Study Title	Feasibility of an Investigational Extended Wear Infusion Set for Continuous Subcutaneous Insulin Infusion (CSII) in Patients with Type 1 Diabetes Mellitus (T1DM)
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Feasibility of an Investigational Extended Wear Infusion Set for Continuous Subcutaneous Insulin Infusion (CSII) in Patients with Type 1 Diabetes Mellitus (T1DM)

CLINICAL INVESTIGATION PLAN
January 27, 2020

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Sponsor & Manufacturer:
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Protocol No. 150-1072-00 Version A

Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale

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1 General Information

1.1 Study Identification

Study Title	Feasibility of an Investigational Extended Wear Infusion Set for Continuous Subcutaneous Insulin Infusion (CSII) in Type 1 Diabetes Mellitus (T1DM) Participants
Short Title	Feasibility of an Extended Wear CSII Set in Participants with T1DM ("FEXIS")
Manufacturer Reference	Protocol Number 150-1072-00 Rev. A
Document Date	July 10, 2019
Revision History	N/A

1.2 Study Sponsor

US Sponsor	Capillary Biomedical, Inc., USA
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Manufacturer	Capillary Biomedical, Inc. 2 Wrigley, Ste 100 Irvine, CA 92618, USA
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1.3 Investigators and Sites

Principal Investigator	Professor David N. O'Neal MD, FRACP University of Melbourne Department of Medicine St. Vincent's Hospital Melbourne, 3065 Victoria, Australia dno@unimelb.edu.au
Co-Investigators	none
Investigational Site	University of Melbourne Department of Medicine St. Vincent's Hospital Melbourne, 3065 Victoria, Australia

1.4 Study Synopsis

1.4.1 Overview

This is a prospective, non-randomized, home-use feasibility study of device performance, usability, tolerability, and safety of an investigational infusion set for continuous subcutaneous

insulin infusion (CSII or insulin pump therapy) in up to 20 participants diagnosed with type 1 diabetes mellitus (T1DM). The Capillary Biomedical, Inc. (CapBio) Achilles infusion set is a sterile single use device designed to be used with commercially available infusion pumps (e.g., Medtronic MiniMed). The investigational Achilles infusion set contains a coil reinforced soft polymer indwelling cannula with one distal and three proximal holes (see item 2 Investigational Device).

The existing patient population at the study center will be screened for study eligibility within 21 days of planned study enrollment. Eligible participants will complete written informed consent and be assigned a study identifier.

The study is comprised of 3 periods. Each period is initiated at the study center and followed by a home-use phase of up to 7 days (Figure 1):

1. Week 1 (t = 7 days): Trial run with saline infusion. Patients will continue to use their own pump and insulin infusion set while wearing the CapBio Achilles infusion set connected to a second pump. The reservoir in this pump will be filled with saline and patients will mimic their insulin basal/bolus pattern on the dummy pump.
2. Week 2 (t ≤ 7 days): After successful completion of *Week 1*, patients will manage their blood glucose (BG) solely with their insulin pump and the Achilles infusion set. BG will be closely monitored with a continuous glucose monitoring (CGM) device. *Week 2* is considered complete when either, (1) an Achilles infusion set failure (see below) occurs and participant needs to insert a commercial CSII set to maintain routine therapy until they return to the study center, or (2) participant has worn Achilles for the total 7-day wear period.
3. Week 3 (t ≤ 7 days): (***Note:*** Initiation of *Week 3* will only occur if Week 2 was completed without any major safety issues, adverse events or other concerns.) After completion of *Week 2* patients will return to study center to receive a fresh Achilles infusion set and continue BG management at home until infusion set failure (see below). BG will be closely monitored with a continuous glucose monitoring (CGM) device. *Week 3* is considered complete when either, (1) an Achilles infusion set failure occurs and participant needs to insert a commercial CSII set to maintain routine therapy until they return to the study center, or (2) participant has worn Achilles for the total 7-day wear period.

Infusion set failure is defined as:

1. The occurrence of unexplained hyperglycemia (glucose >250 mg/dL or >14 mmol/L) occurring more than 2 hours after a meal and not responsive to a pump bolus dose where response to the bolus is defined as a fall of at least 50 mg/dL (3 mmol/L) in blood glucose within one hour,

2. The occurrence of any hyperglycemic episode (glucose >250 mg/dL or >14 mmol/L) not associated with acute intercurrent illness, but with a concurrent ketone level ≥0.6 mmol/L.
3. Signs of infection (e.g. erythema or induration >1 cm in maximal diameter),
4. Occurrence of non-resolvable insulin pump occlusion alarm signal.

During home-use periods, participants will conduct daily visual infusion site inspection and record pain levels and skin reactions. They will use Dexcom G5 CGM (if patient is not routinely using this CGM) to monitor blood glucose and detect hypo-/and hyperglycemic episodes/events. If participant experiences an Achilles infusion set device issue, participants shall insert a commercial CSII set to maintain routine insulin therapy. Participants will be provided with training and written instructions if an Achilles device issue occurs at any time during home wear periods. They are instructed to contact study staff as early as possible after infusion set failure and return to the study site at their earliest convenience.

The primary objective of this study is to determine feasibility and device performance of the CapBio Achilles infusion set over 2 extended home use wear periods of up to 7 days each during routine therapeutic insulin infusion. Feasibility is evidenced by the absence of uncontrolled hyperglycemia and/or suspected infusion set cannula occlusion. Secondary objectives include the assessment of standard glucose control measures obtained from CGM, including observed hyper- and hypoglycemic episodes, patient tolerability (patient comfort) during wear period, cannula dislodgment, inability to pierce skin or leakage, and adverse events (infusion site reaction/infection, etc.). Regarding *Week 1*, patient comfort, cannula dislodgment, inability to pierce skin or leakage, and adverse events such as infusion site reactions/infections, etc. are secondary outcomes of this study.

