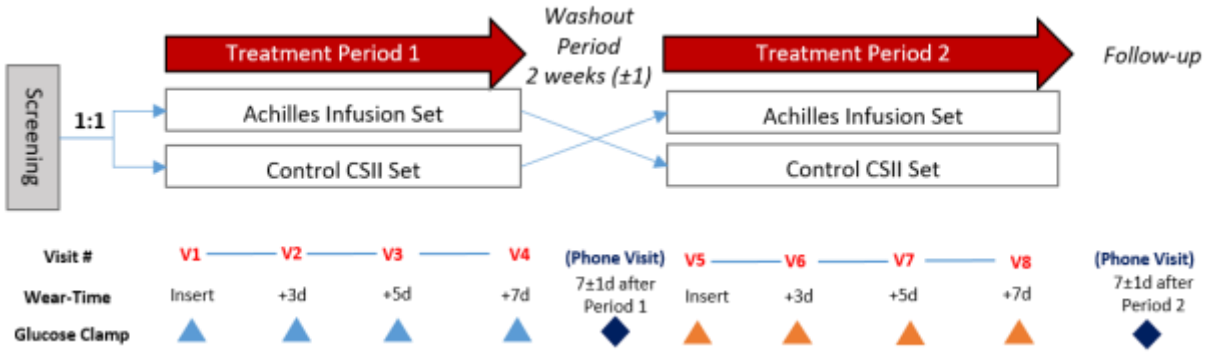


Figure 1: Schematic overview over study design.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Table 2: Schedule of Activities

	Screening	Treatment Period 1				Washout Period		Treatment Period 2				
Study Visit	**Visit 0**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Telephone Follow-up**	**Washout**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Telephone Follow-up**
Day	-28 to -1	0A	3A	5A	7A	7±1 after Period 1	8-28	0B	3B	5B	7B	7±1 after Period 2
Time after CSII insertion [h]			72±3	120± 3	168±3				72±3	120±3	168±3	
Procedures	Screening	Rand. / Insertion/ Clamp	Clamp	Clamp	Clamp	Phone call	Routine	Enrollment/ Insertion/ Clamp	Clamp	Clamp	Clamp	Phone call
Example Day of Week		Fri	Mon	Wed	Fri			Fri	Mon	Wed	Fri	
Labs/Questionnaires/Instructions												
Informed consent	X											
Demographics	X											
Medical history	X											
Urine Pregnancy test[1]	X	X						X				
Physical exam (incl. height/weight)[2]	X							X				
Concomitant medication review	X	X	X	X	X	X		X	X	X	X	
CBC	X										X	
HbA1c	X											
C-Peptide	X											
Basic Metabolic Panel	X											
ECG	X											
Vital signs[3]	X	X	X	X	X			X	X	X	X	
Randomization		X										
Patient Instructions[4]	X	X	X	X	X	X		X	X	X	X	
Adverse event review and evaluation[5]	X	X	X	X	X	X		X	X	X	X	
Device Applications/Removals												
Download Pump and SMBG Data	X	X	X	X	X			X	X	X	X	
Insert CGM sensor	X	X						X				
Review CGM data	X	X	X	X	X				X	X	X	
Remove Participant's infusion set (AM of clamp procedure), insert CSII catheter (abdomen)		X						X				

Remove CSII catheter (& insert patient's routine CSII set)					X[6]						X[6]	

Clamp											
Switch pump to 0.1 U/h at when IV insulin is started (evening before clamp procedure)		X	X	X	X			X	X	X	
Insert 2 IV cannulas for insulin and dextrose infusion (evening before clamp procedure)		X						X			
Prime tubing with insulin and connect to CSII infusion set and then prime cannula		X						X			
PK/PD study (run-in, bolus, clamp)		X	X	X	X			X	X	X	X
Venous sample BG/serum insulin[7]		X	X	X	X			X	X	X	X
Patient meal (at end of clamp procedure)[8]		X	X	X	X			X	X	X	X
Others											
Evaluate insertion site[9]		X	X	X	X	X		X	X	X	X
Video insertion		X						X			
Record CGM and CSII performance issues		X	X	X	X			X	X	X	X

[1] Pregnancy test required for all female participants of child-bearing age without documented menopausal status or removal of key organs.

[2] Only the Visit 1 body weight value will be used to calculate insulin doses and infusion rates for both treatment periods

[3] Vital signs include BP (seated or recumbent), pulse, respiratory rate and temperature; VS should be done every 2 hours ± 30 min during clamp procedures

[4] Ascencia Contour Next glucose monitor and Precision Xtra blood ketone monitor with respective test strips will be provided.

[5] 100 mm Visual Analog Scale (VAS) pain assessment to be performed at Achilles infusion set insertion, daily during home wear period, and at time of Achilles infusion set removal.

[6] End-of-Study (EOS) and Early Termination (ET) Assessments; if participant terminates early because of cannula failure event then glucose clamp will not be done if failed cannula has been removed. Study completion time may differ per participant. Study is considered complete at the end of the second wear period as determined by: ***(1)*** *Participant has worn Achilles infusion sets for 7 days,* ***(2)*** *Participant experiences Achilles set failure requiring change out to commercial CSII set,* ***(3)*** *Participant has hyperglycemic event requiring at home change out to commercial CSII set, or* ***(4)*** *Resolution of device or procedure-related AEs.*

[7] Blood for clamping decisions every 5-15 min for 300 min

[8] Meal and individually determined bolus dose of insulin delivered via pump bolus performed in clinic; participants may be discharged home shortly after meal is completed. The same meal and insulin bolus dose (unless clinically indicated that bolus dose should be modified) to be provided for each participant after all clamp studies

[9] Insertion Site Evaluations for each wear period: Day 0 pre-infusion set insertion and after securing post-insertion; Daily during Day 0 to +7 wear period; Day 7 (or upon infusion set failure) pre-infusion set removal, post-infusion set removal. The site personnel will perform photographic documentation of the insertion site at the time of insertion and at the time of presentation to the study site at the end of each wear period.

2 INTRODUCTION

2.1 STUDY RATIONALE

Currently, a change of insulin infusion sets is recommended every 72 hours for Teflon sets and every 48 hours for steel cannulas. Based on clinical experience, there is evidence that cannula wear time might be extended in some patients without worsening of glucose control. Other patients report a worsening of glycemic control over time, which makes them change the infusion set prior to the recommended 3-day time period.

The objective of this study is to evaluate the insulin pharmacokinetic (PK) and pharmacodynamic (PD) performance over the wear duration of the investigational Achilles infusion set (Achilles device) for up to 7 days post-insertion relative to conventional Teflon infusion sets. Achilles device functionality, patient tolerance and safety events will be collected during routine basal and bolus insulin therapy over the 7-day home use wear period and 4 in-clinic euglycemic clamp procedures.

This study was preceded by a clinical study of the Achilles infusion set, 150-1072 Feasibility of an Investigational Extended Wear Infusion Set for Continuous Subcutaneous Insulin Infusion (CSII) in Patients with Type 1 Diabetes Mellitus.

We hypothesize that the CapBio Achilles cannula not only provides more reliable insulin delivery (both for bolus and basal insulin delivery) but will also demonstrate extended wear time with both improved consistency and reliability of insulin absorption. Previous studies have shown that the PK exposure profile of rapid acting analog insulin accelerates over 3 days of cannula wear time, indicating a need for improved cannula performance over time (see below for literature review).

2.2 BACKGROUND

2.2.1 PRELIMINARY DATA

Insulin absorption from the tissue surrounding a commercial Teflon or steel CSII cannula is slow, variable, and unreliable. The majority of CSII cannulas need to be replaced after 2 to 3 days of clinical use because insulin absorption from the subcutaneous tissue into the circulation becomes more variable and less reliable over time.[1–8] An ideal CSII cannula will produce rapid on/off insulin pharmacokinetics (PK) and pharmacodynamics (PD) and consistent/precise insulin PK-PD for an extended period of time (7 + days). The clinical use of a CSII cannula with rapid on-off PK/PD and low PK variability has the potential to greatly improve BG control, decrease the risk for hypoglycemia, improve compliance and decrease costs.[9] Overall, insulin infusion sets are the Achilles heel of CSII therapy and a critical barrier to progress.[8]

Between 2016 and 2018, CapBio and the Jefferson Artificial Pancreas Center (JAPC, Thomas Jefferson University, Philadelphia, PA) performed preclinical studies in 18 swine funded by JDRF entitled: “CSII cannula with Rapid On/Off PK-PD, Consistent PK-PD, & Extended Lifetime to 14 days”. 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. This set contains a soft, flexible Nylon insulin infusion cannula with wire reinforced walls that prevents kinking, minimizes inflammation and increases the surface-area-to-volume ratio (SA:V) of insulin in contact with adjacent vascular tissue due to multiple holes (1 distal, 3 proximal). The Achilles prototype was well tolerated by all animals (n=3) with no signs of external inflammation or infection. The JAPC was able to show that the Achilles cannula design successfully prevented kinking (0% versus 57% kink rate in Silhouette commercial cannulas, $p<0.001$) and that the placement of holes was adequate to ensure that all holes were located below the skin for optimal insulin delivery into the subcutaneous tissue. As measured in micro-CT, the SA:V of a bolus of insulin/x-ray contrast agent was significantly greater than 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. A layer of thrombus and acute inflammatory tissue formed around each CSII cannula due to leakage of plasma and red blood cells and infiltration with neutrophils, macrophages and fibroblasts. This layer was consistently thinner around Achilles cannulas compared with the commercial Silhouette over 8 days of wear time ($p<0.001$). The overall area of inflamed tissue surrounding the Achilles cannula as measured by an imaging software was significantly larger around Silhouette control catheters compared to the Achilles cannula between 4 and 8 days of wear time ($p=0.003$). When delivering the bolus, the research team measured tubing pressure using a special setup developed at the JAPC. The amplitude and the pattern of the pressure/time curves were found useful to differentiate a “normal” insulin bolus delivery into the subcutaneous tissue from an occlusion or a leak. Interestingly, there was a statistically significant correlation ($R=0.5$, $p<0.05$) between increase in layer thickness and increase in pressure, independent of cannula type, suggesting that the layer forms a barrier to insulin flow into the adjacent SC tissue. Data were presented at several national and international conferences.[10–12]

2.2.2 HUMAN USE

The investigational CSII cannula being developed by Capillary Biomedical has been used to deliver insulin in a human clinical trial in 7 participants in Australia. This study is registered in the Australian New Zealand Clinical Trials Registry under registration number *ACTRN12620000021976*. No serious or unanticipated adverse events have been reported to date.

2.2.3 RELEVANT LITERATURE

Failure Modes and Failure Rates for Current Infusion Sets:

The nationwide pediatric surveillance of CSIIs in Germany and Austria reported that 192 (29%) patients had no CSII issues at all. However, the other 475 (71%) patients reported 1404 events. The most often reported device adverse event was CSII obstruction (33.9%). A total of 14.2% of the patients reported that they had blood in the CSII cannula; 11.1% had skin with redness and 10.1% had bent cannula. It is

impressive to see that 36.2% of the reported complications occurred by day 1 of CSII cannula usage and 82.4% by the end of day 2.[13]

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 T1DM managed with an insulin pump were studied during two 3-month periods. Outcome measures were glycemic control (SMBG and CGM) frequency and nature of device-related and procedure-related adverse events and patient preference. 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.[7]

Renard *et al.* performed a prospective, two-period, observational, multicenter study in 45 T1DM outpatients that managed their diabetes with an insulin pump, CSII cannula and rapid acting insulin. During the initial 1-month period the patients used a Teflon cannula (98% of cases) and crossed over to an investigational CSII cannula (Accu-Chek FlexLink, Disetronic Medical Systems AG) for a 3-month period. The primary endpoint was insertion failure and unexplained hyperglycemia within the first 6h after cannula placement. Secondary end points were cannula replacements for unexplained hyperglycemia, skin irritation and tissue inflammation. 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 with the commercial CSII versus 66 of 488 using the investigational CSII ($P<0.001$). The occurrence of pain, skin reaction, or redness at the infusion site was lower using the investigational CSII cannula.[14]

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 Type 1 Diabetes 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.[15]

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[16], and confirmatory evidence was provided by Swan *et al.*[6], who demonstrated progressive acceleration of PD over 3 days of catheter wear time. This was further confirmed by Vaughn and Muchmore[17].

