Evaluation of Fiasp® (Fast acting insulin aspart) in 670G Hybrid Closed-loop Therapy

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CHAPTER 1: INTRODUCTION

1.1 Study Objectives:

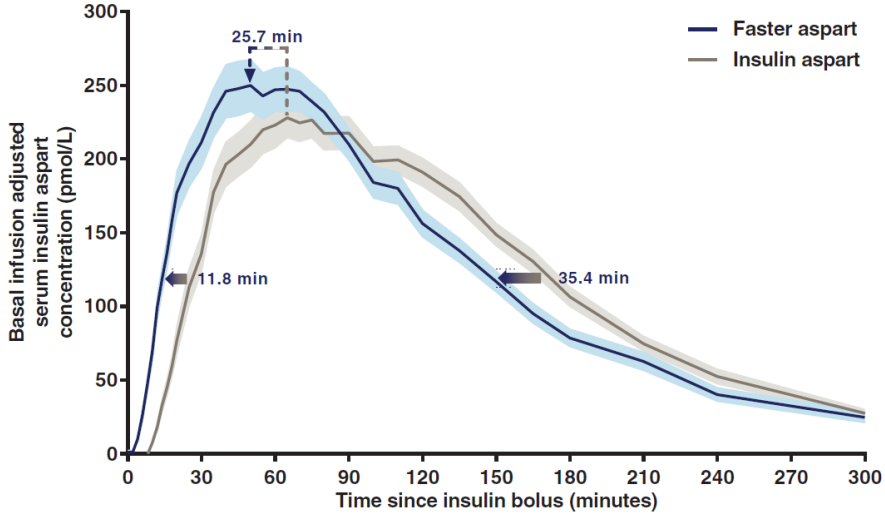
To assess the effect of using Fiasp® in a closed-loop system:
Part 1: To assess how the 670G system adapts to the introduction of Fiasp® insulin
Part 2: To assess changes experienced clinicians will make to the use of Fiasp® insulin in the 670G pump

1.2 BACKGROUND INFORMATION

1.2.1 Fiasp®

Faster-acting insulin aspart (faster aspart or Fiasp®) is insulin aspart in a new formulation that contains two well-known excipients generally recognized as safe (GRAS), niacinamide and L-arginine. These are both listed in the US Food and Drug Administration inactive ingredient database, in products for injection, at higher concentrations than used in Fiasp®. With Fiasp®, niacinamide is considered responsible for faster initial absorption after subcutaneous administration and L-arginine serves as a stabilizing agent. In subjects with type 1 diabetes mellitus (T1DM), Fiasp® administered by subcutaneous injection had twice-as-fast onset of appearance, a 2-fold higher early exposure, and >50% greater early glucose-lowering effect compared with insulin aspart [1,2]. When Fiasp® is administered by subcutaneous insulin infusion pump therapy, the rapid onset of action is even more pronounced. The time to half-maximal activity was reduced by 11.8 minutes, the time to peak activity was reduced by 25.7 minutes, and the duration of insulin activity was reduced by 35.4 minutes when compared to insulin aspart [3] (see Figure 1 below).

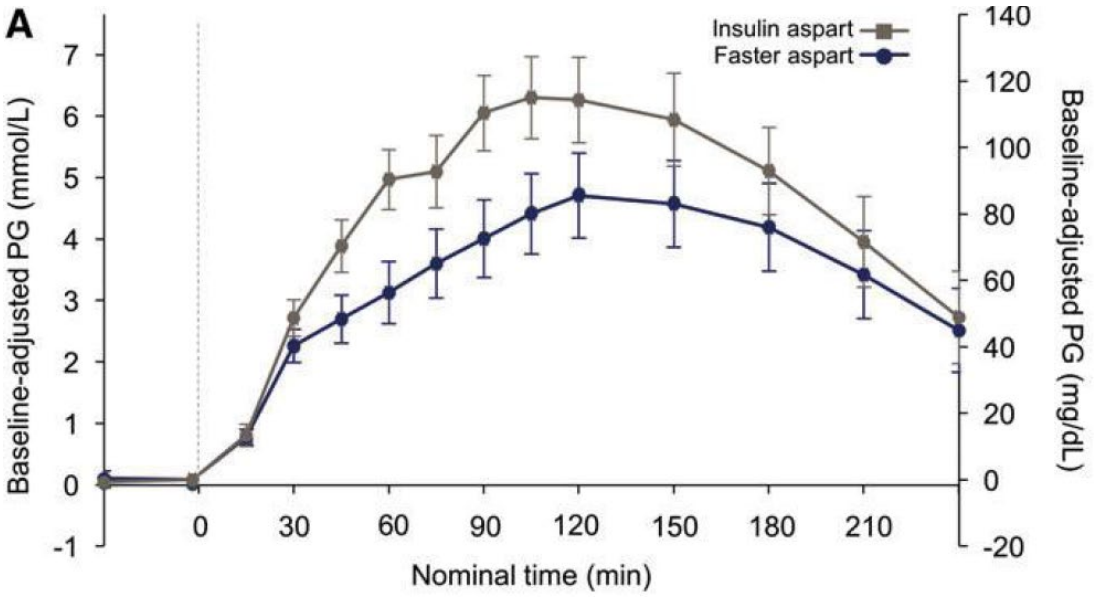
Figure 1-1: Fiasp® Pharmacokinetics. A bolus of 0.15 U/kg of aspart (grey) (n=46) or Fiasp® (blue) (n=44) was given subcutaneously by an insulin pump and serum insulin concentrations were measure.