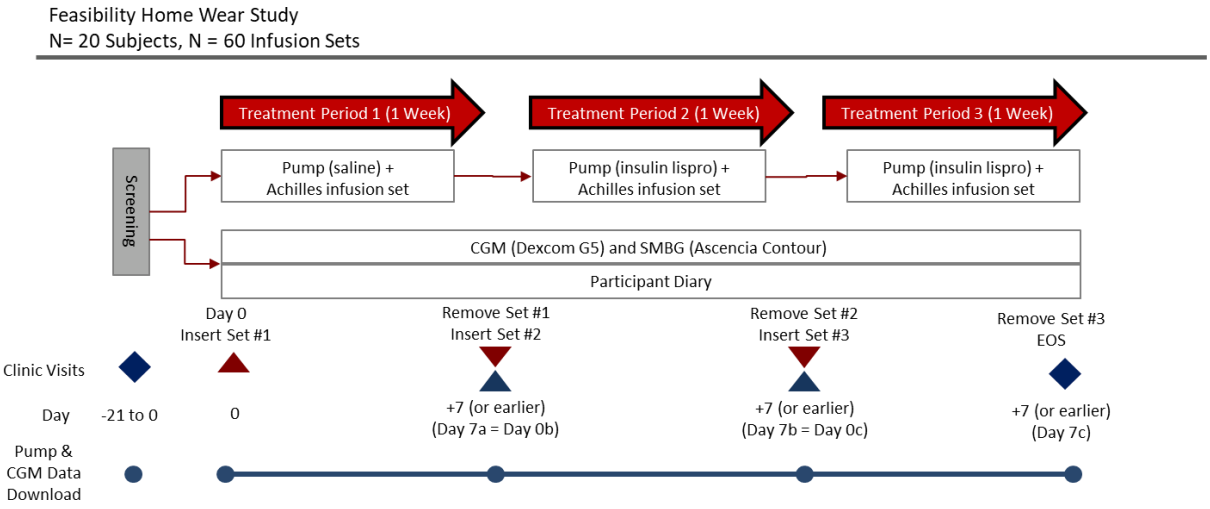

Figure 1. Study Schema

1.4.2 Inclusion Criteria

Participants must meet all of the following criteria to be included in the Study:

1) Participant is 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) Subject can provide a minimum of 14 days of insulin pump data to demonstrate pump use compliance
8) Participant is willing to perform serum ketone measurements whenever the blood glucose is determined to be greater than 250 mg/dL (14 mmol/L) using a ketone meter and strips provided by the sponsor
9) Participant has BMI in the range 20 – 35 kg/m^2 inclusive
10) Participant has experience infusing a rapid-acting insulin analog for at least 6 months
11) Participant has been using an insulin pump with commercially for increase in the number of subjects to be enrolled in the study available infusion sets for at least 6 months (this includes Automated Insulin Delivery systems)

12) Participant has previous experience using a continuous glucose monitor (CGM) and is willing to use a CGM for the duration of the study and perform necessary calibration fingerstick glucose readings
13) Participant has ability to understand and comply with protocol procedures and to provide informed consent
14) AST and ALT ≤120 U/L
15) Creatinine <1.8 mg/dL

1.4.3 Exclusion Criteria

Participants who meet any of the following criteria will be excluded from study participation:

1) Participants whose average total daily insulin dose exceeds 85 units/day (i.e. typically change insulin reservoirs more often than every 3.5 days on average)
2) Participants who routinely change their commercial insulin infusion sets twice weekly or less often (wear time > 3.5 days)
3) Female participant is pregnant or nursing[1]
4) Participant has abnormal skin at intended device infusion sites (existing infection, inflammation, burns, or other extensive scarring)
5) Participant has HbA1C > 8.5% at screening
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

[1] 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.

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 beta-blockers,
    d) growth hormone,
    e) thyroid hormones, unless use has been stable during the past 3 months
13) Subject has significant history of any of the following, that in the opinion of the investigator would compromise the subject'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 subject 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 participation in another clinical drug or device study
17) AST and ALT >120 U/L
18) Creatinine ≥1.8 mg/dL

1.5 Investigator Acknowledgement

I have read the attached protocol and hereby agree that it contains all the necessary details for performing the study. I will provide copies of the protocol to all members of the study team responsible to me who participate in the study. I will discuss this material with them to ensure that all participating staff members are fully informed regarding the investigational device and the conduct of the protocol.

Once the Ethics Committee approves the protocol, I will not modify this protocol without obtaining the prior approval of the Manufacturer and of the Ethics Committee. I will submit the protocol modifications and/or any informed consent modifications to Capillary Biomedical, the local sponsor and the Ethics Committee. Written approval will be obtained from the Manufacturer and the Ethics Committee before any modifications are implemented.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

2 Investigational Device

2.1 Summary Description

The Capillary Biomedical, Inc. (CapBio) Achilles infusion set is a sterile 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 investigational Achilles infusion set contains a coil reinforced soft polymer indwelling cannula with one distal and three proximal holes.

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 (Figure 1). See also reference document 710-1021-00 Achilles Infusion Set, Instructions for Clinical Use.

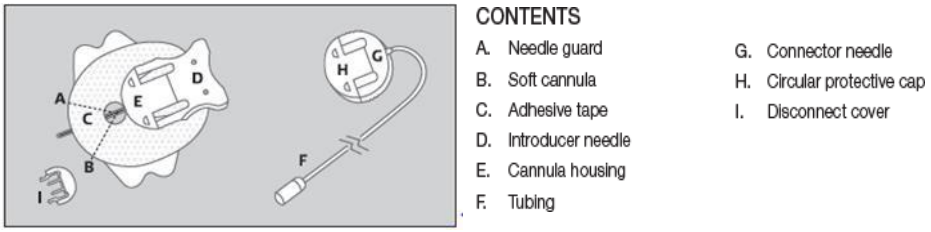

Figure 2: Device Illustration of the Capillary Biomedical Achilles insulin infusion set.

