Longevity of Multi-Slitted Catheter, the Convatec Inset II with Lantern Technology

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CHAPTER 1: Introduction

Study Objective

To determine if the Convatec Inset II with Lantern technology (Convatec Lantern) infusion set with multi-slitted catheter, will have a longer time to failure than a previous infusion set without side ports, the Inset II/Mio.

Background and Rationale

The Diabetes Control and Complications Trial (DCCT) demonstrated that intensive glucose control delays the onset and slows the progression of retinopathy, nephropathy, neuropathy and cardiovascular disease for people with type 1 diabetes [1-2]. Multiple trials have shown improvements in glycemic control and a lower incidence of hypoglycemia in adults and children with diabetes who use insulin pump therapy [3-6]. The weak link in pump therapy is the infusion set that is inserted under the skin. It can become occluded or kinked and local inflammation and infection around the site can result in insufficient insulin delivery and high glucose levels which can lead to diabetic ketoacidosis [7].

Current infusion sets are approved for 2-3 days of wear [8-10], however, sensors are approved for 10 days of wear with greatest accuracy after the first day [11]. Thus, any attempt to create a combined sensor and insulin infusion set requires an infusion set with greater longevity. With the advent of closed-loop control, patients are required to wear both a sensor and insulin infusion set [12]. Out of 1006 people wearing a CGM, 27% discontinued CGM use after one year and 33% said this was because they did not want to have devices on two sites of their body [13-14]. Finding multiple, comfortable sites can be particularly challenging with younger children who have a smaller body surface area. Two groups have attempted to combine a sensor and infusion set into one device but it was not practical due to limited infusion set longevity [15-16].

When the sensor is in one location and the infusion set is in another, it means two separate insertions for the patient, and frequent reapplication of adhesive tapes to keep both devices in place. When the adhesive tape is removed a layer of epidermis is also removed, which is one of the natural barriers to infections. When subjects are wearing multiple devices with multiple adhesives there is also an increased risk for adhesive tape allergies (**Figure 1**). There would be a significant benefit to combining an insulin infusion set with a continuous glucose sensor if they both could be worn for 7-10 days.

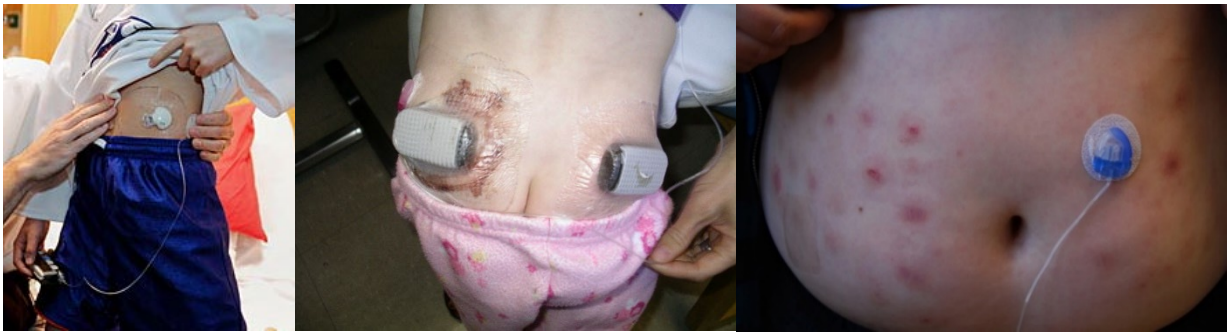

Figure 1. Children wearing sensor and infusion set with limited subcutaneous sites, leading to overcrowding and skin reactions

There are very few studies published on extended use of infusion sets beyond three days. Bode and colleagues studied the safety and efficacy of Novolog insulin in 19 subjects used the same infusion set tubing for 7 days and overall, no negative effects on glycemic control were observed during this period but it was noted that serum glucose levels began to increase the longer the infusion set was used [17]. There have been three published randomized trials assessing length of infusion set wear beyond 3 days. One study compared using insulin lispro to insulin aspart for 5 days of infusion set wear [18]. There was no difference between the two insulins, with an average length of infusion set wear of 98 and 96 hours, respectively. The researchers reported increased glucose levels after 48 hours of wearing an infusion set and recommended changing infusion sets every 2 days. We conducted a randomized, open-label, crossover study of 20 subjects who wore Teflon catheter (Quick-Set) and steel catheter (Sure-T) infusions set for 38 weeks and 39 weeks respectively with no difference in the survival curves of the infusion sets. The mean duration of wear was 5.5 days with a standard deviation of 1.9 days. Intersubject variation and the majority of failures were secondary to uncorrectable hyperglycemia which indicates insulin flow occlusions [19]. Another multicenter, crossover trial showed no difference in infusion set survival or mean glucose in 20 type 1 diabetes subjects wearing the sets in either lipohypertrophied and nonlipohypertrophied tissue [20].