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[18]. 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.

Ruan *et al*. conducted a retrospective study to evaluate the exposure-response relationship of rapid acting insulin and overall glycemic outcomes during closed-loop insulin delivery and sensor-augmented pump therapy. Data from a multicenter randomized control trial involving 32 adults with type 1 diabetes receiving day-and-night closed-loop insulin delivery and sensor-augmented pump therapy over 12 weeks were analyzed. Time-to-maximum-effect [expressed as time-to-peak insulin action ($t_{max,IA}$)] and potency [expressed as insulin sensitivity (SI)] were estimated during both interventions, and correlated with demographic factors such as BMI and glycemic outcomes such as HbA1c. They noted that during both interventions, $t_{max,IA}$ was positively correlated with pre- and postintervention HbA1c ($r = 0.50\text{-}0.52$, $p<0.01$) and mean glucose ($r = 0.45\text{-}0.62$, $P < .05$), and inversely correlated with time sensor glucose, which was in target range 3.9 to 10 mmol/L ($r = -0.64$ to -0.47, $p<0.05$). They observed that increased body mass index was associated with higher $t_{max,IA}$ and lower SI (both $p<0.05$). During closed-loop insulin delivery, $t_{max,IA}$ was positively correlated with glucose variability ($p<0.05$) suggesting that faster insulin action is associated with improved glycemic control during closed-loop insulin delivery and sensor-augmented pump therapy.[19]

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 study participants used a Quick-Set or a Sure-T CSII cannula until the infusion set failed or was worn for 1 week. All participants wore a MiniMed continuous glucose monitoring system for the duration of the study. Infusion set failure was defined as an episode of unexplained hyperglycemia that did not respond to a correction bolus, infection, severe inflammation, or set dislodgement. There were 38 weeks of Sure-T wear and 39 weeks of Quick-Set wear with no difference in the survival curves of the infusion sets. There was, however, a 15% initial failure rate with the Teflon infusion set. 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 33% 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 > 10mm, 5% fell out because of loss of adhesion, and 4% were removed for infection. The main predictor of length of wear was the individual participant. There was no increase in hyperglycemia or daily insulin requirements when an infusion set was successfully used for 7 days.[5]

Alsted studied extended wear of up to 7 days, assessing PK on DOI and days 1, 2, 4 and 7. Overall PK exposure ($AUC_{0\text{-}4hr}$) was steady over 4 days, with progressive acceleration of t_{max} over that interval ($p<.02$). By day 7 t_{max} was still accelerated as compared to DOI but, $AUC_{0\text{-}4hr}$ was reduced by approximately 21% ($p<.04$). The author hypothesized that these changes were due to alterations in local adipose tissue blood flow (ATBF) although attempts to measure this directly were inconsistent, with an apparent increase in ATBF initially, reverting to baseline by day 4. Efforts to document increased local cytokine levels were hampered by technical issues. (*Alsted TS. Device-induced subcutaneous trauma. PhD Thesis. Department of Histology & Delivery, Novo Nordisk A/S, Denmark & Department of Biomedical Sciences, Faculty of Health Sciences, University of Copenhagen, Denmark, November 2010).*

Summarizing these various studies of cannula wear time, it appears that insulin exposure is accelerated during the first few days of CSII cannula wear, and this results in improved response to glucose challenge. With further wear time, PK exposure diminishes. These findings provide challenges for persons with diabetes, who may have to adjust insulin doses and meal strategies as insulin exposure first accelerates and then wanes over cannula wear time.

Effect of dispersed insulin delivery on PK:

Mader *et al.* investigated the impact of two different injection strategies on the PK-PD of insulin aspart in-vivo in an open-label, two-period crossover study and verified changes in the surface-to-volume ratio ex-vivo. Insulin aspart was injected ex-vivo into explanted human abdominal skin flaps. The surface-to-volume ratio of the subcutaneous insulin depot was assessed by microfocus computed tomography that compared 1 bolus of 18 IU with 9 dispersed boluses of 2 IU. These two injection strategies were then tested in-vivo, in 12 C-peptide–negative type 1 diabetic patients in a euglycemic glucose clamp study for 8 h after the sc insulin injection(s). The ex vivo experiment showed a 1.8-fold higher mean surface-to-volume ratio for the dispersed injection strategy. The maximum glucose infusion rates (GIR) were similar for the two strategies; however, times to reach maximum GIR and 50% and 10% of the maximum GIR were significantly reduced by using the 9 x 2 IU strategy. The area under the insulin concentration-time curve and GIR curve were greater during the first 60 minutes. The authors concluded that a dispersed insulin injection strategy enhanced the effect of a fast-acting insulin analog. The increased surface-to-volume ratio of the subcutaneous insulin depot can facilitate insulin absorption into the vascular system.[20]

Edsberg *et al.* performed two human clinical trials to investigate the effect of injecting short acting insulin into the subcutaneous tissue of the abdomen using a sprinkler needle with 14 small holes in the wall and sealed distal tip compared to a conventional needle with one distal hole at the tip. They observed a significantly faster absorption of 8 units of iodine-125 labelled Actrapid during the first 30 minutes with the sprinkler needle compared with the conventional needle. In the second study, they injected 10 U Actrapid into the subcutaneous tissue of 11 T1DM patients immediately before a standardized breakfast meal either by the sprinkler needle or a conventional needle in a randomized order. The plasma free insulin concentration increased more rapidly and to higher concentrations with

the sprinkler needle and the post-prandial glycemic response was considerably diminished compared with the conventional needle injections.[21]

Challenges associated with variability in insulin effect:

A second retrospective analysis was conducted by Ruan *et al.* on the same dataset involving a multicenter closed-loop trial of 32 adults with type 1 diabetes where patients had applied hybrid day-and-night closed-loop insulin delivery in home-use over 12 weeks. The objective of the analysis was to quantify variability of insulin requirements during closed-loop insulin delivery. The research group retrospectively analyzed overnight, daytime, and total daily insulin amounts delivered. The coefficient of variation was adopted to measure variability of insulin requirements in individual participants. Data were analyzed from 1,918 nights, 1,883 daytime periods and a total of 1,564 days were characterized by closed-loop use over 85% of time. Their results showed that variability of overnight insulin requirements (mean [SD] coefficient of variation 31%) was nearly twice as high as variability of total daily requirements (17%, $p<0.001$) and was also higher than variability of daytime insulin requirements (22%, $p<0.001$), concluding that overnight insulin requirements were significantly more variable than daytime and total daily amounts. Ruan further suggested that overnight variability may explain why some people with type 1 diabetes report frustrating variability in morning glycemia.[22]

The high degree of interpatient variability in type 1 diabetes patients requires continuous vigilance of glycemia to treat episodic hyper and hypoglycemia. The advent of CGM enabled insights into the glycemic trends of each patient, who could then adjust insulin dosing parameters to potentially avoid hyper and hypoglycemia patterns. PK/PD variability across patients, however, continues to affect overall glycemic outcomes, and research from Ruan *et al.* suggests that the integration of new therapeutic modalities and technologies which address more rapid and reliable kinetics could yield more consistent and positive glucodynamics/outcomes. Furthermore, if CGM data could be aggregated to generate statistical power within a practice or population, then opportunities emerge to model predictive exposure-response relationships of insulin and systemic glucose levels to address inter and intra-patient variability and support closed-loop advancements.

2.2.4 CLINICAL NEED

Over 1 million people with diabetes globally use an insulin pump, continuous subcutaneous insulin infusion (CSII) catheter and rapid acting insulin to manage their BG levels. The majority of patients insert a new CSII cannula every 2–3 days in order to ensure safe and effective BG control.[4] Patients find this frequent site change and rotation inconvenient and often maintain their infusion site longer than recommended.[3,4,8] The absorption of insulin from the CSII cannula into the circulation is slow, variable and unreliable, especially after using the infusion set for more than 3 days.[4] This can lead to dangerous and costly complications caused by hyperglycemia, hypoglycemia and diabetic ketoacidosis. Patients with poor BG control are at increased risk for myocardial infarction, stroke, heart failure, kidney failure, peripheral vascular disease, neuropathy, dementia, limb amputation, blindness, and premature death.[23] Furthermore, the repeated trauma of CSII cannula insertion contributes to the development of scar

tissue and may result in eventual loss of infusion sites.[24,25] An ideal CSII cannula will provide rapid on/off insulin pharmacokinetics (PK) and pharmacodynamics (PD) and consistent/precise dose to dose insulin PK-PD for an extended period of time (> 3 days). The clinical use of a CSII cannula with rapid on-off PK/PD and low PK variability has great potential to improve BG control, decrease the risk for hypoglycemia, improve patient compliance and decrease costs.[8,26,27] The optimized CSII cannula will also enhance the safety and performance of a closed-loop AP system, perhaps with a CGM and CSII cannula combined into one device capable of a 7+ day wear-time.[9]

2.2.5 TREATMENT ISSUES

This study will compare the safety and efficacy of the Capillary Biomedical, Inc. investigational Achilles infusion set to a commonly used commercial control Teflon infusion set (Medtronic Silhouette) in adult T1DM participants during two wear periods for up to 7 days in each period. Traditional metrics of safety, reliability, insulin PK/PD and glycemic control will be compared using a randomized cross-over study design, with each study participant used as their own control. Infusion set functionality, safety, and patient tolerance will be evaluated. The study design is similar to study methods that have been used in the evaluation of other CSII sets.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 POTENTIAL RISKS

A list of known disease, treatment, CSII sets, glucose pump and CGM product risks and potential risks are listed below. A list of anticipated adverse events and study definitions can be found in Section 8.3 of this protocol. There may be other risks that are unknown at this time and new risks that may be identified during the study.

Fingerstick

- Fingerstick BG tests may produce pain and/or bruising at the test site.

Diabetes Disease Risks

- Hypoglycemia and associated symptoms such as sweating, trembling, difficulty thinking and dizziness
- Hyperglycemia
- Diabetic ketoacidosis
- Coma
- Death

Insulin pump Use/Therapy

- Slight bruising at the site of insertion (common)
- Slight discomfort at the time of insertion of the insulin delivery cannula (common)
- Bleeding at insertion site (rare)

- Clinically significant infection or inflammation at the site of insertion (very rare), due to the extended cannula wear time this risk might be slightly higher but is considered to occur only rarely.
- Allergy to insulin (very rare)

Note: Participants will be instructed to regularly check the insertion site for any skin reactions. Skin reactions shall be noted in the provided diary and the study team shall be contacted via the helpline.

Commercial CSII Catheter Insertion Site Reactions

- Reddening
- Induration
- Purulence
- Itching
- Other non-specified skin irritation

Venipuncture and IV catheter insertion

- Localized infection – an infection in the tissue around the site
- Phlebitis – inflammation of the wall of the vein
- Hematoma – an accumulation of blood within the tissues that clots to form a solid swelling
- Fatigue caused by transient anemia due to frequent blood draws (insulin and glucose concentration determination)
- Thrombus formation and necessary insertion of a new IV catheter

Continuous Glucose Monitoring Risks

- Trivial discomfort at the time of insertion of CGM (common)
- Slight bruising at the site of insertion (unlikely)
- Bleeding at insertion site (rare)
- Infection at the site of insertion (rare)

Humalog (insulin lispro injection, USP [rDNA origin]) for injection (ID: 3273563)

- Allergy
- Anaphylaxis
- Antibody Production
- Hypokalemia
- Lipodystrophy
- Peripheral Edema
- Renal or Hepatic Impairment
- Weight gain

Glucose Clamp Related Risks

Risks of glucose clamp testing are similar to those during routine therapy and include periods of hypoglycemia requiring BG adjustments. Since participant BG levels will be monitored constantly during the glucose clamp study period, it is not anticipated that participants will experience any further risks as compared to routine insulin pump use and monitoring.