2.2 Manufacturer

The Achilles infusion set is manufactured by Capillary Biomedical, Inc. at 8 Faraday, Ste B; Irvine, CA 92618.

2.3 Identification

Each investigational device is identified by a batch number/serial number. In case of infusion set failure, the set will be returned by the subject and labeled appropriately with specific infusion set study ID, subject ID and date of failure.

2.4 Traceability

CapBio catheters are each labeled with a lot reference and within-lot serial number. These references will be recorded on the case report forms to achieve traceability.

2.5 Intended Purpose

The Achilles infusion set is intended for the subcutaneous infusion of medication, including insulin, from an external infusion pump. (See reference document 710-1021-00 Achilles infusion set, Instructions for Clinical Use.)

2.6 Populations and Indications

The Achilles infusion set is intended for the subcutaneous infusion of medication, including insulin, from an external infusion pump. (See reference document 710-1021-00 Achilles infusion set, Instructions for Clinical Use.) Insulin infusion is intended for insulin-dependent patient populations.

2.7 Materials and Safety

Capillary Biomedical, Inc. (CapBio) focused on development of a soft polymer cannula with a coil-reinforced wall, one distal port, and three proximal ports spaced 2 mm apart in a helical pattern. The coil-reinforced wall was designed to eliminate obstruction due to kinking, ease of manufacture, and low-cost. The soft-flexible polymer material (PEBAX, a proprietary nylon blend) was chosen for the cannula due to satisfactory tissue response to implantation and the fact that this material was already used in US FDA-approved catheter/cannula products for short-term implantation. Multiple holes/ports along the cannula shaft provide redundancy (increasing duration of use and reliability) and may spread the insulin into a greater surface area of adjacent vascular tissue for enhanced (more consistent) absorption into the circulation.

An iterative process was used to optimize polymer material modulus, wall thickness, wire diameter, coil density, stylet stiffness, and needle type- to produce a cannula/stylet system that reliably inserted through the epidermis, dermis, and subcutaneous tissue (tested in swine). Stiffer stylets with a sharp cutting needle distal tip produced the most reliable combination for insertion.

Epimed International Inc. (Johnstown, NY, USA), a specialist medical device contract manufacturer, is fabricating the investigational soft multi-port infusion cannulas used in this study. These cannulas are manufactured by a proprietary molding and extrusion process, which overmolds PEBAX material (a proprietary nylon blend) over a reinforcing stainless-steel coil. Then, three holes with 0.05 mm diameters, spaced 2 mm apart from each of the holes' centerlines are laser drilled into the cannulas' shafts. The cannula and infusion set assemblies

were packaged and sterilized for animal use. Manufacturing is performed in accordance with relevant quality system regulations (US 21 CFR 820).

2.8 Training and Experience Required

The Achilles infusion set can be easily inserted following document 710-1021-00 “Achilles infusion set, Instructions for Clinical Use”.

2.9 Clinical Procedures

Existing patient populations at each study center will be screened for study eligibility within 21 days of planned study enrollment. Eligible participants will complete written informed consent and be assigned a unique study ID.

On Day of Insertion (Day 0a during *Week 1*, Day 0b during *Week 2*, and Day 0c during *Week 3*), participants will have the investigational Achilles infusion set inserted by a qualified professional during a clinic visit. Study staff may use three attempts to insert the infusion set. If insertion fails three times on Day 0a, the set is considered failed and subject is exited from the study. If three attempts fail during Day 0b, participants may return another day for their third study visit (Day 0c). If three attempts fail during Day 0c, the study is considered complete for the respective study subject.

Participants will undergo training and be provided written instructions on how to bolus saline during the *Week 1* and for instances of infusion set change out is required during the 7 day wear period in *Week 2* and *Week 3*.

Enrolled study participants will be provided with the following study supplies:

- Saline pre-filled reservoir
- Insulin lispro pre-filled reservoir (Humalog),
- Tubing set compatible with the investigational Achilles infusion set
- Ascencia Contour Next glucose monitor plus SMBG test strips.
- Abbott Precision Xtra ketone monitor plus test strips
- Container and Biohazard bag for failed Achilles infusion set

Participants will be required to manage routine insulin therapy with the study specific supplies for a three hour observation period on Day 0b and Day 0c before starting *Week 2* or *Week 3* home use period, respectively.

During *Week 1*, participants will be required to wear two pumps at the same time. The investigational Achilles infusion set will be connected to a pump containing a saline-filled reservoir. Participants are asked to mimic their basal bolus pattern from their regular pump

containing insulin on the dummy pump. This first week will ensure that any fluid can be reliably delivered through the Achilles infusion set and subject is ready to start routine blood glucose control with his/her own pump the investigational infusion set. *Week 1* evaluation period is complete when subject has worn the Achilles set with dummy pump for a full 7 days.

After insertion of the Achilles infusion set at the study site, participants will be required to manage routine basal/bolus insulin therapy using study specific supplies only with their current insulin pump during two extended wear home use periods of up to 7 days each (*Week 2* and *Week 3*, respectively). Participants will monitor BG levels with Dexcom G5 CGM device to avoid glycemic excursions. Participants will conduct daily visual inspection and record Achilles insertion set location pain levels and skin reactions. If subject experiences an Achilles infusion set device issue, participants shall insert a commercial CSII set to maintain routine insulin therapy. Participants will be provided with training and written instructions if an Achilles device issue occurs at any time during home wear periods. They are instructed to contact study staff as early as possible after infusion set failure. *Week 2* evaluation period is complete when either, 1) an Achilles infusion set failure occurs and subject needs to insert a commercial CSII set to maintain routine therapy until they return to the study center, or 2) subject has worn Achilles for the total 7-day wear period.