Etiology of Infusion Set Failures

The underlying cause of intersubject variation in infusion set wear time is unknown but in the prior infusion set studies time to failure was primarily associated with hyperglycemia which did not improve with correction dose of insulin. In most of these subjects, there was no overt back-pressure error from the pump. “Silent occlusions” would be the most likely causative factor, and the additional slitted openings would reduce the risk of silent occlusions and subsequent hyperglycemia (**Figure 2**). The Lantern is designed to reduce failures due to kinking. Other less common causes for set failure would probably not be affected by the Lantern; these include 10-15% being pulled out by accident (tubing caught on a door handle for example), 6-12% from loss of adhesiveness, 5-13% removed for pain and 5-10% for erythema/induration concerning for infection. Approximately 30% of subjects reporting erythema/induration also reported pain [19-20, unpublished data]. In addition, this will be the first infusion set study to assess attitudes towards diabetes technology, which could also correlate with time to failure and explain some of the intersubject variability.

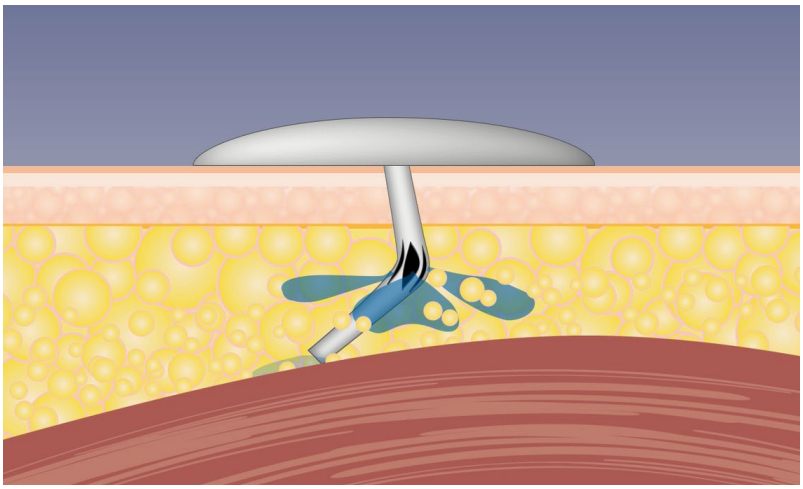

Figure 2. Lantern catheter being kinked by underlying muscle, but insulin continues to be delivered through side openings.

Preliminary Data

The single use infusion set is similar to the already CE approved Inset II infusion set with the addition of below features, and consists of an insertion device with introducer needle that inserts the soft cannula into the skin. The intervention infusion set presents a hydrophilic coated soft cannula with Lantern Technology – 6 slits (**Figure 3**).

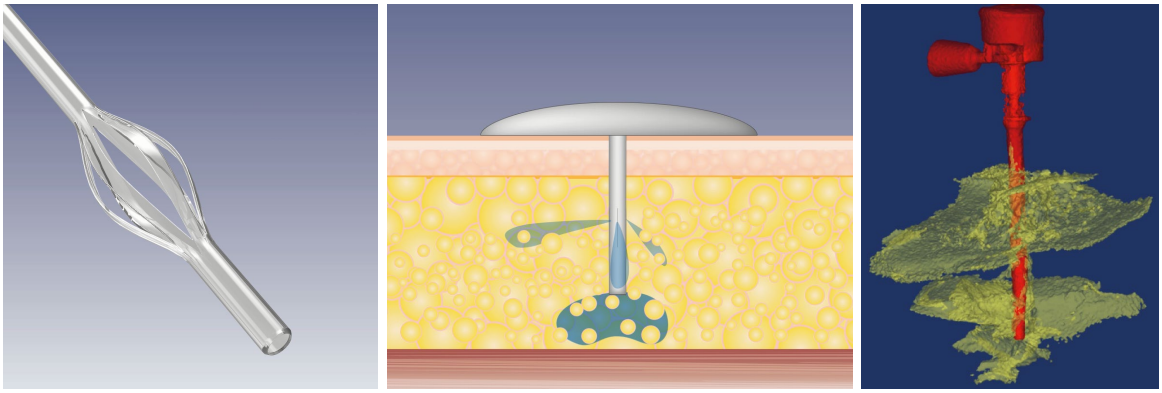

Figure 3. Lantern catheter (left) demonstration of increased surface area (middle) and µCT reconstruction of insulin delivery from an occluded catheter in human skin explant (right).

Materials in fluid paths has been tested with insulin lispro, aspart, glulisine and regular human insulin. A swine study conducted at the Medical University of Graz compared the immune response to insulin infusion systems of different materials over a course of 7 days of wear time in 10 female farm swine. The manufacturer analyzed the inflammatory response to 2 commercially available catheters (Teflon and steel) and 3 Teflon prototypes that were implanted into the subcutaneous adipose tissue for 1 day, 4 days and 7 days. Two of the three prototypes were coated with passive coatings, which suppress the inflammatory response without releasing an anti-inflammatory agent. The third prototype was a new all-in-one catheter design (blinded for investigator) that did not require a separate inserter. The impact of an anti-inflammatory passive coatings on the foreign body response was evaluated. All catheters were tested for a wear time of 1

day, 4 days and 7 days. Tissue was explanted and immune cells and connective tissue were stained using standard histopathological methods. This study indicated potential beneficial effects of passive anti-inflammatory coatings for insulin infusion catheters.