Participants enrolled in this study are adults who have had type 1 diabetes for at least 12 months and at least 6 months of experience with insulin pump therapy. These criteria were set to minimize risk. Additionally, screening assessments will be applied to exclude patients with anemia or known cardiovascular disease who may be at greater risk of procedure-induced anemia or whose hypoglycemia symptoms may be masked by concomitant medication. (See section 5 for inclusion and exclusion criteria.)

Potential risks associated with Achilles infusion set use and/or extended wear include but are not limited to the following:

Infusion Site Reactions

- Localized pain
- Bleeding
- Bruising
- Induration
- Infection
- Itching/ Pruritus
- Purulence
- Reddening (erythema)
- Swelling
- Other
- Non-specified irritation

Infusion Set Issues

- Infusion Set Failure
- Infusion Pump Failure
- Infusion pump dosing error

Achilles Device Related Risks

- Cannula Kinking
- Insulin leak from site
- Insulin leak from set or tubing
- Adhesive failure
- Cannula dislodgement

- Cannula insertion failure (not all holes below epidermis)
- Incomplete tubing prime
- Incomplete cannula prime
- Air Bubbles in tubing
- Defective venting in insulin pump / reservoir / infusion set connection

A list of anticipated adverse events (AAEs) and study specific definitions can be found in Cap Bio Study 150 -004 Feasibility Study Anticipated Adverse Event Definition List, V2. 060619 (Protocol Attachment A). There may be other risks that are unknown at this time and new risks that may be identified during the study.

2.3.2 KNOWN POTENTIAL BENEFITS

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

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

Furthermore, the study adds knowledge to recommendations regarding the timing of infusion set changes in insulin pump therapy and potentially reduced injection site reactions.

2.3.3 RISK BENEFIT ANALYSIS

This study includes T1DM participants who undergo routine diabetes treatment and glucose control methodology. A standardized study protocol, case report forms, study and investigational device use training will be provided to all study investigators/staff and study participants prior to any study related intervention or testing.

The study population consists of adult volunteer participants who have been diagnosed with T1DM, and have used an insulin pump for at least 6 months for basal and bolus insulin therapy to control their blood glucose. T1DM diagnosis will be confirmed at screening by c-peptide lab test.
Only insulin pump users with at least 6 months of experience with pump therapy will be enrolled to minimize the risk of pump use errors. Each potential study participant will be required to submit a minimum of 14 days of pump data to confirm pump use compliance. Patients who routinely wear their infusion set for > 4.5 days will be excluded from participation to ensure a homogenous patient population of participants who adhere to infusion set labeling restrictions. Screening including physical exam, ECG and laboratory testing will rule out patients with anemia or known cardiovascular disease who may be at greater risk of procedure-induced anemia or whose hypoglycemia symptoms may be masked by concomitant medication.

The primary risks associated with extended wear of the Achilles infusion set are increased risk of hyperglycemic or hypoglycemic episodes and/or infusion site irritation or infection. To ensure patient safety while using the newly developed infusion sets, patients are required to wear a CGM sensor throughout the study. Only patients with at least 3 months of CGM experience will be recruited. The personal CGM should be set with alarm systems engaged throughout study duration. Study staff will be able to monitor each patient's interstitial glucose remotely and will be notified via text in case of alarm. Participants will be instructed to contact their study site for any issues.

Commercial subcutaneous insulin infusion sets have a known failure rate of approximately 15 - 25% prior to their labelled 3 day (72 hour) wear duration. Therefore, T1DM patients are accustomed to frequent change outs with commercial infusion sets. In response to these known issues, the Capillary Biomedical Achilles infusion set incorporates a kink-resistant coil-reinforced soft polymer cannula. This cannula contains one distal and three proximal holes to ensure redundancy and extended wear-time of up to 7 days.

Failure of the investigational Achilles infusion set may occur during the 7 day extended wear period. However, if Achilles infusion set failure occurs at any time during the home wear period, the participant will simply be instructed to change out the investigational device for their standard commercially available set to maintain CSII therapy. This is the same risk associated with a use of commercially available infusion sets.

CSII set infusion site irritation and infection are familiar risks to insulin pump users. The investigational Achilles infusion set will be manually inserted and secured (taped) to an appropriately selected body location by a trained study staff member. Participants will be observed at the study center for 3 hours to ensure initial Achilles infusion set function prior to clinic discharge and start of home-use period. Study staff may attempt infusion set insertion three times. If insertion is not successful after 3 attempts, the Achilles infusion set is considered failed for this study participant.

Study participants will be instructed to check the infusion site for any skin abnormalities on a daily basis. All findings of skin irritation/infection (including tape reactions or cannula dislodgement) will be carefully monitored and recorded in a participant diary. If there is evidence of an infection at the infusion site, participants will be instructed to remove the infusion set and insert a fresh insulin infusion set as per their clinical routine. The Achilles infusion set will be placed in a provided container and biohazard bag. Participants are instructed to photograph the inflamed infusion site and contact the study staff via the provided study hotline.

As per routine pump therapy, participants will be instructed to closely monitor their blood glucose levels during the home wear period using standardized methods including SMBG, CGM, patient diaries, etc. Risks associated with extended Achilles infusion set/cannula use will be carefully monitored by the participant and study team, and documented daily in a patient diary. The insertion sites for both the Achilles and comparator set will be visually inspected and photographed pre- and post- infusion set

insertion. Emergency contact information will be provided in the case of Achilles device issues (site infection, infusion set failure, or need for cannula replacement). Any new risks identified during the study period will be promptly communicated to the investigational sites.

Alternate treatment with a commercial infusion set is available to study participants at any point during the feasibility evaluation and is not considered to increase participant risk. All other therapy will be conducted per standard of care for T1DM patients.

Risk Benefit Statement

Insulin infusion sets fail early and fail often. Research from Stanford University found that the majority of infusion set failures are due to cannula kinking or a clogged insulin port (see Table 3). This high failure rate prevents wider adoption of insulin pump therapy that could improve current patient outcomes and expand pump access to users still depending on multiple daily manual injections.

Table 4: 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 users still depending on multiple daily manual injections.

Recent data (discussed below) indicate that this 65% failure rate at seven days likely overstates the actual failure rate likely to occur when using the Silhouette infusion set for up to seven days. In the Patel study, out of eighty possible seven-day wear periods in the twenty study participants studied, infusion set failure was attributed to non-correctable hyperglycemia in only 30% of the wear periods (regardless of infusion set type). Other modes of failure were noted to account for the remaining failure events (infusion site erythema, infection, infusion site pain, accidental removal, adhesive failure). Thus, one-half of the infusion sets that did not perform through seven days were removed for reasons other than hyperglycemia.

15% of Teflon sets (Medtronic QuickSet) used in the Patel study were removed due to kinking upon insertion, which was diagnosed within the first few hours of use by the development of uncorrectable hyperglycemia or a pump occlusion alarm. This suggests that only about 23% of sets in the study (30% of steel infusion sets and 15% of Teflon infusion sets) failed due to uncorrectable hyperglycemia occurring after the first few hours of wear time. No cases of ketosis were reported in the study, meaning that study participants were able to detect and attempt to correct hyperglycemia before the

development of more serious metabolic derangement. It should be noted that the paper was published in 2014, well before the introduction of more sophisticated and accurate CGM systems that are now in use.

Recent data presented in February 2020 in Madrid by Medtronic indicated a 49% survival rate at seven days for the QuickSet (as compared to 32% in the Patel study), again suggesting that the expected failure rate in the control arm of the proposed study is not likely to be as high as that observed in the Patel study.

Therefore, the risk associated with infusion failure in the control arm with extended use for up to seven days is not considered to be unreasonable or detrimental to the study participants. The risk will be appropriately managed with a combination of modern real time CGM, close supervision by study site personnel, and appropriate education of study participants.

Results from pre-clinical animal and bench studies of the Capillary Biomedical infusion set design have shown a lower rate of cannula kinking (0% vs 57% in an equivalent commercial infusion set, $p<0.001$) and improved infusion set functionality for extended use periods beyond 3 days. These pre-clinical data further demonstrate that kinking is much less likely using the Silhouette set as compared to the QuickSet in humans. This finding suggests that early failure with the Silhoutte should be much lower than that observed in the Patel study. This finding in swine mirrors anecdotal reports from clinical practice and again suggests that the failure rate quoted in the Patel study overstate the expected outcome in the control arm of the proposed study, correspondingly reducing overall risks to participants.

This study is designed to evaluate if similar results can be reproduced in human participants using routine insulin pump therapy for two extended use (up to 7 days) use wear periods of the Achilles infusion set. Participants will frequently monitor their blood glucose levels to ensure adequate glycemic control. Infusion set change out for any reason will be performed per standard therapy with no additional risk to the study participant or ongoing therapy.

3 OBJECTIVES

3.1 PRIMARY OBJECTIVE

To assess the reliability of delivery using the investigational Achilles infusion set by evaluating the rate of decline of the glucose lowering effect of insulin from DOI through day 7 (0, 3, 5, and 7 days post insertion) compared to the commercially available control. .

3.2 SECONDARY OBJECTIVES

1. To assess other pharmacodynamics (PD) parameters of insulin within and across treatments following subcutaneous delivery using Achilles vs Teflon control set on DOI (day 0) and days 3, 5, and 7 post insertion

2. To assess pharmacokinetic (PK) parameters within and across treatments following subcutaneous insulin delivery using Achilles vs Teflon control set on DOI and days 3, 5 and 7 post insertion.

3. To assess continuous glucose monitoring (CGM) data, comparing data within and across treatments.

4. To assess performance of investigational infusion set on DOI (day 0) through +7 (8th calendar day of wear) for each treatment

3.3 SAFETY OBJECTIVES

To assess safety and tolerability of investigational infusion set on DOI through day +7 post insertion (8th calendar day of wear) for each treatment as measured by infusion set failure.

4 STUDY DESIGN

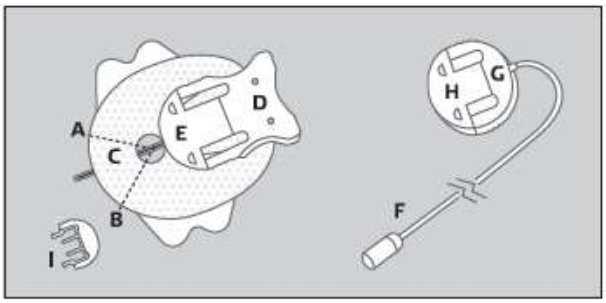
4.1 OVERALL DESIGN

This is an open, single-center, 2-way randomized, cross-over trial investigating the survivability, consistency, efficacy, and safety of an extended wear time investigational insulin infusion set (CapBio Achilles). This is achieved by measuring PK and PD profiles of a bolus of rapid acting insulin on 4 separate days of CSII set wear time during 2 separate wear periods in up to 30 adult patients with T1DM.

4.1.2 ACHILLES INFUSION SET DEVICE DESCRIPTION

The Achilles infusion set is a sterile, non-pyrogenic, single use device for continuous subcutaneous insulin infusion (CSII). Achilles infusion sets are designed to be used with commercially available infusion pumps (e.g., Medtronic MiniMed). The use of the Achilles infusion set is identical to the commercially available MiniMed Silhouette control device (see reference document 710-1021-00 Achilles infusion set, Instructions For Clinical Use). The investigational Achilles infusion set differs from the commercial Silhouette device only in the materials (coil-reinforced soft polymer vs. Teflon) and construction (three side ports vs. single distal port) of the indwelling cannula.