Upon completion of *Week 2* wear period (either after full 7 days or earlier), participants are asked to return to study center. Data will be downloaded from the subject's insulin pump, ketone monitors and CGM. Patient Diaries will be collected after each wear period. All study supplies will be replenished as needed.

Week 3 evaluation begins when study center inserts another Achilles infusion set (Day 0c). Participants will maintain insulin pump therapy per standard of care. *Week 3* home use evaluation is considered complete when, 1) an Achilles device issue requires subject to insert a commercial CSII set; or 2) subject has worn Achilles for a second total 7 -day wear period.

Participants who do not participate in *Week 3* will exit the study at time of declination. All data up the point of study exit will be documented and included for analysis. Participants may exit the study at any time without prejudice to their ongoing medical care. The time and reason for early exit will be recorded, and all data up to the point of study exit shall be documented and included for analysis.

Subject will have completed all study protocol requirements at the end of the third extended wear period (*Week 3*) regardless of actual total days of Achilles infusion set wear. See Figure 1 for a Study Schema overview.

3 Study Justification

3.1 Clinical Need

Over 1 million people with diabetes globally use an insulin pump, a 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.[1] Patients find this frequent site change and rotation inconvenient and often maintain their infusion site longer than recommended.[1–3] 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.[1] 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.[4] Furthermore, the repeated trauma of CSII cannula insertion contributes to the development of scar tissue and may result in eventual loss of infusion sites.[5,6]

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.

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.[2,7,8] 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]

3.2 Preclinical Testing

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 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. Several posters were presented on the data of this study and 3 manuscripts for publication are currently underpreparation.[10–12]

3.3 Previous Clinical Experience

The Capillary Biomedical Achilles cannula has not been used to deliver insulin in human participants. Human subject safety and tolerability will be assessed in this study.

4 Risk and Benefits

4.1 Anticipated Clinical 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 insulin infusion set
- Reduction in the number of required infusion set insertions/reduction of number of infusion sites
- Reduction in infusion site (skin/tissue) reactions
- Improved glucose control (e.g., more stable insulin kinetics)
- Improved CSII and insulin pump therapy options

4.2 Anticipated Adverse Device Effects

The anticipated adverse device effects (ADEs) for the Achilles infusion set are the same as those for commercially available CSII sets used by patients eligible for enrolment in this study. These are described in section 14 of this document. 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.

4.3 Residual Risks from Device Risk Analysis

The Achilles Infusion Set has been analysed for possible hazards using the methods in ISO 14971:2007 Medical Devices, Application of Risk Management to Medical Devices. The results of this risk analysis are summarized in section 6.1, Risk Analysis, of the Clinical Investigator's Brochure, manufacturer document 150-1073-00. Capillary Biomedical, Inc. considers the Achilles Infusion Set to be adequately safe to justify its use in clinical trials based on the benefits compared to overall risk.

4.4 Risks of Participation

This study includes T1DM participants that 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 subject 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 >3.5 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 participants with previous CGM experience and willingness to wear a CGM will be recruited. The Dexcom G5 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 subject 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 subject.

Study participants will be instructed to check the Achilles 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 Patient 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 subject and study team, and documented daily in a patient diary. The insertion site will be visually inspected and photographed pre- and post-Achilles 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 investigationalsites.

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 subject risk. All other therapy will be conducted per standard of care for T1DM patients.

4.5 Potential Interactions

There are no known interactions between the materials used in the Achilles infusion set and possible concomitant medical treatments.

Based on the biocompatibility test report 150-1010-00 performed by the Medical Research OrganizationNorth American Science Associates, Inc (NAMSA®), it was concluded that “considering all gathered data, this risk assessment indicates that the likelihood of a toxic effect from Achilles Infusion Set is low. No further testing is recommended on this feasibility device.”

4.6 Risk Management Measures

The following measures will be taken to manage and minimize risk:

1. In-depth patient instructions, oral and written
2. 24/7 study helpline

3. Only include patients who have been using an insulin pump and rapid acting insulin for at least 6 months
4. One week run-in period (*Week 1*) with saline infusion through the Achilles infusion set to assess number of dislodged infusion sets and/or skin tolerability

4.7 Risk-to-Benefit Rationale

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 2).

Table 1: Infusion Set Failure Rate by Duration of Use

Day (s) of Use	Failure Rate
Day 1	> 15%
Day 3	> 25%
Day 7	> 65%

This high failure rate prevents wider adoption of insulin pump therapy that could improve current patient outcomes and expand pump access to users still depending on multiple daily manual injections.

Results from pre-clinical animal and bench studies of the Achilles 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. 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 subject or ongoing therapy.

5 Study Objectives

5.1 Primary Objective

The primary objective of this study is to evaluate feasibility and device performance of the Achilles infusion set over three extended home use wear periods of up to 7 days each during routine therapeutic insulin infusion.

5.2 Secondary Objectives

Secondary objectives include evaluation of:

- Standard glucose control measures obtained from Continuous Glucose Monitoring (CGM), including observed hyper- and hypoglycemic episodes
- Subject tolerability (subject comfort) during wear period
- Adverse events (infusion site reaction/infection, etc.)

5.3 Hypotheses to Test

This study is a first-in-human observational study of device feasibility in a known subject population. As such, there is no definitive relevant statistical hypothesis. A sample size was selected based on similar studies of insulin infusion set functionality (3,27,28).