Another study conducted at the Joanneum Research Institute, Graz assessed the insulin distribution in subcutaneous adipose tissue when using infusion set with Lantern Technology. The infusion set was inserted into fresh human adipose tissue explants with the aim to investigate the effect of catheter designs on the formation of subcutaneous insulin depots. The study showed that the full functionality of the novel insulin catheter is guaranteed independent of whether the catheter is open, kinked or distally occluded. Therefore, it is not necessary to replace a kinked catheter or a catheter with a clogged tip from the viewpoint of proper insulin delivery, which reduces the incidence of unexplained hyperglycemia and even ketoacidosis which can be associated with infusion set failures, as well as decreasing the discomfort for patients of inserting multiple infusion catheters as a result of early failure. Study investigators concluded that the new infusion catheter can provide a valuable contribution to patients' well-being and safety.

In data that will be presented at the American Diabetes Association 2018 meeting, glucose clamp studies were conducted in Graz among 16 patients with type 1 diabetes (age 44.2 ± 15.4 years, BMI 24.5 ± 2.3 kg/m^2, HbA1c 55 ± 8 mmol/mol, diabetes duration 20 ± 9 years) with type 1 diabetes. All 16 patients wore the set for 7 days without severe hypoglycemia or diabetic ketoacidosis. Geometric means of maximum glucose infusion rates were comparable for days 1, 4 and 7. This preliminary data strongly supports the safety of this infusion set and the need for real world testing of longevity.

Protocol Synopsis

<u>Part 1: Pilot Safety and Extended Wear Tolerability Study</u>

This is a pilot study to obtain preliminary data upon which to base the length of wear for the second part of the study. The study is not intended for registration purposes or to support a 510(k) submission. The study will be conducted at one site: Stanford University.

This study will enroll 24 subjects to establish the maximum length of Lantern infusion set wear when 80% of sets are still functional (excluding accidental "pull-outs"). We will plan for a staged enrollment, the first 10 subjects will be 18 or older. If there are no untoward effects we will begin enrolling participants age 15-18. Each participant will place the set and wear it for 10 days or until set failure and data will be collected on the cause of set failure. If a set is accidentally pulled out, it can be replaced by the subject. Subjects will either complete a daily online questionnaire or they will be contacted daily by research staff to determine if a set has failed, the cause of failure, and to record measured erythema and edema at a failed infusion site. Failures are based on:

1. Presence of serum ketones with hyperglycemia
2. Unexplained hyperglycemia
3. Signs of infection at the infusion site

4. Pump occlusion alarm
5. Adhesive failure

Since infusion set failures will occur after variable lengths of wear, regularly scheduled visits are unlikely to capture the day of an infusion set failure. Instead the subject will be taught how to insert the set, measure erythema and induration with a ruler marked in millimeters and to take a picture of the infusion site. Subjects will be instructed to text the study team when they remove their infusion set and to send a picture of the infusion site and measurements. If there is any evidence of an infection (≥10 mm of erythema or induration), they will be asked to come in that day for an unscheduled visit.

<u>Part 2: Extended Wear Randomized Controlled Crossover Study</u>

This will be a masked, randomized controlled crossover study at Stanford University (**Figure 4**). The study is intended for registration purposes and to support a 510(k) submission. The planned duration of wear and visit schedule will be determined by the results of Part 1. Participants, age 15 and over, will be randomized to wear the masked investigational or control infusion set first. The control set is the Mio (used with Medtronic pumps) or Inset II (used with other pump models) which are the precursors to the Convatec Lantern and do not contain slits. Each participant with wear both the investigational and control infusion set. Subjects will act as their own control.

At home subjects will examine their infusion site when they are changing an infusion set and assess for signs of bleeding, local tissue reaction or infection. They will record redness, induration, and bruising in mm, and call one of the investigators if there is more than 10 mm of erythema or induration. They will be given a ruler for making these measurements. If there is more than 3 mm of induration or redness they will be asked to take a picture and enter these measurements and send a text to the study coordinator.

They will be instructed to replace the infusion set for:

1. Presence of serum ketones with hyperglycemia
2. Unexplained hyperglycemia
3. Signs of infection at the infusion site
4. Pump occlusion alarm
5. Adhesive failure