Each infusion set has two basic components: the infusion set body with an indwelling cannula and a tubing set for connection to the infusion pump reservoir. The Achilles infusion set body is provided individually packaged. The infusion set body is then connected to the tubing set from a commercially available infusion set with the proprietary pump reservoir connector (e.g., Medtronic Paradigm) for use with specific infusion pumps.



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C. Adhesive tape
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E. Cannula housing
F. Tubing
G. Connector needle
H. Circular protective cap
I. Disconnect cover

Figure 2: Achilles Infusion Set

4.1.2 INDICATION/INTENDED USE

The Achilles infusion set is intended for the subcutaneous infusion of medication, including insulin, from an external infusion pump.

4.1.3 CAUTIONS, WARNINGS AND PRECAUTIONS

CAUTION

Investigational device. Limited by United States law to investigational use.

WARNINGS

The Achilles infusion set is only sterile and non-pyrogenic if the packaging is unopened and undamaged. Do not use it if the packaging is already opened or is damaged.

Go through instructions for use carefully before inserting Achilles, as failure to follow instructions may result in pain or injury.

Inaccurate medication delivery, infection and/or site irritation may result from improper insertion and maintenance of infusion site.

When using Achilles for the first time, do so in the presence of a healthcare provider.

Achilles is a single-use item, which must be disposed of after usage. Do not clean or re-sterilize.

Be sure that the needle guard is removed before insertion.

People with small or large amounts of subcutaneous fat should choose the insertion angle carefully, as the cannula could be placed in underlying muscle or dermal layer and thus reduce or block medication delivery. Normal insertion angle is between 30 - 45°. Consult your healthcare provider concerning this matter.

Do not leave air in the infusion set. Make sure to fill Achilles completely.

Do not put disinfectants, perfumes, deodorants or other products containing alcohol or disinfectants in contact with the tubing connector and the tubing, as these may affect the integrity of the infusion set.

Replace the infusion set if the adhesive tape becomes loose.

Check the infusion set frequently to ensure that the soft cannula remains firmly in place. Replace if it is not secured. Since the cannula is soft, it will not cause any pain if the soft cannula becomes fully or partially dislodged from the skin, and this may take place without notice. The soft cannula must always be completely inserted to receive the full amount of medication.

Replace the infusion set per your healthcare provider's instructions.

If the infusion site becomes inflamed, replace the set and use a new site until the first site has healed.

Do not re-insert the introducer needle into the infusion set. Re-insertion could cause tearing of the soft cannula, which would result in unpredictable medication flow.

Never prime the infusion set or attempt to free a clogged tubing while the set is inserted. You may accidentally inject too much medication.

Use aseptic techniques when temporarily disconnecting Achilles, and seal the cannula housing with the cover provided. Consult with the healthcare provider on how to compensate for missed medication when disconnected.

Protect Achilles from direct sunlight. Store at room temperature.

Reuse of the infusion set may cause infection, site irritation, or damage to the cannula/needle. A damaged cannula/needle may lead to inaccurate medication delivery.

When infusing insulin, carefully monitor BG levels when disconnected and after reconnecting.

When infusing insulin, and BG level becomes unexplainably high, or occlusion alarm occurs, check for clogs and leaks. If in doubt, change the infusion set since the soft cannula could be dislodged, crimped or partially clogged. Discuss a plan for rapid replacement of insulin with the healthcare provider should any of these problems arise. Test BG level to make sure the problem is corrected.

When infusing insulin, check the BG level 1-2 hours after introducing Achilles, check the infusion site several times a day, and measure your BG regularly. When infusing insulin, do not change the infusion set just prior to bedtime, unless BG can be checked 1-2 hours after insertion

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This study is designed as a cross-over study to allow each participant to serve as their own control in effort to address intra-participant variability associated with insulin absorption, glucose lowering effect and cannula tolerability. This study will enroll up to 30 CSII-experienced adults with T1DM. An active control of insulin delivery using a commercialized CSII set will be used since administration of a placebo is infeasible. To minimize bias of a sequence effect, the sequence of treatment assignment will be randomized. Furthermore, a washout period that is equal to a minimum of five half-lives of rapid acting insulin will be required in order to eliminate any treatment effect between treatment periods and to allow the study participants to recover from blood loss associated with clamp procedures.

4.3 JUSTIFICATION FOR DOSE

A bolus of commercial U-100 insulin lispro (0.15 units/kg) will be infused through an investigational or commercial infusion set into the SC tissue of the abdomen at time zero (t0 on DOI and on Days 3,5 and 7) of each glucose clamp PK/PD study using a Medtronic pump. The concentration of BG will be maintained approximately in the 95±15 mg/dL range using an IV infusion of 20% dextrose and/or insulin infusion.. The IV dose may range from 0.1 to 3.0 units/h depending on the patient's regular basal rate.

This insulin lispro bolus dose (0.15 units/kg) is slightly higher than a typical dose used to cover an average sized meal for a T1DM patient with an average insulin/carbohydrate ratio

(0.15 units/kg x 70 kg = 10.5 units). The majority of the published PK/PD studies utilized a 0.15 unit/kg bolus dose, some used a 0.20 units/kg bolus dose, and a few studies used a 0.10 or 0.12 unit/kg dose.

Insulin lispro will be infused through the same investigational or commercial insulin infusion set after each glucose clamp (or until CSII failure) using a Medtronic insulin pump and a basal/bolus pattern of delivery. The basal infusion rate, meal bolus dose and correction dose will be adjusted by each study patient according to their routine clinical methods [SMBG glucose measurements, CGM glucose measurement (if available), insulin to carbohydrate ratio, meal size and meal composition]. Study participants requiring a large daily insulin dose may require a change out of their pump reservoir with fresh insulin as needed during each treatment period.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in Section 1.3 and Figure 1.

5 STUDY POPULATION

5.1 INFORMED CONSENT

An informed consent, written in accordance with the Declaration of Helsinki will be obtained from each participant before commencing any trial-related activities. The person/physician responsible for recruitment will explain the nature, purpose and potential risks of the study and will provide the participant with a copy of the signed informed consent.

5.2 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Participants are 18 – 70 years of age inclusive
2. Participant is in generally good health, as determined by the investigator
3. Participant is willing and able to individually complete written informed consent and agrees to comply with all study related testing and examinations
4. Participant must be geographically stable (e.g., expects to be available and capable of returning for all study specified test and examinations) during the study period
5. Participant has been diagnosed with T1DM for at least 12 months
6. C-peptide <0.6 nmol/L at screening
7. Participant has been using insulin pump therapy for at least 6 months and is currently using a Medtronic MiniMed pump, model series 530 or higher. Use of 670G in auto mode is acceptable.
8. Participant can provide a minimum of 14 days of insulin pump data to demonstrate pump use compliance

9. Participant is willing to perform frequent (4 times per day or more) self-monitoring of blood glucose (SMBG), including before meals and before bed, and using a meter and test strips provided by the sponsor during the two weeks of active treatment. This includes participants who are currently using real-time continuous glucose monitoring and may continue to do so, but must also collect SMBG values as instructed.
10. Participant is willing to perform serum ketone measurements whenever the blood glucose is determined to be greater than 250 mg/dL after extended fasting (e.g. overnight or more than five hours after a meal) using a ketone meter and strips provided by the sponsor
11. Participant has BMI in the range 20 – 35 kg/m^2 inclusive
12. Participant has experience infusing a rapid-acting insulin analog for at least 6 months
13. Participant has been using or is willing to use CGM (reading data available for at least 80% of time for a week of data collection during the screening period). Participants already using Dexcom G6 real time CGM may continue to use their own CGM unit; participants not using the G6 will be provided with a G6 monitor. All participants will be provided with CGM disposables for use during the treatment period.
14. Participant has ability to understand and comply with protocol procedures and to provide informed consent
15. HbA1c ≤8.5%
16. Stable body weight in the 3 months prior to enrollment (change in body weight <5%)

5.3 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1) Participants whose average total daily insulin dose exceeds 85 units/day (i.e. typically change insulin reservoirs more often than every 4 days on average)
2) Participants who routinely change their commercial insulin infusion sets on average less often than every 4.5 days[1]
3) Female participant is pregnant or nursing[2]
4) Participant has abnormal skin at intended device infusion sites (existing infection, inflammation, burns, or other extensive scarring)
5) Participant has hemoglobin <12.0 g/dL or potassium < 3.5 mEq/L at screening

[1] This will be determined during screening by evaluating the data downloaded from the patient's Medtronic pump. The pump data includes date and time of "cannula prime" events which can be used as surrogate for infusion set change time.

[2] Documented negative pregnancy test results for female participants required unless participant is menopausal without any spontaneous menstrual cycles for >12 months or key organs have been removed.

6) Participant has documented history in last 6 months of severe hypoglycemia associated with cognitive dysfunction sufficiently severe to require third party intervention or a history of impaired awareness of hypoglycemia.
7) Participant has a history of diabetic ketoacidosis in the last 6 months
8) Participant has known cardiovascular disease considered to be clinically relevant by the investigator
9) Participant has known arrhythmias considered to be clinically relevant by the investigator
10) Participant has known history of:
    a) Cushing's Disease,
    b) pancreatic islet cell tumor, or
    c) insulinoma
11) Participant has:
    a) Lipodystrophy,
    b) extensive lipohypertrophy, as assessed by the investigator
12) Participant is undergoing current treatment with:
    a) Systemic oral or intravenous corticosteroids,
    b) monoamine oxidase (MAO) inhibitors,
    c) non-selective systemic beta-blockers,
    d) growth hormone,
    e) thyroid hormones, unless use has been stable during the past 3 months
    f) SGLT2 inhibitors
13) Participant has significant history of any of the following, that in the opinion of the investigator would compromise the participant's safety or successful study participation:
    a) Alcoholism,
    b) drug abuse
14) Significant acute or chronic illness, that in the investigator's opinion, might interfere with participant safety or integrity of study results
15) Planned operation, MRI or CT which require removal of infusion set or CGM sensor during wear periods
16) Current treatment with systemic (oral or IV) corticosteroids, monoamine oxidase (MAO) inhibitors, non-selective beta-blockers, growth hormone, herbal products that, in the opinion of the investigator, may alter insulin sensitivity or confer undue risk to the participant's participation in the study or non-routine vitamins. Furthermore, thyroid hormones are not allowed unless the use of these has been stable during the past 3 months.
17) Current participation in another clinical drug or device study
18) Inability of the participant to comply with all study procedures or to understand the participant instructions

5.4 STUDY VISIT EXCLUSION CRITERIA

These exclusion criteria should be checked in the evening before each clamp procedure to ensure compliance with study eligibility criteria.

1. Strenuous exercise within the last 24 hours prior to dosing
2. Any medical condition which, in the opinion of the Investigator could interfere with PK and/or glucose metabolism

5.5 LIFESTYLE CONSIDERATIONS

During this study, participants are asked to:

- Refrain from use of analgesics 12 hours prior to pain assessment
- Abstain from alcohol for 24 hours before the start of each clamp
- Refrain from strenuous exercise 24 hours before each clamp
- Refrain from eating a high-carb meal (e.g. Pizza) before admission to the study center
- Keep a diabetes diary provided by the study staff
- Wear a CGM during each 7 day study period provided by the study staff (Dexcom G6®)

5.6 SCREEN FAILURES

Patients who fail screening due to hemoglobin <12.0 g/dL and potassium < 3.5 mq/L eligibility criteria may be rescreened 1 time up to 2 weeks later.