5.4 Intended Performance/Success Criteria

Results of this study will be compared to those of Patel et al. (3), who observed that 30% of infusion sets performed adequately (no premature failure due to mechanical malfunction and no episodes of uncorrectable hyperglycemia prior to the end of 7 days of infusion set wear time), and, among infusion sets that did not exhibit mechanical malfunction, 60% performed adequately by the glucose control metrics for the 7-day wear period. Success criteria will be considered met if the Achilles infusion set exceeds these performance outcomes.

5.5 Risks and Anticipated Adverse Device Effects

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

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 Dexcom G5 CGM sensor throughout the study.

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 subject 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.

6 Study Design

6.1 General

6.1.1 Study Type and Rationale

This is a prospectively enrolled, non-randomized feasibility study of device performance, tolerability and safety of the investigational Achilles infusion set during two 7-day home use periods. This study has been designed to mimic other studies of insulin infusion set functionality and infusion site reactions, and to collect early human data using the Achilles infusion set (cannula) design and feasibility for extended wear periods.

6.1.2 Measures to Minimize Bias

This study is designed as a single arm device feasibility evaluation. All eligible patients who complete informed consent shall be considered for study participation. No randomization is required. Due to the nature of the disease state and to minimize unknown effects of extended wear of an infusion set, only adult patients will be considered for study participation. Female patients who are pregnant or nursing shall be excluded from the study. To maintain consistent insulin kinetics and blood glucose monitor, participants will be provided with the same insulin analog during the study, study assigned blood glucose and ketone monitors and test strips for study duration. Participants will independently record any device issues, skin irritation or other adverse events that occur during routine home wear and therapy.

6.1.2 Primary Endpoint

Week 2 and Week 3:

The primary endpoint of this study is Insulin delivery through the Achilles infusion set cannula, as evidenced by the absence of uncontrolled hyperglycemia/suspected occlusion, defined as:

The occurrence of unexplained hyperglycemia (glucose >250 mg/dL or 14 mmol/L) occurring more than 2 hours after a meal and not responsive to a pump bolus dose where response to the bolus is defined as a fall of at least 50 mg/dL (3 mmol/L) in blood glucose within one hour, or

- The occurrence of any hyperglycemic episode (glucose >250 mg/dL or 14 mmol/L) not associated with acute intercurrent illness, but with a concurrent ketone level ≥0.6 mmol/L.

Other evidence of infusion set failure includes:

- Signs of infection (e.g. erythema or induration >1 cm in maximal diameter), or
- occurrence of a non-resolvable insulin pump occlusion alarm signal

NOTE: Cannula function criteria refer to hyperglycemic episodes that participants recognize and attempt to correct with an insulin bolus or document with ketone elevation. Participants may take SMBG measurements in case of unexplained hyperglycemia or if for any other reason the subject questions the CGM readout.

Week 1:

The primary endpoints for Week 1 of this study are the following:

- Cannula dislodgement from subcutaneous space (with or without liquid leakage at the cannula infusion site), or
- other Achilles device malfunction (e.g., inability to pierce skin, bending, kinking or other malformation that might impact insulin infusion, securement failure).

6.1.3 Secondary Endpoints

The secondary endpoints of this study include:

- Achilles infusion set device function as evidenced by the absence of device failure with or without uncontrolled hyperglycemia. Device failure is defined as:
  - Cannula dislodgement from subcutaneous space (with or without liquidleakage at the cannula infusion site), or
  - other Achilles device malfunction (e.g., inability to pierce skin, bending, kinking or other malformation that might impact insulin infusion, securementfailure).

    SEE ABOVE NOTE
- Standard glucose control measures obtained from Continuous Glucose Monitoring, including observed hyper- and hypoglycemic episodes.
- Subject tolerability levels for the initial manual Achilles infusion set insertion, daily wear and final removal will be assessed using a visual analog pain scale (VAS).
- The incidence, seriousness and potential relationship infusion site to the investigation device of all adverse events will be documented and reported.

6.1.4 Variables to Assess

The variables assessed in this study include:

- Frequency of pump prime events (i.e infusion set change out) as evaluated from the 14d pump data downloaded during the screening visit as well as during the evaluation periods

- Interstitial glucose values as measured by the CGM, downloaded at each visit to the study center
- Capillary blood glucose values measured by fingerstick measurements, downloaded from the glucose meter/recorded in Patient Diary
- Ketone values measured by fingerstick measurements, downloaded from the ketone meter/recorded in Patient Diary
- Daily pain assessments from the VAS recorded in Patient Diary
- Number of Achilles infusion set failures per definition in sections 6.1.2 and 6.1.3
- Number of hyperglycemic events (CGM, Patient Diary)
- Number of hypoglycemic events (CGM, Patient Diary)

6.1.5 Test Equipment to Use

- Dexcom G5CGM (calibration differs per model) for continuous monitoring of blood glucose level and collection of data. For the G5 model, calibration is needed at least once every 12 hours with a manual BG meter measurement.
- Ascencia Contour Next glucose monitor plus SMBG test strips for manual blood glucose monitoring for confirmation of CGM data and in the case of adverse events. Calibration with a control solution is recommended when using the meter for the first time, new box of test strips is opened, or to verify meter and test strips are working properly.
- Abbott Precision Xtra ketone monitor plus test strips for confirming hyper/hyperglycemic events. Calibration with a control solution is recommended when using the meter for the first time, new box of test strips is opened, or to verify meter and test strips are working properly.