In a 6 week double-blind, randomized, crossover active-controlled trial comparing aspart to

Fiasp® using continuous subcutaneous insulin infusion (CSII) pump therapy, the Fiasp® two hour post prandial glucose levels were significantly lower following a standardized meal test [4] (Figure 1-2)

Figure 1-2: Mean baseline-adjusted plasma glucose levels following either insulin aspart (in grey) or Fiasp® (in blue) given as an insulin pump bolus at the onset of a standardized liquid meal (Boost) which has 102 grams of CHO. The bolus calculator in their pump was used for each meal dose.



The more rapid onset of action and shorter duration could be very beneficial to full closed-loop control allowing an earlier onset of insulin action to cover the postprandial glucose rise, and decreasing the residual insulin after a meal to prevent late hypoglycemia. Fiasp® has not been tested in a hybrid closed-loop system.

Fiasp® was approved by the FDA on September 29, 2017 for people with type 1 and type 2 diabetes in a pre-filled FlexTouch® pen and in 10 ml vials. It was approved to be given by injection, but not for use in pumps. In Europe it was approved for use by injections and in insulin infusion pumps. In both the US and Europe it was approved for use in pregnancy. There has been one study published on pump compatibility of Fiasp® [5] which showed a premature end of infusion set wear in 10% of 210 Fiasp® infusions, and 4% of 98 aspart infusions (p=ns).

1.2.2 Medtronic 670G Hybrid Closed-loop

The Medtronic 670G hybrid closed loop system is the first fully integrated system designed for continuous day and night closed-loop control. The system requires meal announcement with an estimate of carbohydrate intake and a premeal insulin bolus to optimize glucose excursions. We published the first results of using this system in 2015 in adolescents attending a diabetes camp [6], and the 670G system was approved for commercial sale by the FDA on September 28th, 2016. We have had adolescents using this system for 2 ½ years, 7-14 year olds using the system for 15 months, and 5 to 6 year olds have been using

this system at Stanford for over 3 months as part of the pivotal trials with extended use of the system after the initial 3 month pivotal phase. Both the adult and pediatric clinics now have patients using the 670G system.

Figure 1-3: Medtronic 670G system: Medtronic 670G pump, Guardian 3 continuous glucose sensor, and Bayer Link glucose meter.

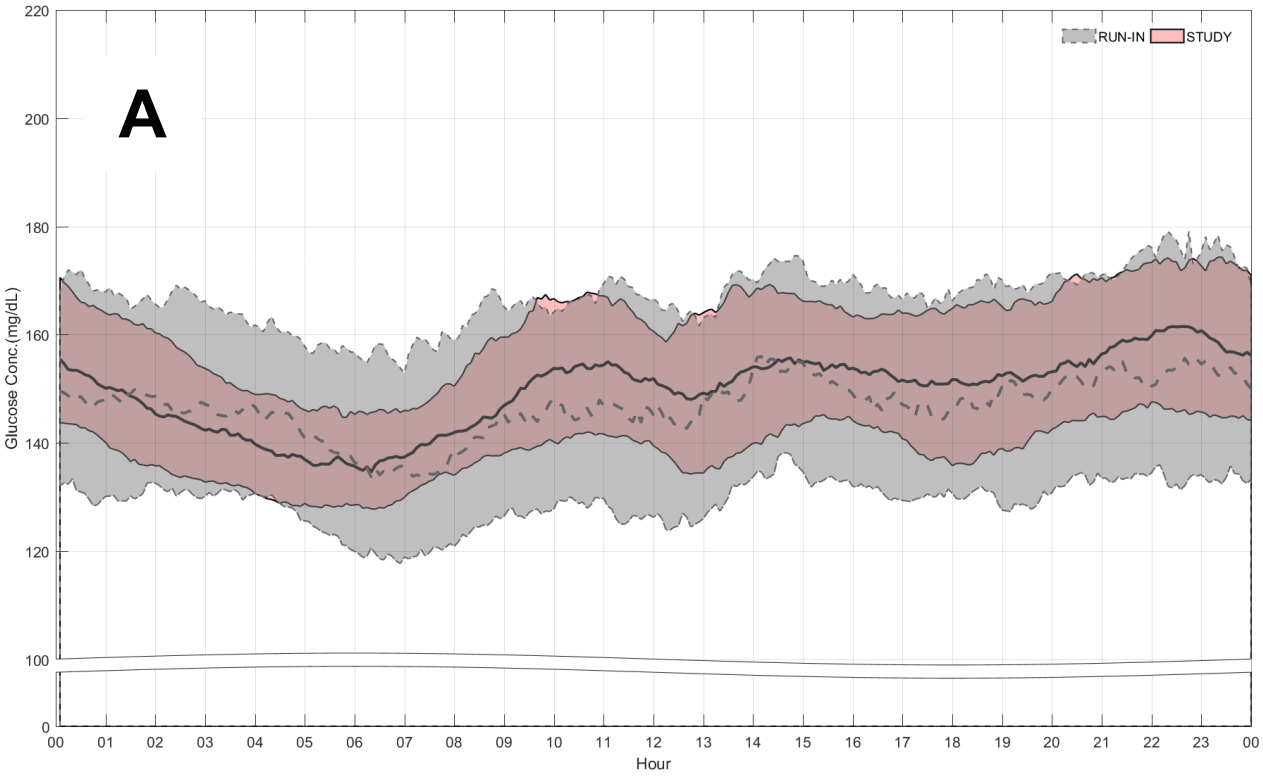
The safety and effectiveness of the in-home use of a hybrid closed-loop (HCL) system was investigated in adolescents (n = 30, ages 14–21 years) and adults (n = 94, ages 22–75 years) with type 1 diabetes in a multicenter pivotal trial [7]. The 670G system was used during a 2-week run-in phase without HCL control, or Auto Mode, enabled (Manual Mode) and then in Auto Mode during a 3-month study phase. Data from the trial is seen below, in Table 1.