The site may rescreen one time for A1C >8.5% and/or C-peptide. ≥0.6 nmol/L up to 2 weeks after the participant screen failure.

5.7 STRATEGIES FOR RECRUITMENT AND RETENTION

Study participants will be recruited from existing T1DM patient populations already under care for their disease at the study center and via referrals from other diabetes treatment clinics in surrounding areas.

Patients who have had experience with frequent CSII set change outs or who desire to contribute to the evaluation of an extended CSII set will be given the opportunity to participate in the Achilles extended wear feasibility study. This study has been designed as a short (< 30 day) period trial and should not interfere with patient's usual routine, work or social life. Clinical visits and study requirements have been minimized so as to not interfere with daily activities.

Recruitment materials may include written, broadcast and/or internet advertising to facilitate broad patient participation. All recruitment materials shall be submitted to the IRB for review prior to use.

Participants will receive a study stipend for study participation and will be prorated based upon the number of clamps they complete.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

6.1.1.1 POINT OF ENROLLMENT

Potential patients will be screened for study participation based on the eligibility criteria given in Section 5.1 above. After completing written informed consent, eligible participants shall be assigned a unique

study identifier. Eligible participants will be considered "enrolled" once they signed the informed consent form.

6.1.1.2 SCREENING AND BASELINE (DAY -21 TO DAY -1, VISIT 0)

Participants will be screened and tested to verify study eligibility criteria including a physical exam, complete medical history and laboratory testing. Female participants of child-bearing age, who do not have a documented history of menopause (defined as at least 12 months without menses and/or removal of key organs) must undergo a urine pregnancy test within 7 days of the planned intervention date. All participants must also undergo a urine drug/alcohol screen test, complete blood and metabolic panels within the required screening period (Table 5).

- Patients who fail screening due to hemoglobin <12.0 g/dL and potassium <3.5 mq/L eligibility criteria may be rescreened for study eligibility 1 time up to 2 weeks later.
- Patients who fail the drug/alcohol screening test may be rescreened for study eligibility one (1) time up to 2 weeks later.

If participants are not currently using and/or are not familiar with the Dexcom G6® CGM sensor, study staff will insert the study sensor during the screening visit and are asked to familiarize themselves with the sensor for 7 days. After one week, CGM data will be downloaded and assessed. If CGM data shows readings for approximately 80% of sensor wear time, the participant may be enrolled in the study. If readings are less than 80%, the participant will be given another week of training. If after the second training period, the threshold of 80% is still not met, the participant is not eligible to participate in the trial.

Participants will be provided with diabetes diaries and a bag of material (see 6.1.1.8) for times spent at home in between study visits to the CRU. Participants will be reminded to fast 12 hours prior to Visit 1 and to avoid a high-carb dinner (e.g. pizza). They are furthermore instructed to refrain from strenuous exercise and alcohol during the 24 hours preceding Visit 1.

Table 5: Screening and Baseline Required Exams

Requirement	Comments
Inclusion criteria	Ensure patients meets all of the inclusion and none of the exclusion criteria
Informed consent	Written consent required by participant
Demographics	Age, gender, race, ethnicity
Medical history	All co-morbidities, prior interventions, Indication for Treatment
Urine Pregnancy test	Female participants of child-bearing potential who are not documented post-menopausal or have undergone extirpation of key organs
Urine Drug/Alcohol Screening	Participants who test positive for drug/alcohol at screening are excluded from study participation. Participants may retest one (1) time within 2 weeks of original test date.
Physical exam	Height, Weight, BMI
Vital Signs	BP, Temperature, Pulse, Respiratory Rate

Concomitant Medications	All prescription and OTC medication and supplement use
CBC	Hgb, HCT, WBC , Differential, Platelet count
C-Peptide	Participants who do not have T1DM as defined in eligibility criteria are excluded
HbA1C	Participants with Hb1AC>8.5% are excluded from study
Basic Metabolic Panel	Sodium, Potassium, Bi-carbonate (also known as carbon dioxide, or CO2), Chloride, BUN, Serum Creatinine *Potassium <3.5 mg/L are excluded
ECG	12 lead ECG required
Participant Training	Insertion site visual inspection, Achilles infusion set change-out, and device return instructions
Study CGM	Insertion and training as needed
Personal CGM	Optional use; if used record Model/Serial number

6.1.1.3 RANDOMIZATION

Participants will be randomized at Visit 1 1:1 to either undergo glucose clamp testing with the Achilles investigational cannula or commercially available control CSII set. If participant is randomized to Achilles cannula in *Treatment Period 1*, they will undergo *Treatment Period 2* with the Teflon control and vice versa. This allows the participant to act as their own control and minimizes user bias. (See section 1.2 for schema.)

After an overnight stay and glucose stabilization, glucose clamp PK/PD experiments will be performed on a Friday, Monday, Wednesday, and Friday schedule, followed by a 2±1 week wash-out period, followed by a second week of glucose clamp PK/PD experiments on a Friday, Monday, Wednesday, and Friday schedule. Alternate days of the week scheduling maybe employed as needed to meet participant and research unit flexibility.

6.1.1.4 OVERNIGHT STABILIZATION

Participants arrive at the clinical site the evening prior to clamp experiment study visits. Site may provide dinner. Participant eligibility will be rechecked (Section 5.4) and those participants eligible to participate will stay onsite overnight. Two intravenous (IV) catheters will be inserted into a peripheral vein, one in each hand/arm: one for blood sample acquisition and one for the infusion of dextrose/insulin. To target a glucose level around 85-115 mg/dL the following morning, participants may be administered insulin at the investigator's discretion by IV infusion using U100 insulin dissolved in saline. Once the IV insulin has been initiated, the participant's insulin pump will be set at a basal rate of 0.1 U/h overnight and throughout the clamp procedure the next day. The concentration of plasma glucose will be determined using a reference analyzer (YSI 2300 Plus) and also by glucose meter/test strips per investigator's discretion. If BG is low, IV infusion of dextrose may be necessary.

A commercial CGM (Dexcom G6) will be inserted into the SC tissue of each study participant using aseptic technique to record the interstitial fluid glucose concentration. The CGM device will be removed by study site personnel at the final clamp day (or sooner if cannula failure has occurred prior to Day 7) during each of the 2 treatment periods.

Food will be withheld (NPO except for water and glucose tablets as needed) for 12 hours prior to and during each glucose clamp experiment. Clamp will take place the following morning.

6.1.1.5 VISIT 1 (FRIDAY)

In the morning, a new infusion set (experimental or control) will be inserted by study personnel, the infusion site will be photographed, and the glucose clamp procedure will be initiated.

The hand/arm used for blood sample acquisition will be gently warmed using a heating pad to produce "arterialized" blood samples. Failure to sample blood from an IV catheter may require insertion of one or more additional IV catheters to complete each 5-hour clamp study.

The reservoir of the insulin pump will be filled with insulin lispro. The reservoir of the participant's pump will be removed and replaced with the insulin prepared by the study personnel. The 23" insulin tubing will be connected to the pump and primed. The infusion set plastic hub will be over-taped with Simpatch kinesthesiology tape to further ensure that cannula dislodgement will be unlikely during the treatment period. Areas of lipohypertrophy/lipodystrophy and areas of recent CSII insertion will be avoided. The participant's own commercial infusion set will be removed, and a commercial/investigational cannula will be inserted at an angle of approximately 30 degrees into the subcutaneous tissue of the abdomen using aseptic technique, approximately 3 cm lateral to the midline and, following a cannula prime procedure. The pump immediately started on a constant basal rate of 0.1 U/h which will be maintained throughout the clamp. There should be a suitable insertion site on the contralateral abdomen at approximately the same rostral/caudal level to be used during the second treatment period.

The run-in period should last no longer than 3.5 hours, if BG is not stable after this time, the participant cannot continue in the study and is sent home. He/she may return another day. Once the BG level of approximately 95±15 mg/dL has been maintained for at least 40 minutes (measured every 10 minutes), the IV insulin (dextrose) is discontinued, and the baseline will be recorded for 20 min (blood draw every 5 min). 20 minutes after discontinuation of IV insulin, a SC bolus of lispro insulin (0.15 U/kg) is administered via the pump (t0). Baseline plasma glucose level is defined as mean plasma glucose at time points t-20, t-15, t-10, t-5, and t0. After t0, blood samples for PK analysis are drawn every 3 minutes for 15 min (Clamp Part I), every 5 minutes for 40 minutes (Clamp Part II), every 10 min for 30 min (Clamp Part III), and every 15 minutes for 45 minutes. In the Final Phase, blood is drawn every half an hour until clamp termination at 300 minutes (see Table 6). Up to 15 blood samples will be obtained overnight prior to the day of the glucose clamp procedure, and 8 additional blood samples will be obtained during stabilization on the morning of the clamp procedure prior to administration of the insulin bolus. Blood samples for immediate glucose determination will be drawn every 5 minutes for 60 minutes following insulin bolus, and then every 10 minutes for the remainder of the clamping period at 300 minutes post-bolus. Blood samples will be acquired using aseptic technique and double stopcock technique to minimize blood loss. A maximum of 66 samples (24 x 1.5 mL [for BG and insulin] + 6 x 1.0 mL [for PK only] + 36 x 0.5 mL for BG only = 62.0 mL] will be drawn during the stabilization period and the clamp procedure, resulting in a total blood loss of 248 mL during 4 clamps over each week. Combining both

clamping weeks, this represents less than 1 unit of blood (=525 mL). Blood samples will be centrifuged to plasma, plasma glucose concentration measured, and plasma frozen in 2 aliquots for future measurement of insulin concentration. The detailed clamp sampling schedule is summarized in Table 6.

Table 6. Clamp visit sampling schedule

Phase	Approximate Clock Time (hh:mm)	Nominal Time (min)	No. of samples	Volume/Sample (mL)	Total Volume (mL)
Stabilization, over night			15	0.5	7.5
Baseline Part I	7:00	-60	5	0.5	2.5
	7:10	-50		0.5	
	7:20	-40		0.5	
	7:30	-30		0.5	
	7:40	-20		0.5	
Discontinue IV insulin & Dextrose					
Baseline Part II	7:45	-15	3	1.5	4.5
	7:50	-10		1.5	
	7:55	-5		1.5	
Bolus	8:00	0	1	1.5	1.5
Clamp Part I	8:03	3	7	1	6.5
	8:05	5		0.5	
	8:06	6		1	
	8:09	9		1	
	8:10	10		0.5	
	8:12	12		1	
	8:15	15		1.5	
Clamp Part II	8:20	20	9	1.5	13.5
	8:25	25		1.5	
	8:30	30		1.5	
	8:35	35		1.5	
	8:40	40		1.5	
	8:45	45		1.5	
	8:50	50		1.5	
	8:55	55		1.5	
	9:00	60		1.5	
Clamp Part III	9:10	70	3	1.5	4.5
	9:20	80		1.5	
	9:30	90		1.5	
Clamp Part IV	9:40	100	10	0.5	8.0
	9:45	105		1	

Phase	Approximate Clock Time (hh:mm)	Nominal Time (min)	No. of samples	Volume/Sample (mL)	Total Volume (mL)
	9:50	110		0.5	
	10:00	120		1.5	
	10:10	130		0.5	
	10:15	135		1	
	10:20	140		0.5	
	10:30	150		1.5	
	10:40	160		0.5	
	10:50	170		0.5	
Final Phase	11:00	180	13	1.5	11.5
	11:10	190		0.5	
	11:20	200		0.5	
	11:30	210		1.5	
	11:40	220		0.5	
	11:50	230		0.5	
	12:00	240		1.5	
	12:10	250		0.5	
	12:20	260		0.5	
	12:30	270		1.5	
	12:40	280		0.5	
	12:50	290		0.5	
	13:00	300		1.5	
Observation at site			**66 total samples**		
				Total volume per clamp =	**62.0 mL**

During the 5-hour clamp plasma glucose concentration will be maintained at 95±15 mg/dL with IV infusion of dextrose (0.1 to 4 mg/kg/min), titrated using a computerized dosing algorithm according to frequent BG measurements. The trigger plasma glucose concentration for onset of glucose infusion will be a value that is 5 mg/dL below the mean obtained during Baseline Part II (i.e. -15, -10 and -5 minutes before bolus delivery at T=0). The dosing calculator will be used to determine the optimal glucose infusion rate (GIR) for each subsequent time period between BG measurements. If insulin is infused, glucose infusion must be stopped and vice versa. The dextrose infusion rate will be increased to match insulin lispro's glucose lowering effect over time until the glucose lowering effect of the insulin lispro bolus reaches baseline (i.e. glucose infusion rate of 0) or 5 hours after bolus administration.