6.2 Participants

6.2.1 Inclusion Criteria

Patients must meet all of the following criteria to be included in the Study:

1) Participants are 18 – 70 years of age inclusive
2) Subject is in generally good health, as determined by the investigator
3) Subject is willing and able to individually complete written informed consent and agrees to comply with all study related testing and examinations
4) Subject 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) Subject has been diagnosed with T1DM for at least 12 months
6) C-peptide <0.6 nmol/L at screening
7) Subject can provide a minimum of 14 days of insulin pump data to demonstrate pump use compliance

8) Subject is willing to perform serum ketone measurements whenever the blood glucose is determined to be greater than 250 mg/dL using a ketone meter and strips provided by the sponsor
9) Subject has BMI in the range 20 – 35 kg/m^2 inclusive
10) Subject has experience infusing a rapid-acting insulin analog for at least 6 months
11) Subject has been using an insulin pump with commercially available infusion sets for at least 6 months (this includes Automated Insulin Delivery systems)
12) Subject has been using a continuous glucose monitor (CGM) for at least 3 months
13) Subject has ability to understand and comply with protocol procedures and to provide informed consent
14) AST and ALT ≤120 U/L
15) Creatinine <1.8 mg/dL

6.2.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study participation:

1) Participants whose average total daily insulin dose exceeds 85 units/day (i.e. typically change insulin reservoirs more often than every 3.5 days on average)
2) Participants who routinely change their commercial insulin infusion sets twice weekly or less often (wear time > 3.5 days)
3) Female subject is pregnant or nursing[2]
4) Participant has abnormal skin at intended device infusion sites (existing infection, inflammation, burns, or other extensive scarring)
5) Subject has HbA1C > 8.5% at screening
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

[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.

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) Subject is undergoing current treatment with:
    a) Systemic oral or intravenous corticosteroids,
    b) monoamine oxidase (MAO) inhibitors,
    c) non-selective beta-blockers,
    d) growth hormone,
    e) thyroid hormones, unless use has been stable during the past 3 months
13) Subject has significant history of any of the following, that in the opinion of the investigator would compromise the subject'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 subject 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 participation in another clinical drug or device study
17) AST and ALT >120 U/L
18) Creatinine ≥1.8 mg/dL

6.2.3 Withdrawal

Any study participant who has been enrolled (i.e. had a first attempt to insert the Achilles infusion set) and decides either to discontinue participation or withdraw from the study prior to the end of week 1 evaluation period will be considered a study dropout. If a participant withdraws from the study due to an adverse event/complication, the subject should be followed and all data collected through resolution of the adverse event.

Participant will be exited at the time of discontinuation/withdrawal or upon resolution of any medical complications/adverse events. All data up to the point of study exit will be documented

and entered into the study database. Participants who are dropouts or exit the study before completion of both 7-day evaluation periods will be counted in the total cohort enrollment and Intent-to-Treat and Per Protocol analysis populations.

6.2.4 Point of Enrollment

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

Eligible participants will be considered “enrolled” at the time of the first attempt to insert the investigational Achilles infusion set. Enrolled participants will have an Achilles infusion set inserted and secured by study staff, followed by three extended home wear periods of up to 1 week (0-7 days) each.

6.2.5 Duration

Including screening up to 21 days prior to first study visit (Day 0a), the study duration for each patient will be about 6 weeks.

6.2.6 Number of Participants

20 participants will be enrolled in this feasibility home use trial.

6.3.7 Enrollment Period

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 a spontaneous menstrual period 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 complete blood and metabolic panels within the required screening period.

Patients with positive c peptide value (defined as c-peptide >0.6 nmol/L) may be rescreened for study eligibility one time within 2 week of initial test date.

6.3 Study Procedures

6.3.1 Clinical Investigation

See Section 2.9 and Figure 1.

6.3.2 Sponsor Representative Involvement

The Sponsor and Manufacturer Capillary Biomedical will provide all investigational Achilles infusion sets. The Local Sponsor is responsible for supplying and all relevant study material such as glucose meters, ketone meters, test strips, and CGM and reimbursing study participants and insurance.

6.3.3 Potential Factors That May Compromise Outcome or Interpretation

Potential factors that may affect the outcome of the study or interpretation of the data include but are not limited to the duration of CSII therapy and/or CGM sensors and the resulting changes in skin/tissue structure. Frequent rotations of infusion/sensor sites can compromise the skin structure due to connective tissue disruption and scarring. (E.g., the skin and subcutaneous tissue of a patient who has been on CSII therapy for only 2 years may differ substantially from that of a patient who has been using an insulin pump for a decade.) In order to minimize the influence of scar tissue on study outcomes, areas of scar tissue and/or lipohypertrophy will be avoided as sites for insulin infusion or CGM.

6.4 Monitoring Plan

6.5.1 Safety Oversight

Unanticipated Adverse Device Effects and Serious Adverse Events will be reported to the Sponsor within 24 hours of knowledge of the event. Sponsor shall endeavor to review such events within 24 hours of notification. Preliminary event seriousness and device relationship will be assessed by the principal investigator or a qualified designee.

A qualified clinician shall act as the study Medical Monitor. Adverse events shall be reviewed at least monthly by Sponsor and/or Medical Monitor. Serious or unanticipated adverse events shall be reviewed upon receipt of full documentation of the event, including any sequelae and treatment required for resolution. The Medical Monitor will document event review and adjudication.

6.5.2 Clinical Monitoring

Clinical monitoring is an ongoing process conducted to ensure that the rights and well-being of study 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 applicable Good Clinical Practices and regulatory requirement(s).

Capillary Biomedical or a qualified designee shall be responsible for site monitoring. Monitors will be qualified by training and experience. Monitor(s) will be familiar with the investigational product, protocol, consent form and any other written information given to the participant,

study SOPs, GCP and other relevant regulatory requirements. Training and qualification of Monitor(s) shall be documented in writing.