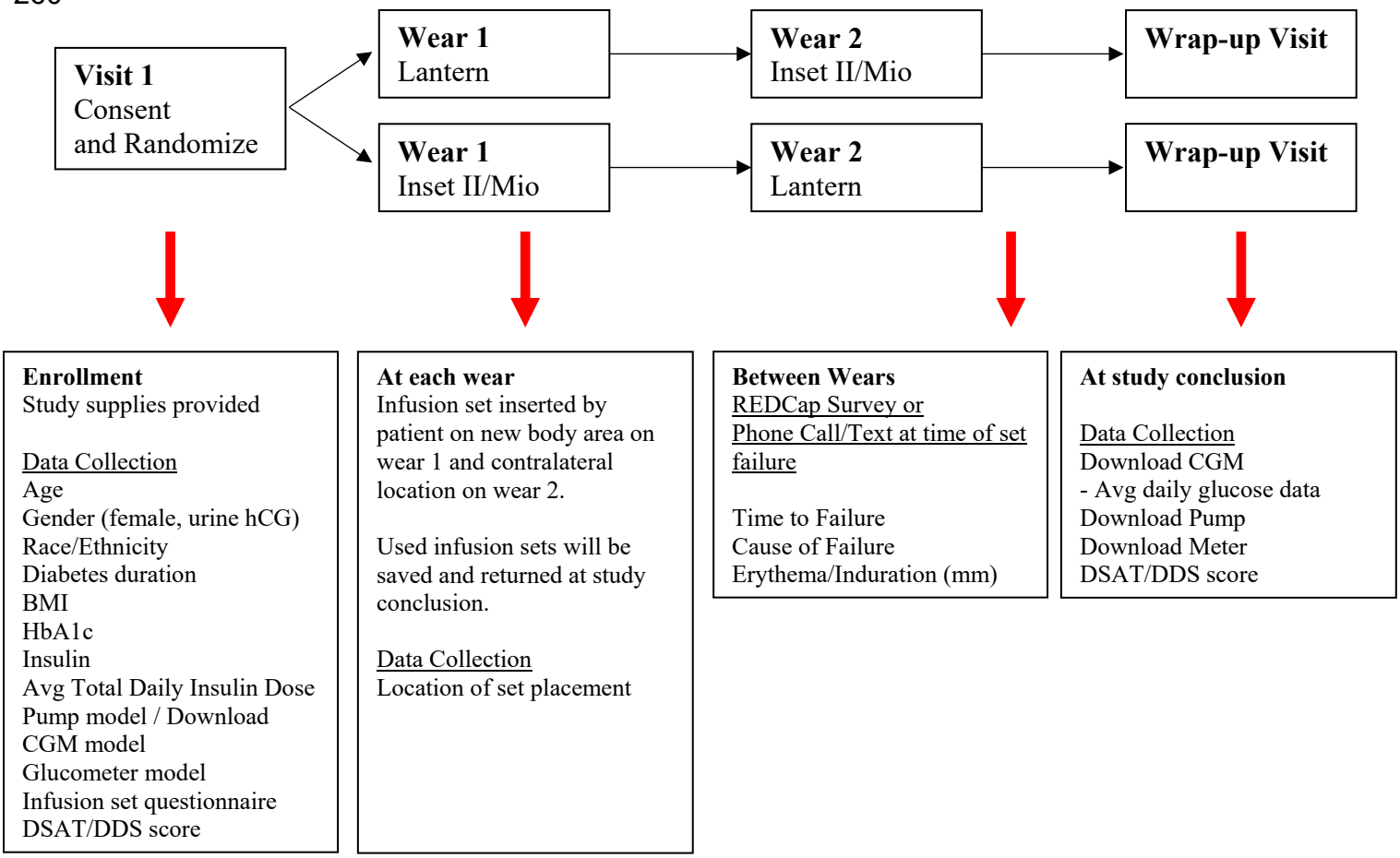

Figure 4. Study Diagram

General Considerations

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

CHAPTER 2: Subject Enrollment and Study Initiation

Study Enrollment and Duration

Part 1: 24 subjects – Maximum of 10 days of wearing a single Lantern infusion set.
Part 2: 40 subjects – Each subject will wear control (Inset II/Mio) and experimental (Lantern) infusion set for the number of days determined from Part 1

Eligibility Criteria

To be eligible for the study, a subject must meet the following criteria:

1. Age 15 and over
2. On tethered insulin pump therapy with any rapid acting insulin, for at least 3 months
3. Hemoglobin A1c level less than or equal to 10%
4. Eating more than 60 grams of carbohydrate each day
5. For females, not currently known to be pregnant
6. Understanding and willingness to follow the protocol and sign informed consent
7. Willingness to wear the experimental infusion sets
8. Willingness to have photographs taken of their infusion sites
9. Ability to speak, read and write in the language of the investigators

Exclusion Criteria

The presence of any of the following is an exclusion for the study:

1. Diabetic ketoacidosis in the past 3 months
2. Severe hypoglycemia resulting in seizure or loss of consciousness within 3 months prior to enrollment
3. Pregnant or lactating
4. Known tape allergies
5. Active infection
6. A known medical condition that in the judgment of the investigator might interfere with the completion of the protocol
7. Known cardiovascular events in the last 6 months
8. Known acute proliferative diabetic retinopathy
9. Known adrenal disorder
10. Current treatment for a seizure disorder
11. Inpatient psychiatric treatment in the past 6 months
12. Lack of stability on medication 1 month prior to enrollment including antihypertensive, thyroid, anti-depressant or lipid lowering medication.
13. Use of SGLT inhibitor
14. Suspected drug or alcohol abuse
15. Dialysis or end stage kidney disease

Note: Adequately treated thyroid disease and celiac disease do not exclude subjects from enrollment.

Recruitment Plan

We will contact subjects using our existing database of patients who have consented to be contacted about future diabetes research studies. A short description of the present study will be given to them via email, phone or in-person. We will also recruit subjects at the time of their scheduled appointments. A one-page brochure will be prepared and sent to providers who have referred patients to us in the past. Information on the study will also be posted on our website, and the information provided on the brochure will also be made available to diabetes support groups in our area. If a person expresses interest, then the study will be presented in detail. The study will be eligible to people with type 1 diabetes who are not currently enrolled in other intervention studies. Subjects participating in a registry study (no interventions) may participate.