In the case of persistent hyperglycemia (BG>250 mg/dL) over 30 minutes without dextrose infusion, the clamp will be terminated early. A correction bolus will be given via the pump and the BG measured to determine whether BG was lowered by 50 mg/dL within 1 hour. If this is not the case, the CSII catheter is

considered failed, a new fresh commercial insulin infusion set inserted and another bolus is given. Patients will stay at the CRU until they have finished their meal and their BG has dropped as assessed by two blood glucose meter measurements in the range of 90 – 200 mg/dL separated by at least 30 minutes.

The study participant will be provided with a meal at the conclusion of the clamp visit. Insulin lispro will be infused through the study investigational or commercial CSII catheter using the participant's typical basal/bolus pattern of delivery during home care between study visits. Study personnel will call the participant the same evening to ensure the participant's wellbeing.

6.1.1.6 VISITS 2, 3, AND 4

Participants arrive the prior evening for stabilization and procedures explained above in section "Visit 1" are repeated (except insertion of CSII catheters). If CGM failed, a new CGM will be inserted by trained study staff.

If the CSII catheter does not fail before day 7, the investigational/commercial CSII set will be removed upon completion of the clamp experiment on Visit 4A/Visit 4B. The site and cannula will be photographed, and the cannula inspected under a microscope. A fresh CSII catheter (as routinely used by the participant) will be inserted at a different site, the pump connected, and routine glycemic management resumed. The change-out will be documented in the appropriate source documents and CRF.

6.1.1.7 HOME CSII TREATMENT PHASE

During the home CSII treatment phase participants will use the investigational/control CSII catheter in combination with the Medtronic MiniMed insulin pump for diabetes management. Participants will follow their regular lifestyle, adjusting basal infusion rate, meal bolus doses and correction doses according to their routine clinical methods. They will use their diabetes diaries to document VAS pain score, signs/symptoms of hypoglycemia, treatment of hypoglycemia, CSII catheter issues, and overall health. BG will be measured continuously by the CGM device.

Study participants will receive detailed instructions regarding diabetes care plan, including dietary guidelines, treatment of hyperglycemia, hypoglycemia, and the management of CSII catheter failure. Participants will be instructed to monitor their blood ketone levels if their CGM or SMBG values are greater than 250 mg/dL for more than 2 hours or they develop signs/symptoms of diabetic ketoacidosis.

Table 7: Participant instruction for at home use

Patient Diary (daily)	Participant records: ▪ Hypo-/hyperglycemic episodes ▪ Insertion site assessments ▪ Insertion set failure ▪ Other device issues or complications ▪ VAS Pain Scale (daily insertion site comfort levels)
Insertion Site Assessment (daily)	Participant visually inspects and records insertion site findings (i.e. skin reaction or infection)
Dexcom G6® CGM	Records glucose values throughout study

6.1.1.8 STUDY TESTING COMPLETION

Discontinuation from the study intervention (infusion of insulin through a CSII catheter) does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. The need to discontinue clinical use of the investigational or commercial CSII catheter prior to Visit 4A/Visit 4B is expected in some study participants and is not considered an adverse event. If an unplanned change-out of either the Achilles investigational cannula or control CSII set is required during a study visit/clamp, participant's study participation in the respective treatment phase is considered completed at the time of infusion set change. If change-out occurs during *Treatment Phase 1*, the participant is asked to return for *Treatment Phase 2* after the washout period. If change-out occurs during Treatment Phase 2 the participant should return to the study site for a final study visit.

Before the study participant can be exited from the protocol, the following evaluations must be completed:

- Inspect/photograph insertion site
- Collect patient diary/photos

After completion of final evaluations, participant may be exited from the study.

6.1.1.9 ANCILLARY PRODUCTS AND ACCESSORIES

During Visit 0, Participants will be provided with diabetes diaries and a bag of material for times spent at home in between study visits to the CRU.

Contents of bag:

- Achilles infusion set change out and device return instructions
- Glucose meter (handling is explained by study staff)
- Ketone meter (handling is explained by study staff)
- Glucose strips
- Ketone strips
- Glucose tabs
- Diary

- Cap for infusion set (in case of failure)
- Ruler/Cutout to measure erythema
- Container & biohazard bag for CSII catheter (in case of failure)
- Alcohol swabs

Study sponsor shall provide the following study materials and products for study use only:

- Dexcom G6® CGM
- Fast-acting insulin (Insulin Lispro U100/Humalog)
    - *NOTE:* Participants who are using other pump insulins will be switched to lispro after screening and informed consent to participate have been completed.

6.1.9 STUDY VISIT WINDOWS

Study visits are scheduled as indicated above; however, it is recognized that study participants may not be able to return for scheduled visits at precisely the date required. Therefore, study visit windows have has been defined for each visit per Table 8 below.

Table 8: Schedule of Follow-Up Visits and Visit Windows

Visit	Visit Window
Screening/Baseline	-28 to -1 days
Wear Period	DOI to +7 days inclusive
Study Completion	8th calendar day or upon infusion set failure
Follow-up	Patients will receive follow-up phone call by staff 1 day after each period

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

Sterile study devices (Achilles infusion sets) shall be provided by the Sponsor and stored in a cool, dry, secure location at each study site. Insulin lispro shall be stored and dispensed per site requirements. Study BG and ketone monitors, test strips and study CGMs shall be stored per the labeling. All ancillary study products will be labeled and distributed to the sites to be provided to each study participant on Day of Insertion (Day 0). All study device and drug inventory must be returned to the study center or pharmacy before the participant officially exits the study.

6.2.1 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Achilles infusion sets come packaged sterile and single use only in a Tyvek pouch. Sufficient quantities of investigational infusion sets will be provided to the study center prior to study start. Replacement and/or additional units shall be provided upon site request to Sponsor.

Insulin lispro will be provided per standard packaging and labeling by the affiliated study center pharmacy. Insulin will be dispensed per the study protocol and only for the study duration to any eligible study participant.

6.2.2 PREPARATION

Achilles infusion sets shall be prepared and applied to the participant as described in reference document "*710-1021-00 Achilles infusion set, Instructions for Clinical Use*". For this 7-day study, 23" (60 cm) tubing from commercially-available MiniMed Silhouette infusion sets shall be used.

The infusion set hub shall be secured to the body with a kinesiology tape over-bandage. If the participant routinely under-bandages or over-bandages using other dressings with their normal infusion set they should continue to do so when using the Achilles infusion set.

Insulin lispro, infusion pump, BG and ketone monitors and study CGM shall be prepared per the applicable product instructions for use. IV insulin will be prepared by the investigational site pharmacy or equivalent. Insulin reservoirs are filled with insulin lispro and inserted into the participant's pump on Visit 1 or other clamp days (depending on the participant's insulin requirements, 1 reservoir may last the entire treatment period or less).

6.2.3 ACHILLES INFUSION SET DEVICE ACCOUNTABILITY

The Sponsor shall keep records to document the physical location of all investigational devices from shipment of investigational devices to the investigation sites until return or disposal. The principal investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the investigational devices, which shall include the date of device receipt, investigational device identification (batch, serial or unique study ID code), expiry date if applicable, date or date(s) of use, related participant study ID, data device was returned/removed from participant, date of return of unused or expired device inventory. Product accountability returns and/or exchanges shall be documented per Sponsor standard operating procedures and investigational product release and return procedures.

Ancillary products shall be labeled with the participant's study ID number. Records of study provided glucose and blood ketone monitors and CGM will be tracked as required above. Insulin will be dispensed per pharmacy standard operating procedures to study participants only.

6.3 MEASURES TO MINIMIZE BIAS

Participant treatment will be assigned in a randomized sequence to avoid sequence bias. A washout period of 2±1 week will be used to avoid treatment bias.

6.4 STUDY COMPLIANCE

Study compliance will be assessed during the initial participant instruction period, and by review of daily diary and Dexcom G6 app entries. The investigational device will be applied to the study participant only after the participant has demonstrated an understanding of the study instructions, change out activities, the need to complete all study test requirements as written. If the study staff become aware of participant non-compliance to protocol requirements or follow-up evaluations, multiple attempts will be made to contact the participant to ensure patient safety and protocol adherence.

Adherence to glucose test procedure will be assessed by study personnel at site. All CRFs must be completed and CGM data will serve as electronic source documentation for hyperglycemic and hypoglycemic adverse events. Additionally, inquiries documented in clinic notes will be used for source documentation of patient-reported AEs. Photographs of infusion site will serve as source documentation for infusion site reactions.

The following will be collected regularly and documented:

- Study participant's insulin pump records
- Interstitial fluid glucose data from Dexcom G6® CGM throughout each study period (assessed by study staff at each study visit)
- BG measurements per Bayer Contour NEXT device will be used by participants for SMBG data collection as mandated by protocol requirements. Data will be downloaded at each clinic visit
- Serum ketones - measured by Abbott Precision Xtra Ketone meter (in case of hyperglycemia occurring during fasting or acute illness)
- Study participant diary (Pain score, SMBG)

6.5 CONCOMITANT THERAPY

The use of concomitant medications is permitted with the exception of non-selective beta-blockers that may mask the symptoms of hypoglycemia and analgesics such as acetaminophen taken 12 hours prior to a pain assessment to minimize the risk of confounding VAS scores.

6.5.1 RESCUE MEDICINE

Standard of care rescue medicine will be allowed to treat:

- Transient hyperglycemia (insulin using commercial CSII cannula)
- Transient hypoglycemia (juice or glucose tabs or, as needed, glucagon or IV glucose)

7 DISCONTINUATION AND WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 INFUSION SET CHANGE-OUT/EARLY DROPOUT

Independent of the time point for infusion set removal/change out, study staff is to follow the SOP for Infusion Set Removal and the reason for change-out is to be documented in the applicable source document and CRF.

We anticipate several commercial and/or investigational CSII catheters to fail prior to the fourth glucose clamp experiment on day 7. Participants will be instructed to contact the research investigator by telephone (24/7) to confirm the diagnosis of a failed CSII catheter. If the CSII catheter does not fail before day 7, the investigational/commercial CSII set will be removed upon completion of the clamp experiment on Visit 4A/Visit 4B. The site and cannula will be photographed, and the cannula inspected under a microscope.

The following are objective criteria that define a CSII catheter/infusion set failure:

1. The occurrence hyperglycemia (glucose >250 mg/dL) not responsive to a pump bolus dose where response to the bolus is defined as a fall of at least 50 mg/dL in blood glucose within one hour.
2. The occurrence of hyperglycemia (glucose >250 mg/dL) after prolonged fasting (e.g. overnight or more than 5 hours following a meal), not associated with acute intercurrent illness, but with a concurrent ketone level ≥0.6 mmol/L.
3. Signs of inflammation/infection at the infusion site including pain, erythema or induration >10 mm in diameter.
4. Occurrence of an insulin pump occlusion alarm signal.