Monitoring will be performed as a combination of periodic on-site and remote monitoring based on enrollment rate, occurrence of adverse events, and site compliance issues to assess consent procedures, subject eligibility, adverse events, device accountability, and primary endpoint data. Monitoring reports shall be due to Sponsor management per applicable SOP timeframes.

6.5.3 Quality Assurance and Quality Control

All measures have been taken to minimize subject risks before, during and at the end of the study. Standard operating procedures will be employed during study planning, conduct and analysis stages.

A standardized protocol, case report forms, data sheets, diaries and examination schedules will be used to collect data consistent with the study objectives and evaluation endpoints. Written informed consent will be required from each subject prior to initiation of any study specific testing or examinations.

Study investigators shall perform the study per the currently approved protocol requirements and procedures. Protocol deviations shall be documented in writing and reported to the governing IRB. The clinical site staff shall be responsible for study conduct per protocol, the collection, labeling and storage of biological specimens per site requirements and all applicable patient privacy rules, the documentation and completion of study case report forms, logs, etc.

Periodic source document monitoring shall be conducted throughout study conduct and follow-up periods. Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial has been conducted in compliance with the protocol, biological specimens are collected, documented (recorded), and reported in compliance with all local and federal requirements, applicable Good Clinical Practices and all other applicable regulatory requirements.

The investigational site will be required to provide access to all study source data/documents to sponsor and sponsor representatives for monitoring purposes as well as to regulatory authorities during inspections.

7 Statistical Analysis

7.1 General Approach

As a routine evaluation of the data during analysis, consistency of the study variables to properties of statistical tests will be checked. Descriptive statistics shall be used for independent variables.

For tabulated continuous variables, descriptive analyses will present the mean, standard deviation, median, minimum and maximum. For tabulated categorical variables, the number with the characteristic, the total number evaluated and the percent will be provided.

Unless otherwise specified, statistical analyses will be performed using vendor specified software products.

7.2 Populations for Analysis

Intent-to-Treat (ITT) Analysis Population: All participants who meet all eligibility criteria and have undergone a first attempt to insert an investigational Achilles infusion set shall be included in the ITT analysis population.

Safety Analysis Population: All participants who had an investigational cannula inserted.
Per-Protocol (PP) Analysis Population: All patients who completed any part of the 7-day Achilles infusion set evaluation period.

The primary effectiveness analysis will be based on the ITT subject population. Sensitivity analyses of the primary effectiveness endpoint will be generated based on the PP population. The ITT population may contain some patients who did not complete the evaluation interval. This will require the use of imputation methods for missing values. Last observation carry forward will be used in such case.

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

7.3 Analysis of the Primary Efficacy Endpoint

The primary study endpoint is the proportion of Achilles infusion sets that function each day of use, up to 7 days. This endpoint will serve as both the preliminary effectiveness and safety endpoint during the feasibility evaluation.

7.4 Analysis of the Secondary Endpoint(s)

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

7.5 Safety Analyses

Tolerability of the extended wear Achilles cannula will be assessed by VAS scores from day of insertion through Day 7 of use. These data will be summarized using descriptive statistics.

All adverse events (AEs) will be defined and classified per study definitions. Descriptive statistics (number of participants and per-subject incidence) will be presented by level of seriousness and relationship to the study device.

7.6 Baseline Descriptive Statistics

Descriptive statistics will be utilized to summarize the demographic and baseline data.

For continuous endpoints, descriptive statistics will be presented, including the number of participants with the measurement, mean, standard deviation, median, minimum and maximum. For categorical endpoints, descriptive statistics will include the number with the event or characteristic, the number evaluated and the percentage presented.

7.7 Tabulation of Individual participant Data

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

7.8 Exploratory Analyses

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

8 Data Management

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. Data will be captured using applicable CDASH data element standards.

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

Hard copy worksheets may be provided for use as source document worksheets for recording on-site participant data. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

All clinical data (including applicable patient diary entries) shall be entered into a 21 CFR Part 11 compliant data system provided by a qualified data management vendor. Such a system will

include password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Data handling, cleaning and analysis shall be performed per Standard Operating Procedures by a qualified vendor. Missing or erroneous data anomalies will be communicated to the site(s) for clarification and correction.

8.2 Study Records Retention

Investigational centers shall retain all study records for a minimum of three years from the date of Federal Financial Report submission, or for up to 7 years from the date of product market clearance. No records will be destroyed without the written consent of the Sponsor. The Sponsor shall inform the study sites when the study records are no longer needed to be retained.

8.3 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 in addition to the clinical information relating to study 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.

All data obtained in the context of clinical trial are subject to data protection. The subject's name in addition to other data related to persons (excluding date of birth/age, and gender) are not to be disclosed by the investigator.

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 personal 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.

8.4 Future Use of Stored Specimens and Data

Data collected for this study will be analyzed and stored at the Sponsor or a qualified third party data management vendor. 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.

All study data remain the property of the study Sponsor.

9 Amendments

All protocol changes, modifications or amendments shall be initiated by the Sponsor and documented in writing. The Sponsor shall notify the Principal Investigators and submit changes for applicable regulatory authority for review. IRB/Ethics approval of the protocol changes must be received by Sponsor in writing before any change may be implemented at the study sites.

Withdrawal of IRB/Ethics approval must be submitted to Sponsor within five (5) business days of the change.

10 Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCPs, study manual, monitoring or analysis plans. 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.

Deviations shall be reported by the study site or study monitor to the Sponsor or qualified designee. Protocol deviations shall be sent to the reviewing Institutional Review Board (IRB) or local Ethics Committee per review board policy and/or to the Sponsor and IRB/Ethics Committee within 10 working days of knowledge of the event. These practices are consistent with ICH E6 GCP and 21 CFR Parts 50 and 56.