Informed Consent Plan and HIPAA Authorization

The subject will be allowed sufficient time to read over the IRB approved consent form and given opportunity to have all questions answered. The consent will contain a brief description of the research project, as well as the procedures and treatments to be undertaken, and the risks of each treatment and procedure. Consent form will be obtained by delegated research staff. The PI and study staff will be available to fully discuss consent with the subjects as needed. Subjects have the right to withdraw at any time during the study. For eligible subjects, the study will be discussed with the subject (and parent/legal guardian if the subject is a minor, referred to subsequently as 'parent'). The subject/parent will be provided with the Informed Consent Form to read and will be given the opportunity to ask questions. If the subject agrees to participate, the Informed Consent Form will be signed. A copy of the consent form will be provided to the subject and another copy will be added to the subject's clinic chart. Written informed consent must be obtained from the subject prior to performing any study-specific procedures that are not part of the subject's routine care not part of the subject's routine care.

Eligibility Assessment and Baseline Data Collection

Potential subjects will be evaluated for study eligibility through the elicitation of a medical history, performance of a physical examination by study personnel. A history will be elicited from the subject and additional information may be extracted from available medical records. The history will include the subject's diabetes history, current diabetes management including insulin pump download, other past and current medical problems, past and current medications, and drug allergies. A diabetes focused physical exam (including vital signs and height and weight measurements) will be performed by the study investigator or designee (an attending physician, fellow, nurse practitioner or a physician assistant). Particular attention will be given to insulin infusion sites for chronic and acute skin and subcutaneous changes including reactions to adhesives, lipohypertrophy, subcutaneous nodules and scarring. Participants will receive a questionnaire regarding experiences with infusion sets. We will also perform previously validated questionnaires, the "Diabetes-Specific Attitudes about Technology Use" (DSAT) [21] and "Diabetes Distress Scale" (DDS) [22].

HbA1c level will be measured using on site point-of-care testing. HbA1c measurements performed as part of usual clinical care within 2 weeks prior to obtaining informed consent for participation in the trial may be used. In female participants a urine pregnancy test will be performed.

Authorization Procedures

As part of the informed consent process, each subject (and parent for minors) will be asked to sign an authorization for release of personal information. The investigator, or his or her designee, will review what study specific information will be collected and to whom that information will be disclosed. After speaking with the subject (and parent for minors), questions will be answered about the details regarding authorization.

CHAPTER 3: Protocol Procedures

Part 1: Pilot Safety and Extended Wear Tolerability Study

First Visit

Informed Consent Process: The protocol will be reviewed with the subjects, they will be given time to read the informed consent and ask any questions about the study. Demographic information for eligibility including age, gender, diabetes duration and duration of pump use will be collected.

History and physical exam: Race/ethnicity will be recorded, as well as information about diabetes care including diabetes duration, insulin (Aspart, Lispro, Fiasp or Glulisine), average total daily insulin dose, carbohydrate consumption, pump model, CGM model, glucometer model and infusion set questionnaire. Physical exam will be performed including vital signs, height, weight, BMI and examination of skin where infusion set, and sensor will be inserted.

Laboratory Studies: Point-of-care hemoglobin A1c, and pregnancy test for all females.

Initiation visit and placement of infusion set: At the enrollment visit, subjects are provided with study supplies that they do not already have, including Dexcom G6 CGM, glucometer, and Precision Xtra ketone meters. Glucometers will be tested with control solutions by study staff to ensure accuracy before being provided to patients. Education will be provided on the use of these devices. Subjects will continue to use their personal insulin pump and insulin as usual. The patient's insulin pump will be downloaded. Infusion sets will be placed in a suitable subcutaneous location without lipohypertrophy by the patient. If a set failure occurs prior to 10 days, they will return to using their usual infusion set. If a set fails within 24 hours of insertion, it will be replaced and the second set worn up to 10 days. As in the prior studies [19-20], participants will be contacted by the study investigators to collect data regarding the site (erythema/induration measured in millimeters) and set failure on a daily basis, either through REDCap, a text message exchange, or a phone call.

Home Monitoring

Training on home procedures: Subjects will use Dexcom G6 according to manufacturer labeling. While the G6 system is FDA approved for non-adjunctive use without calibration, we will ask patients to confirm their blood glucose with their study glucometer prior to removing an infusion set. Subjects will be instructed to check blood ketones using a blood ketone meter if there is unexplained hyperglycemia. Unexplained hyperglycemia refers to high glucose levels outside of the usual times they may occur, such as in the initial few hours following a meal. If the CGM stops functioning during the study, the subjects will insert a new sensor which will be provided to them. If there is an accidental removal of an infusion set the participant will have access to a replacement which he or she will be taught to place.

Determination of an infusion set failure:

They will be instructed to replace their infusion set, in the following situations.