In the case that any of the above occurs during home-use, the participant is asked to call the 24/7 helpline and confirm catheter failure with the study staff. The study participant will insert a new commercial CSII catheter (as used routinely by this patient) into the subcutaneous tissue at an alternate location and connect it to the insulin pump for routine glycemic management. The failed CSII catheter will be left in place. The participant is asked to measure erythema around the catheter and photograph the site. The study participant will return to the study site as soon as practicable so the research staff can remove and observe the failed CSII catheter. Study staff is to follow the SOP for catheter removal.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request. An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Severe hyperglycemia or ketoacidosis during the study
- Adhesive allergy/intolerance developed during the study
- Any condition or change in condition compromising the safety of the participant as judged by the PI or someone in the team
- Pregnancy.
- Significant study intervention non-compliance.
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.
- Study participant unable to participate in the second series of glucose clamp experiments after 2±1 week wash-out period.
- DKA, characterized by hyperglycemia with ketosis (serum ketones elevated to >1.5 mmol/L) and metabolic acidosis with depressed serum bicarbonate level to less than 18 mmol/L and/or arterial pH less than 7.30.

The reason for participant discontinuation or withdrawal from the study will be recorded on the CRF. Participants who sign the informed consent form and are randomized but do not receive the study intervention (placement of the first CSII catheter) may be replaced. Participants who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for one scheduled visit and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within a day and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study. Instructions shall be provided to the participant on returning to the site for EOS assessments and product return, if the participant decides to withdraw from the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Multiple samples will be taken during each clamp procedure and plasma insulin levels will be analyzed using insulin assays.

8.2 SAFETY AND OTHER ASSESSMENTS

The following labs and procedures will be conducted to ensure patient safety:

- **Physical examination** (e.g., height and weight, organ systems, motor or vision assessment, or other functional abilities). If appropriate, discuss what constitutes a targeted physical examination.
- **Vital signs** (e.g., temperature, pulse, respirations, blood pressure while seated). Carefully consider which vital signs (if any) should be measured to ensure that only essential data are collected. Include any specific instructions with respect to the collection and interpretation of vital signs.

- **Biological specimen collection and laboratory evaluations**. Urine pregnancy test, CBC to exclude anemic conditions, C-Peptide tests to confirm T1 diabetes and rule out T2 diabetes, and HbA1c levels at screening. Electrocardiogram to evaluate cardiac status. Frequent BG measurements to titrate D20% IV administration rate and keep patients in euglycemia range.
- **Special assays or procedures required.** Multiple plasma samples will be frozen and stored to measure insulin levels via radioimmunoassay (RIA)
- **Counseling procedures, including any dietary or activity considerations**: Patients will be trained on study procedures and will be asked to maintain their usual diet and exercise regimens during the course of the entire study. Prior to clamp visits, however, they are asked to refrain from strenuous exercise and eating meals high in carbohydrates.
- **Assessment of study intervention adherence:** a CGM device will be applied to identify any hyperglycemia or hypoglycemia.
- **Administration of questionnaires or other instruments** will be utilized to collect pain scores (VAS) and maintain AE records (phone visit and diary during washout period). Additionally, usability questionnaires will collect patient and clinician perspective on product usability to identify sources of user error.
- **Assessment of adverse events.** Reported AEs and SAEs will be reviewed by the investigator or designee and Medical Monitor.

8.3 ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS

An Adverse Event (AE) is defined any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

Investigational device adverse events/effects shall be reported as anticipated or unanticipated per CFR 812.3, and drug reactions and/or adverse drug effects shall be reported as described in CFR 312.32. Events shall be reported to the Sponsor per protocol and to the governing IRB per IRB requirements and all applicable study regulations.

A list of anticipated (expected) adverse effects related to the study device, study intervention or testing procedures and known complications of diabetes disease, insulin use, treatments and treatment equipment have been provided in reference document 150-1004-02 Feasibility Study Anticipated Adverse Event Definitions.

8.3.2 SERIOUS ADVERSE EVENTS AND UNANTICIPATED ADVERSE DEVICE EFFECTS

A Serious Life-threatening Adverse Event or Life-threatening Suspected Adverse Reaction is defined as an adverse event/effect or suspected effect that is considered “life-threatening” that if, in the view of either the investigator or sponsor, its occurrence places the patient or participant at immediate risk of death.

Serious adverse event (SAE)

A serious adverse event or serious suspected adverse reaction - defined as an adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

death,

a life-threatening adverse event,

inpatient hospitalization or prolongation of existing hospitalization,

a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,

or a congenital anomaly/birth defect.

A suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Per federal regulations "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event.

Unexpected Adverse Event or Unexpected Suspected Adverse Reaction

An unexpected adverse event/effect is defined as an adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

Unanticipated Adverse Device Effects (UADE)

An unanticipated adverse device effect is defined as “any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants.”

For consideration of device safety and performance, an unanticipated adverse event is an event that has not been described in the investigational plan, study protocol, attachments, Instructions for Use, product labeling, or other product descriptions including those of ancillary study products.

A UADE must be directly related to the device under investigation.

The Sponsor is responsible for promptly reviewing any and all information relevant to the device or drug product and considering the impact of the all adverse event (s) on study continuation.

8.3.3 ADVERSE EVENT/EFFECT CLASSIFICATION

All adverse events shall be classified based on their relationship to the investigational device, intervention or test period; underlying disease state, pre-existing co-morbidity or concomitant therapy as described below:

Related – Anticipated AE known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.

Unrelated – Definite assessment that there is no reasonable possibility that the study intervention caused the event, and no defined temporal relationship between the study intervention and adverse event onset, or an alternate etiology has been established.

Unknown - A determination of relationship to the product, test procedure or co-morbidity cannot be established.

Not Assessable - There is insufficient data to determine a relationship to the investigational product, procedure or other condition.

8.3.4 TIME PERIOD AND FREQUENCY OF ADVERSE EVENT ASSESSMENT

Adverse event assessment and reporting shall occur continuously throughout the study. In the case of home use events, participants will be instructed to document issues in the provided Patient Diary and notify their respective study center per written instructions. Adverse events will be reviewed by a Medical Monitor as outlined in 10.1.6 – Safety Oversight.

8.3.5 ADVERSE EVENT REPORTING

A complication, adverse event (AE), serious adverse event (SAE) or Unanticipated Adverse Device effect (UADE) may become known to study personnel during study visits, participant interviews or during a study monitoring visit.

All adverse events (including UADEs and SAES) as well as local and systemic reactions shall be captured on the appropriate case report form (CRF). Data must include an event description, event start time, severity assessment, relationship to study product, resolution or event stabilization time/date.

NOTE: Co-morbidity and medical conditions present at baseline shall be considered pre-existing conditions and will not be reported as an adverse event. However, if a participant's condition deteriorates at any time during the study and requires medical intervention to resolve, this shall be captured as a study adverse event.

All adverse events and complications, regardless of relationship, severity or seriousness shall be fully documented and recorded.

8.3.6 ADVERSE EVENT REPORTING TIMEFRAMES

Adverse device or drug effects, including an unanticipated adverse device effect (UADE) or serious adverse event (SAEs) shall be reported to the Sponsor within 24 hours of knowledge of the event. All UADEs or SAEs shall be reported to the IRB either per site IRB regulations, or at a minimum, no later than 5 days after knowledge of the event.

8.3.7 REPORTING ADVERSE EVENTS TO STUDY PARTICIPANTS

Reportable events shall be reviewed and summarized in a timely manner. A report of these events shall be provided to the study investigators and shared with study participants at the investigator's discretion.

8.3.8 REPORTS OF SPECIAL INTEREST

In this study, hypoglycemia should not be reported as an adverse event unless it is designated as a Serious Adverse Event (See Section 8.3.2). Hypoglycemic events will be collected and categorized according to American Diabetes Association criteria as follows:

- Level 1: Glucose value ≤ 70 mg/dL
- Level 2: Glucose value < 54 mg/dL
- Level 3: Severe hypoglycemia associated with cognitive impairment requiring external assistance for recovery

Level 3 hypoglycemia episodes should be reported as a serious adverse event per section 8.3.2.

Hypoglycemia data will be collected from SMBG meter uploads, CGM data and participant diaries.

8.3.9 REPORTING OF PREGNANCY

Female participants who become pregnant during the intervention or testing period shall return to the investigational site for a physical exam to ensure safety. Upon potential or confirmed pregnancy, female participant shall be exited from the study and no further testing or evaluations will be made, UNLESS participant is experiencing an adverse event. If participant is experiencing an adverse event related to study intervention or testing, the AE should be reported as above in Section 8.3.5 and participant should be followed until resolution or stabilization of the event.

8.4 UNANTICIPATED PROBLEMS

This study is considered to be a low risk device evaluation. However, if an Investigator or Sponsor become aware of an issue that is "Unexpected in terms of nature, severity, or frequency, or related or possibly related to participation in the research or puts the research participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized", these events shall be reported to the Sponsor and governing IRB within 24 hours of knowledge of the event(s).

8.4.1 UNANTICIPATED ISSUE REPORTING TO IRB

See Section 8.3 above.

8.4.2 UNANTICIPATED ISSUE REPORTING TO PARTICIPANTS

See Section 8.3 above.

9 STATISTICAL CONSIDERATIONS

A formal Statistical Analysis Plan (SAP) will be completed prior to database lock and un-blinding of the study data. The SAP generally includes additional statistical analysis detail (e.g., calculation of derived variables, data exclusion rules, listings of tables, figures and listings produced, etc.).

9.1 STATISTICAL HYPOTHESES

- Null Hypothesis: There is no difference in the population mean rates of decline for the Achilles and control infusion sets, as measured by the slope (s) contrast for the $\ln(AUC_{0\text{-}300(GIR)})$ assessed over study days DOI, day 3, day 5, and day 7.
- Alternative Hypothesis: The rate of decline (slope coefficient s) for the Achilles infusion set is less that the corresponding rate for control

9.2 SAMPLE SIZE DETERMINATION

A sample size of 24 participants is sufficient to generate 90% power for a 2-tailed p=0.05 comparison of the $\ln(AUC_{0\text{-}300(GIR)})$ slope contrasts(=control minus Achilles), within this 2x2 crossover design. In addition to the usual regularity assumptions for the 2x2 crossover design (i.e. no carryover effects), this computation was based on the following assumptions:

1. The $\ln(AUC_{0\text{-}300(GIR)})$'s are normally distributed.

2. The within participant variance is 40% of the total variance.

3. The study day correlation matrix of the within-participant $\ln(AUC_{0\text{-}300(GIR)})$ assessments is AR(autoregressive model) with correlation r=0.5.

4. The within plus among participant variance for the $\ln(AUC_{0\text{-}300(GIR)})$'s is 0.21 (based on previous studies).

5. The difference in slopes (Achilles minus control) is at least 0.07.

9.3 POPULATIONS FOR ANALYSES

Intention-to-Treat (ITT) Analysis Population: all patients that meet all inclusion criteria and none of the exclusion criteria and are randomized to treatment sequence and complete at least one glucose clamp procedure will be included in the ITT population.

Safety Analysis Population: all patients who had either an investigational or control cannula implanted.

Per-Protocol (PP) Analysis Population: all patients who completed both treatment sequences with no major protocol violations.

The primary effectiveness analysis will be based on the ITT participant population. Sensitivity analyses of the primary effectiveness endpoint will be generated based on the PP population. The ITT population may contain some patients that complete the first treatment, but not the second, and vice versa. This will require the use of imputation methods for missing values, which are documented in Section 9.4.2.

The primary safety analysis will be based on the Safety population. All secondary and exploratory effectiveness analyses will use the PP population.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

As a routine evaluation of the data during analysis, consistency of the study variables to properties of statistical tests will be checked. The parameter for the primary analysis will be log-transformed, and the rest of the PK as well as PD parameters will be log-transformed as appropriate before analysis. With categorical data, exact statistical test procedures will be used to minimize test assumptions, except when Wilson Score confidence intervals can be calculated.