11 Device Accountability

Access to the investigational device shall be controlled and the Achilles infusion set shall be used only in this clinical investigation and according to the Clinical Investigation Plan presented here.

Capillary Biomedical, Inc. 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

a) the date of receipt,

b) identification of each investigational device (batch number/serial number or unique code),
c) the expiry date, if applicable,
d) the date or dates of use,
e) participant identification,
f) date on which the investigational device was returned/explanted from subject, if applicable, and
g) the date of return of unused, expired or malfunctioning investigational devices, if applicable.

12 Statements of Compliance

12.1 Declaration of Helsinki

This study will be conducted in accordance with the ethical principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013).

12.2 Standards and Regulations

This study will be conducted in compliance with this protocol, ISO 14155, designated Standard Operating Procedures, and with local laws and regulations relevant to the use of new medical devices in Australia.

12.3 Ethics Committee Approval

The clinical investigation proposed here shall not begin until the required approval from the local Ethics Committee and/or regulatory authority have been obtained.

12.4 Insurance

The study is sponsored and funded by Capillary Biomedical, Inc. Costs necessary to perform the study will be agreed upon prior to study start. Capillary Biomedical will arrange with the local sponsor for subject insurance for all participating participants. The investigators shall receive a copy of the insurance certificate and the insurance conditions. The latter must be known to the participants and made available on request.

13 Informed Consent Process

13.1 General

Informed consent shall be obtained in writing from the subject and the process shall be documented before any procedure specific to the clinical investigation is applied to the subject.

13.2 Process of Obtaining Informed Consent

The general process for obtaining informed consent shall be documented in the CIP and shall

a) ensure that the principal investigator or his/her authorized designee conducts the informed consent process,
b) include all aspects of the clinical investigation that are relevant to the subject's decision to participate throughout the clinical investigation,
c) avoid any coercion or undue improper influence on, or inducement of, the subject to participate,
d) not waive or appear to waive the subject's legal rights,
e) use native non-technical language that is understandable to the subject,
f) provide ample time for the subject to read and understand the informed consent form and to consider participation in the clinical investigation,
g) include personally dated signatures of the subject and the principal investigator or an authorized designee responsible for conducting the informed consent process,
h) provide the subject with a copy of the signed and dated informed consent form and any other written information, and
i) ensure important new information is provided to new and existing participants throughout the clinical investigation.

14 Adverse Events

14.1 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 21 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 150-1072-02 Feasibility Study Anticipated Adverse Event Definitions.

14.2 Adverse Device Effect (ADE)

All device deficiencies related to the identity, quality, durability, reliability, safety or performance of an investigational medical device shall be documented throughout the clinical investigation and appropriately managed by the sponsor.

14.3 Serious Adverse Event (SAE)

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 subject at immediate risk of death.

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.

The Principal Investigator or, at the direction of the Principal Investigator, study personnel will complete a serious adverse event (SAE) report and provide the information to the US and local sponsor contacts within 1 working day of the occurrence of the SAE. The Principal Investigator will inform the Ethics Committee of any Serious Adverse Events.

14.4 Serious Adverse Device Effect (SADE)

A Serious Adverse Device Effect is an event which resulted in any of the consequences characteristic of a SAE and is related to or associated with the investigational device.

14.5 Severity of Adverse Events

The following definitions for rating severity of adverse events may be used:

- Mild: Awareness of signs or symptoms, but easily tolerated, are of minor irritant type, causing no loss of time from normal activities, symptoms would not require medication or a medical evaluation, signs and symptoms are transient.

- Moderate: Discomfort severe enough to cause interference with usual activities, requiring medical treatment but not extended hospitalization or further intensive care for the subject.

- Severe: Incapacitating or debilitating, even of a temporary nature, causing inability to do work or usual activities, signs and symptoms may be of systemic nature or require medical evaluation and/or treatment, requiring additional hospitalization or intensive care (or prolonged hospitalization).

14.6 Relationship of Adverse Event to the Study Device

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.

14.7 Anticipated Adverse Device Effects (ADEs)

The anticipated adverse device effects for the Achilles infusion set are the same as those for commercially available insulin infusion sets (see section 5.5).

14.8 Unanticipated Adverse Device Effect (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, seriousness, , 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.

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 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.

15 Vulnerable Population

Individuals whose willingness to volunteer in a clinical investigation could be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of retaliatory response from senior members of a hierarchy in case of refusal to participate are considered vulnerable. This study is designed so that only adult patients in full control of their disease may participate (i.e. non-vulnerable populations).

16 Termination

Each subject's participation in the clinical study will be terminated following the post- monitoring examination or when all adverse events have been resolved. Prior to this time, the subject may voluntarily withdraw at any point in the study or the Investigator and/or CapBio may determine that it is in the best interests of the subject to be removed from the study.

The clinical study in its entirety will be considered complete upon receipt of reports for study monitoring activities, completion of a site closeout visits, and upon issuance of a final clinical study report. This final clinical study report will include all safety and performance data.

Upon completion or termination of a clinical study or Investigator's part in the study, or at Sponsor's request, an investigator shall return to Sponsor any remaining supply of the device or otherwise dispose of the device as Sponsor directs.

17 Publication Policy

All clinical information derived or obtained during this study shall be considered Sponsor confidential. The identity of individual participants will be kept confidential in so far as the law and safe medical practice allow. It is planned that the results of this study will be submitted for publication in scientific journals; patient identities will not be disclosed.

The Principal Investigator has the right to publish the methods, results of, and conclusions from the study. Sponsor will be furnished with a copy of any proposed publication for review and comment prior to submission for publication. Manuscripts will be forwarded to Sponsor at least 30 days prior to submission and abstracts at least 7 days prior to submission. At the expiration of the 30- or 7-day period, the investigator may proceed with submission for publication.

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