1. The presence of serum ketones >0.6 mmol/L with meter glucose >250 mg/dL, in the absence of illness, vigorous fat burning exercise, starvation or alcohol.
2. Unexplained hyperglycemia, >250mg/dL, outside anticipated periods of carbohydrate consumption, illness, missed insulin doses and menstruation. This hyperglycemia cannot be reduced with appropriate correction doses of insulin (such as a decrease of at least 50mg/dL in 1 hour following a correction dose).
3. Signs of infection at the infusion site including pain, erythema or induration >10 mm in diameter.
4. Pump occlusion alarm
5. Adhesive failure (only the adhesive on the infusion set will be used)

Recording of infusion site information: At home they will examine their infusion site each day for signs of redness and/or induration. If they detect redness or induration they will record them in mm and send a text to study staff. At the time an infusion set is removed they will record redness and induration in millimeters, and call one of the investigators if there is more than 10 millimeters of erythema or induration. They will be given a ruler for making these measurements. Subjects will record the time and date that infusion sets or sensors are removed, and document why they removed the set and take a picture of the infusion site after the infusion set is removed if there is ≥3 mm of erythema. The picture and infusion site measurements will be sent via text or e-mail to study staff, if there is not concern about infection.

Final Visit

Within fourteen days after the study infusion set was inserted, subjects will have their final study visit. At the final study visit all infusion sets, glucose sensors, study pumps and transmitters provided by the study will be returned.

Part 2: Extended Wear Randomized Controlled Crossover Study

First Visit

Informed Consent Process: The protocol will be reviewed with the subjects, they will be given time to read the informed consent and ask any questions about the study. Demographic information for eligibility including age, gender, diabetes duration and duration of pump use will be collected.

History and physical exam: Race/ethnicity will be recorded, as well as information about diabetes care including diabetes duration, insulin (Aspart, Lispro, Fiasp or Glulisine), average total daily insulin dose, carbohydrate consumption, pump model, CGM model, glucometer model and infusion set questionnaire. DSAT and DDS questionnaires will be performed to assess attitudes towards diabetes technology. Physical exam will be performed including vital signs, height, weight, BMI and examination of skin where infusion sets and sensors will be inserted.

Laboratory Studies: Point-of-care hemoglobin A1c, and pregnancy test for all females.

Initiation visit and placement of infusion set: Subjects will be block randomized to initially wear a Lantern infusion set or an Inset II/Mio (standard infusion set). At the enrollment

visit, subjects are provided with study supplies that they do not already have, including Dexcom G6 CGM, glucometer, and Precision Xtra ketone meters. Glucometers will be tested by study staff to ensure accuracy before being provided to patients. Education will be provided on the use of these devices. Subjects will continue to use their personal insulin pump and insulin as usual. The patient's insulin pump will be downloaded. Subjects will be instructed on inserting both infusion sets, which share a common insertion procedure. Infusion sets will be placed in a suitable subcutaneous location without ipsilateral or contralateral lipohypertrophy by the patient. Duration of wear will be determined from study part 1. If a set fails within 24 hours it will be replaced with a research infusion set for the study arm they are assigned to. If a set failure occurs after 24 hours, they will return to using their usual infusion set.

Home Monitoring

Training on home procedures: Subjects will use Dexcom G6 according to manufacturer labeling. While the G6 system is FDA approved for non-adjunctive use without calibration, we will ask patients to confirm blood glucose with glucometer prior to removing an infusion set. Subjects will be instructed to check blood ketones using a blood ketone meter if there is unexplained hyperglycemia. Unexplained hyperglycemia refers to high glucose levels outside of the usual times they may occur, such as in the initial few hours following a meal. If the CGM stops functioning during the study, the subjects will insert a new sensor which will be provided to them. If there is an accidental removal of an infusion set the participant will have access to a replacement which he or she will be taught to place.

Determination of an infusion set failure:

They will be instructed to replace the infusion set, in the following situations.

1. The presence of serum ketones >0.6 mmol/L with meter glucose >250 mg/dL, in the absence of illness, vigorous fat burning exercise, starvation or alcohol.
2. Unexplained hyperglycemia, >250mg/dL, outside anticipated periods of carbohydrate consumption, illness, missed insulin doses and menstruation. This hyperglycemia cannot be reduced with appropriate correction doses of insulin (such as a decrease of at least 50mg/dL in 1 hour following a correction dose).
3. Signs of infection at the infusion site including pain, erythema or induration >10 mm in diameter.
4. Pump occlusion alarm
5. Adhesive failure (only the adhesive on the infusion set will be used)

Recording of infusion site information: At home they will exam their infusion site each day for signs of redness and/or induration. If they detect redness or induration they will record them in mm and send a text to study staff. At the time an infusion set is removed they will record redness and induration in millimeters, and call one of the investigators if there is more than 10 millimeters of erythema or induration. They will be given a ruler for making these measurements. Subjects will record the time and date that infusion sets or sensors are removed, and document why they removed the set and take a picture of the infusion site after the infusion set is removed if there is ≥ 3 mm of

induration or erythema. The picture and infusion site measurements will be sent via text or e-mail to study staff, if there is not concern about infection.

Second infusion set placement: After the duration of wear established from study part 1 elapses the patient will place the second infusion set type in the contralateral body area. The same failure criteria and reporting will be used for the other set.

Final Visit

After the last infusion set was inserted, subjects will have their final study visit to evaluate the infusion site. The insertion sites will be examined, erythema, induration and local skin reaction will be measured and photographs taken for any significant changes. Their insulin pump, CGM, blood glucose and ketone meter will be downloaded. All infusion sets, glucose sensors, study pumps and transmitters provided by the study will be returned. Additionally, the DSAT and DDS questionnaires will be repeated.