All data will be tested for normality using the Shapiro-Wilk test. Data that is highly skewed or contains outliers even after the log transformation will be analyzed using the rank transformation, namely analyzing the ranks of the assessments within the combined sample. The paired measurements will be analyzed with dependent *t* tests or Wilcoxon signed rank tests, as indicated. AUC data will be calculated with the trapezoidal rule for defined PK/PD time points. Post hoc analyses will be performed after confirmation of significant main effects. Unless otherwise specified, data will be reported as mean ± SD with $p<0.05$ considered statistically significant.

A data convention used in this analysis is as follows: for tabulated continuous variables, the descriptive analyses will present the mean, standard deviation, median, minimum and maximum. And for tabulated categorical variables, the number with the characteristic, the total number evaluated, the percent and the 95% Wilson Score confidence intervals will be provided.

For secondary endpoint analyses, two-tailed significance tests will be performed with significance level $p=0.05$.

For the estimation of catheter failures, we used data from the study of Patel *et al.* who investigated steel and Teflon infusion sets worn over a 7-day period.5 They reported that 42% of participants could consistently wear an infusion set for 6-7 days (58% failure) without a deterioration in glucose levels. It should be noted that their failure rate also included accidental removal of catheters, removal due to pain, and removal due to poor adhesion of catheter pad (total 32%). Since our participants will be in a more controlled setting (i.e. clinical research staff will be inserting and carefully securing the devices

using an aseptic technique), we anticipate having lower failure rates related to early catheter removal. We therefore assume a 40-50% failure rate to be a reasonable estimate of total anticipated failures and have added 6 additional participants for an anticipated total sample size of n=30. (Statistical analyses were performed using Systat version 13.)

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The $\ln(AUC_{0\text{-}300(GIR)})$ on DOI (day 0) and days 3, 5, 7, periods 1 and 2 will be calculated using the trapezoidal rule. A mixed-effects (repeated-measures) linear model with treatment and period as fixed effects and participant as a random effect will then be fit to this data. Estimates of the slopes by treatment will be generated as contrasts based on the least squares means. Treatment comparisons and confidence bounds on the difference in slopes will be presented. Details will be provided in the Statistical Analysis Plan

The natural log of each AUC mean slopes for the two treatment groups will be compared in a mixed-effects (repeated-measures) linear model with treatment and period as fixed effects and participant as a random effect.

The primary analysis will be conducted on the ITT population; the mixed-effects model accounts for missing data using a missing at random (MAR) assumption, which will be checked.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Secondary analyses will use the both ITT and PP populations for analysis.

The survival of the Achilles and control infusion sets will be compared using a discrete lifetable analysis over study days 0, 3, 5, and 7 and the discrete form of the log-rank test.

All pharmacokinetic parameters (AUCs, t_{50}, C_{max}, t_{max}, MRT for the insulin concentration by time curve, etc.) will be estimated using non-compartmental models and log-transformed before analysis. Means for the two treatment groups will be compared in a mixed-effects (repeated-measures) linear model with treatment and period as fixed effects and participant as a random effect. The mean difference between treatments (on the log-scale) will be compared with a two-sided test using significance level α=0.05. Then mean ratio and its 95% confidence interval will be calculated by inverse-transforming the mean difference and its 95% confidence interval.

All pharmacodynamic parameters (AUCs, onset time and time to return to baseline for the glucose concentration by time curve, etc.) will be estimated using non-compartmental models. Means for the two treatment groups will be compared in a mixed-effects (repeated-measures) linear model with treatment and period as fixed effects and participant as a random effect. The mean difference between treatments will be compared with a two-sided test using significance level α=0.05. Wilcoxon signed rank tests will be used if the data is significantly skewed.

9.4.4 SAFETY ANALYSES

Tolerability of infusion sets will be assessed by comparing the mean VAS scores from day of insertion through Day 7 of use with a mixed-effects (repeated-measures) linear model with treatment, period and day as fixed effects and participant as a random effect. The mean difference between treatments will be compared with a two-sided test using significance level α=0.05.

Adverse events (AEs) will be coded using CTCAE v4.0. Descriptive statistics (number of participants and per-participant incidence) for device-related AEs will be presented by System Organ Class, Preferred term, severity and treatment. Unanticipated and serious device-related AEs will be presented separately by treatment.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

The following baseline variables and demographics will be compared for the two randomization groups: age, gender, race, ethnicity, baseline HbA1c, and BMI category.

9.4.6 PLANNED INTERIM ANALYSES

An unblinded interim futility analysis may be conducted after 12 participants have completed the study. Futility is defined as a participant incidence of >5 SAEs, a failure rate of $\geq$90% on Day 5 for the investigational infusion set, or a forecasted probability of primary endpoint success at the end of the trial that is too low to justify continuing.

9.4.7 SUB-GROUP ANALYSES

N/A

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Listings of the primary and secondary endpoints will be presented by patient and by time point for each treatment

9.4.9 EXPLORATORY ANALYSES

Exploratory analyses will use the both ITT and PP populations for analysis. All pharmacokinetic parameters (AUCs, t_{50}, C_{max}, t_{max}, MRT for the insulin concentration by time curve, etc.) will be estimated using non-compartmental models and log-transformed before analysis. Means for the two treatment groups will be compared in a mixed-effects (repeated-measures) linear model with treatment, day and period as fixed effects and participant as a random effect. The mean difference between treatments (on the log-scale) will be compared with a two-sided test using significance level 0.05. Then mean ratio and its 95% confidence interval will be calculated by inverse-transforming the mean difference and its 95% confidence interval. Trends over time within treatments will be compared with two-sided tests using significance level α=0.05.

Kaplan-Meier device survival curves will be constructed for each device and then compared with a Cox regression analysis with a frailty term that accounts for the repeated-measures on participants.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

In obtaining and documenting informed consent, the investigator must comply with applicable regulatory requirements (e.g., 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56) and should adhere to ICH GCP. Prior to the beginning of the trial, the investigator should have the IRB's written approval for the protocol and the written informed consent form(s) and any other written information to be provided to the participants.

10.1.1.1 CONSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

The consent form contains all required regulatory elements.

10.1.1.2 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. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.1.3 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the Sponsor to study participants, investigator, and sponsor. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility
- Three or more participants develop DKA
- Three or more participants develop severe hypoglycemia

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, and IRB.

10.1.2 CONFIDENTIALITY AND PRIVACY

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

All research activities will be conducted in as private a setting as possible.

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

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

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Sponsor. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Sponsor 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 Sponsor.

10.1.3 FUTURE USE OF STORED SPECIMENS AND DATA

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

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage may not be possible after the study is completed.

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

10.1.4 KEY ROLES AND STUDY GOVERNANCE

Contact information of the PI and the Medical Monitor can be found in Table 9.

Table 9: Study Governance

Principal Investigator	Medical Monitor	Independent Safety Monitor
Timothy S Bailey, MD President & CEO, AMCR Institute 625 W. Citracado Pkwy, # 112 Escondido, CA 92025 Telephone: 760 466 1520 E-mail: tbailey@amcrinstitute.com	**Doug Muchmore, MD** Senior Clinical Advisor Capillary Biomedical, Inc. 2 Wrigley, Ste 100 Irvine, CA 92618 Telephone: (858) 947-8148 1. E-mail: doug.muchmore@capillarybio.com	**Rayhan Lal, MD** Clinical Instructor Endocrinology Academic Office, Stanford University 300 Pasteur Dr, Room G-313 Medical Center Stanford, CA, USA 94305-5208 Telephone: 650 725 2908 E-mail: inforay@stanford.edu

10.1.5 SAFETY OVERSIGHT

Serious Adverse Events will be reviewed within 24 hours of notification. Preliminary assessment will be conducted by the principal investigator or qualified designee. The sponsor Medical Monitor will be responsible for review all SAEs within 24 hours of notification. Non-serious adverse events will be reviewed per monitoring plan and at least monthly by sponsor Medical Monitor. Sponsor Medical Monitor will be a licensed clinician, e.g., MD, DO, PA, or RN. SAEs will be assessed by an MD or DO.

Upon review of the report, an adjudication will be issued: no action may be taken, the consent form may be revised, study procedures may be modified, or approval of the study may be suspended, pending further inquiry.

The qualifications of the Medical Monitor must be provided to NIDDK for approval.

10.1.6 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonization Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

Monitors will be appointed by Capillary Biomedical. Monitors will be trained with scientific and/or clinical knowledge and his/her qualifications will documented. The Monitor will be familiar with the investigational product, protocol, consent form and any other written information given to the participant, sponsor's SOPs, and GCP and the relevant regulatory requirements.

Monitoring will be conducted with a combination of remote monitoring and on-site from time to time based on enrollment rate, occurrence of adverse events, etc. to assess ICF, eligibility, AE, device accountability, and primary endpoint data as further defined in the Monitoring Plan. Sponsor management will be provided copies of monitoring reports within 10 days of the visit.

An Independent clinical audit may be conducted by Sponsor to ensure that monitor is following the CMP.

10.1.7 QUALITY ASSURANCE AND QUALITY CONTROL

The clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP), and applicable regulatory requirements.

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

10.1.8 DATA HANDLING AND RECORD KEEPING

10.1.8.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into EDC, a 21 CFR Part 11-compliant data capture system provided by the EDC Vendor. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.8.2 STUDY RECORDS RETENTION

The investigator(s) will retain all study records for a minimum of 15 years from the date of Federal Financial Report submission. No records will be destroyed without the written consent of the sponsor (Capillary Biomedical, Inc.). The sponsor will inform the investigator(s) when the study records are no longer need to be retained.

10.1.9 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

All deviations must be addressed in study source documents, reported to the sponsor. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details

about the handling of protocol deviations will be included in the MOP. Deviations involving risk to participants will be reported to the IRB and the sponsor within 10 working days.

10.1.10 PUBLICATION AND DATA SHARING POLICY

The clinical trial investigators will determine the authorship of peer publications based upon the work effort performed. Data and samples/specimen are owned by the university and shared with the Sponsor.

10.1.11 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the medical device industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the National Institutes of Health- NIDDK has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest. All investigators will disclose all actual and perceived conflicts of interest to the Conflicts of Interest Committee and establish/implement a plan to manage the conflict.

10.2 ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
BG	Blood Glucose
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CGM	Continuous Glucose Monitor
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRU	Clinical Research Unit
CSII	Continuous Subcutaneous Insulin Infusion
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DRE	Disease-Related Event
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram

eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
IV	Intravenous
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous(ly)
SMBG	Self-monitored Blood Glucose
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States
VAS	Visual Analogue Scale

10.3 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale
A	2/12/2020	Initial release	As submitted to FDA
B	3/19/2020	Respond to FDA requests	IDE G190079-S001 approved
C	4/16/2020	Clarify clamp procedures, extend screening time duration and allow Dexcom G6 run-in period	Support recruitment at Study Center during COVID-19
D	7/20/2020	Revised blood sampling schedule and clarified other procedures; specified independent safety monitor	Align to Study Center procedure
E	10/15/2020	Increased basal stabilization period from maximum of 3.0 to 3.5 hours and revised glucose infusion “trigger” value during euglycemic clamp from 90 mg/dL to be a value 5 mg/dL less than the mean of the three values obtained during Baseline Period II	These changes improve the likelihood of achieving a stable baseline prior to initiating the clamp procedure and also reduce the risk of hypoglycemic overshoot in the early phase of the clamp procedure
F	11/24/2020	Clarify procedure; added one time rescreen for A1C and C-peptide	Align to Study Center procedure; Capillary Biomedical’s standard procedure has been to allow for a single rescreen attempt for key labs (e.g. A1C and c-peptide).

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