CHAPTER 4: Adverse Event Reporting and Protocol Monitoring

Definition

A reportable adverse event is any untoward medical occurrence that meets criteria for a serious adverse event or any unexpected medical occurrence in a study subject that is study or device-related. Skin irritation from sensor wear will be recorded in specific sections of the case report forms. An adverse event form is only completed if skin irritation is severe or antibiotics are required.

Hypoglycemic events are recorded as Adverse Events if the event required assistance of another person due to altered consciousness to actively administer carbohydrate, glucagon, or other resuscitative actions. This means that the subject was impaired cognitively to the point that he/she was unable to treat him or herself, was unable to verbalize his or her needs, was incoherent, disoriented, and/or combative, or experienced seizure or coma. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. If plasma glucose measurements are not available during such an event, neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

Hyperglycemic events are recorded as Adverse Events if the event involved diabetic ketoacidosis, as defined by the DCCT, and had all of the following:

1. Symptoms such as polyuria, polydipsia, nausea, or vomiting
2. Serum ketones greater than 1.6 mM, or large/moderate urine ketones
3. Either arterial blood pH <7.30 or venous pH <7.24 or serum bicarbonate <15
4. Treatment provided in a health care facility

Recording of Adverse Events

Throughout the course of the study, all efforts will be made to remain alert to possible adverse events or untoward findings. The first concern will be the safety of the subject, and appropriate medical intervention will be made.

The investigator will elicit reports of adverse events from the subject at each visit and complete all adverse event forms online. Each adverse event form is reviewed by the Coordinating Center to verify the coding and the reporting that is required.

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

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

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

Adverse events will be coded using the MedDRA dictionary.

Definitions of relationship and intensity are listed on the website data entry form.

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

Reporting Serious or Unexpected Adverse Events

A serious adverse event is any untoward occurrence that: Results in death; is life-threatening (a non life-threatening event which, had it been more severe, might have become life-threatening, is not necessarily considered a serious adverse event); requires inpatient hospitalization or prolongation of existing hospitalization; results in a disability or permanent damage which causes a substantial disruption of a person's ability to conduct normal life functions; results in a congenital anomaly/birth defect; requires intervention to prevent permanent impairment or damage (Devices); or any other serious (Important Medical Event) which may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent a serious adverse event.

An Unanticipated Adverse Device Event is defined as an adverse event caused by, or associated with, a device, if that effect or problem was not previously identified in nature, severity, or degree of incidence.

Serious or unexpected adverse events must be reported to the Principal Investigator immediately.

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The principle investigator will notify all participating investigators of any adverse device event that is both serious and unexpected. Notification will be made within 10 days after becoming aware of the event.

Each investigator is responsible for informing his/her IRB of serious study-related adverse events and abiding by any other reporting requirements specific to their IRB.

If a serious or unexpected adverse event occurs, the Principal Investigator will prepare a report to the study sponsor within 5 days, and a report will also be sent to the IRB and FDA within 10 days if the adverse event is serious or an unexpected device event. The

principal investigators will meet to decide the appropriate action to be taken, i.e. continue study unmodified, modify study or stop study.

Potential Risks and Side Effects

Local Reaction

With insulin infusion sets there is a low risk for developing local skin infections which may be increased by the prolonged wear of infusion sets from the recommended 3 days to 10 days for this study. Itchiness, redness, bleeding, and bruising at the insertion site might also occur. Local tape allergy is a possibility as well. These risks may also be increased when patients use insulin infusion sets for longer than 3 days.

Invasive Testing

All subjects will be required to perform fingerstick blood glucose tests and fingerstick for measurement of HbA1c. While part of routing diabetes care, this can be painful and distressing to some patients. There is a very slight risk of infection and bruising at the site of the fingerstick.

Hypoglycemia

As with any person having insulin-dependent diabetes, there is always a risk of having a low blood sugar (hypoglycemia). The frequency of nocturnal hypoglycemia should be no more than it would be as part of daily living with diabetes. Symptoms of hypoglycemia can include sweating, jitteriness, and not feeling well. Just as at home, there is the possibility of loss of consciousness or seizures (convulsions) and that for a few days you may not be as aware of symptoms of low blood sugar. Even if severe low blood sugar does occur, it almost always goes away quickly with treatment to raise the blood sugar.

Hyperglycemia

Since we are asking subjects to wear an insulin infusion set for 10 days, there will be a higher risk for hyperglycemia occurring than would occur if infusion sets were changed every three days. A delayed change in an infusion set could therefore cause an additional episode of hyperglycemia with extended infusion set wear. Since subjects will be performing frequent monitoring of their blood glucose and monitoring blood ketone levels in the event of hyperglycemia, these events should be of limited duration and ketosis should be detected early and easily treated.

Protection against Risks and Treatment of Side Effects

Subjects will be given descriptions of possible local side effects with insulin infusion sets or sensor insertion sets. They will be told to contact the study staff if they see any signs of a skin reaction. Based on the severity of local skin reaction, topical anti-inflammatory medications can be used (such as topical steroids).

Subjects will be instructed on the signs and symptoms of hypoglycemia and hyperglycemia, and appropriate management to correct these states. They will be instructed in the use of glucagon emergency kit for reversal of severe hypoglycemia. For hyperglycemia, they will be instructed to ensure the insulin pump is appropriately

functioning, and there are no obstructions in the insulin infusion set. They will also be instructed to check serum ketones. If hyperglycemia persists, they will be instructed to use subcutaneous insulin injections, and change to a new insulin infusion set.

All subjects that wish to have a topical anesthetic applied prior to inulin infusion set and Continuous Glucose Monitoring (CGM) sensor insertion will have this option available to them.

Other Risks

Some subjects may develop skin irritation or allergic reactions to the adhesives used to secure the CGM sensor or infusion set. If these reactions occur, different adhesives or "under-taping" (such as with IV 3000, Tegaderm, etc.) will be tried, sites will be rotated frequently, and a mild topical steroid cream or other medication may be required.

Whenever the skin is broken there is the possibility of an infection. The CGM sensor and insulin infusion set sites are inserted under the skin. It is possible that any part that is inserted under the skin may cause an infection. These occur infrequently, but, if an infection was to occur, oral and/or topical antibiotics can be used, and they generally respond quickly to a short course of oral antibiotics such as cefaclor. The risk of skin problems could be greater if a sensor or infusion set is used for extended periods of time. Therefore participants will be carefully instructed about daily inspection of their sensor and infusion set sites.

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

CHAPTER 5: Miscellaneous Considerations

Potential Benefits

Continuous Glucose Monitoring (CGM) data will provide each subject individualized information about their glucose response to variables such as meals and exercise that may help in their management of diabetes.

The ability to wear an infusion set for extended periods may help decrease local skin reactions from the frequent insertion and removal of infusion sets which results in removal of portions of the top layer of the epidermis which may lead to a higher risk of infections if a new infusion set or sensor is inserted into this area before the epidermis is completely healed.

If there is less unexplained hyperglycemia and fewer episodes of ketosis with prolonged infusion set wear as a result of the Lantern infusion set, this would be a significant benefit to all people using insulin infusion pumps.

If the Lantern infusion set could extend the use of a subcutaneous infusion sets to 7-10 days, this would allow of the future development of a combination infusion set and continuous glucose sensor. Such a platform would play an integral role in the development of a simplified closed-loop artificial pancreas system.

Subject Compensation

Subjects will be compensated $50 for each outpatient study visit and $20 for each entry into REDCap or contact with a study investigator. Maximum payment of $280 for all study visits in Part 1 and $530 for participating in Part 2. Compensation of partial participation will be prorated.

Subject Withdrawal

Participation in the study is voluntary, and a subject may withdraw at any time. The investigator may withdraw a subject who is not complying with the protocol. For subjects who withdraw, their data will be used up until the time of withdrawal.

Subject Discontinuation Criteria

Subjects who become pregnant will be discontinued from the study. The investigator may withdraw a subject who is not complying with the protocol. Withdrawal of a subject will be considered for the following reasons:

1. Failure to monitor their sensor and infusion sites on a daily basis
2. Developing >1.0 mmol/L ketones on 2 or more occasions and failing to change their infusion set or a single episode of diabetic ketoacidosis due to an infusion site failure

For subjects who withdraw or who are withdrawn, their data will be used for analysis purposes up until the time of withdrawal.

Confidentiality

For security and confidentiality purposes, subjects will be assigned an identifier that will be used instead of their name. De-identified subject information may be provided to the funder.

Level of Risk

This research proposal in children is consistent with United States Department of Health and Human Services, Protection of Human Subjects, Subpart D, Section 46.404 (Research not involving more than minimal risk).

Planned Duration of the Entire Study

Planned duration of the entire study will be 12 months.

CHAPTER 6: Statistical Considerations

Part 1

Before beginning a larger cross-over study we would perform this pilot study to determine the maximum length of Lantern infusion set wear when 80% are still functional if failure was not due the infusion set being accidentally pulled out. This study is not statistically powered.

Part 2

Primary Outcome

Our primary outcome will be time to failure of each infusion set. We have reviewed 353 weeks of infusion set wear from prior studies [19-20, unpublished data] and subjects who wear the control set have an average length of wear of 5.1 days with a standard deviation of 1.7 days and intra-subject correlation of 0.69. For a meaningful clinical benefit, the subjects who wear the treatment set should extend wear by at least 1 day to an average length of wear of 6.1 days. A sample size of 40 subjects will provide 95% power to detect a difference of 1 day in the average length of wear in a two-sided test with an alpha level of 0.05. A minimum of 25 subjects must be recruited for 80% power.

Exploratory Outcomes

Other outcomes will include – BMI, cause of infusion set failure, measurements of erythema and induration, pump insulin delivery data, glucometer readings, ketone meter data, average daily CGM blood glucose, DSAT/DDS score and infusion set questionnaire.

We will summarize the other secondary measures using means, standard deviation, medians, ranges, proportions and 95% confidence interval, as appropriate. We will also explore the relationship between BMI, DSAT/DDS score and the time to failure primary outcome. Finally, we will test if there is a significant change in the DSAT/DDS score following participation in the clinical trial.

CHAPTER 7: References

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