Table 1: Comparison of glucose control and insulin doses from the 2 week baseline data compared to the 3 months of 670G hybrid closed loop use [8]

	Run In (Baseline)	**3 month Data**	**p**
HbA1c	7.4 ± 0.9	6.9 ± 0.6	<0.001
% <70 mg/dL	6.4 ± 5.3	3.3 ± 2.0	<0.001
% 71-180 mg/dL	66.7 ± 12.2	72.2 ± 8.8	< 0.001
% >180 mg/dL	27.4±13.7	24.5±9.2	< 0.001
Mean Glucose	150.2±22.7	150.8±13.7	NS
Within Day CV	33.5±4.3	30.8±3.3	< 0.001
TDI	47 ± 22	51 ± 27	< 0.001

The adolescents used the system for a median 75.8% of the time, and adults used the system for a median 88.0% of the time. From baseline run-in to the end of study phase the adolescent HbA1c decreased from 7.7% to 7.1% ($P < 0.001$) and adult HbA1c levels decreased from 7.3% to 6.8% ($P < 0.001$). The proportion of overall in-target (71–180 mg/dL) sensor glucose (SG) values increased from 60.4% to 67.2% ($P < 0.001$) in adolescents and from 68.8% to 73.8% ($P < 0.001$) in adults. Figure 1-4 provides a graph of the sensor values for both adolescent and adult subjects comparing their baseline data to their data using the 670G. There were no severe hypoglycemic or diabetic ketoacidosis events in either cohort.

Figure 1-4: Graph of the median and interquartile range sensor values over a 24 hour day comparing the values obtain at baseline with regular care (in grey), to the data over 3 months of using the Medtronic 670G pump for the adult and adolescent patients. The gray band and dotted line represent data from the run-in phase; the pink band and solid line represent data from the study phase. [7]



1.2.3 Use Of A Standard Breakfast To Assess Insulin Pharmacodynamics Data In An Outpatient Setting.

In a study to assess the effect of hyaluronidase administration on insulin pharmacodynamics, 14 subjects were instructed to eat the same breakfast meal each day, give an insulin bolus based on their usual insulin-to-carbohydrate ratio and correction factor, and they were instructed not to eat for at least 3 hours following breakfast. Subjects were required to document their food intake each morning at breakfast and the carbohydrate content was verified on the pump download bolus history. Postprandial glucodynamic parameters including peak glucose concentration (C_{max}), time to C_{max} (t_{max}),

and estimated average glucose excursions were assessed using sensor glucose values at a time interval of 0 to 180 minutes after breakfast bolus. If a bolus was given between 120-180 minutes following the breakfast bolus, CGM values were only used up to the time of the bolus. The glucose at the time of the breakfast bolus (Time 0) was set to 0 mg/dL for each meal, and the remaining CGM values were adjusted proportionally to allow analysis of postprandial glucodynamic parameters. We utilized a mixed-effects model accounting for crossover study design of the study with the sequence of treatment nested within the patient, and this was the random effect. Breakfast meals were excluded from postprandial analysis if: 1) the rate of change was greater than 0.5mg/dL/min in the 1 hour prior to breakfast, 2) subjects gave a subsequent bolus prior to 120 minutes following the breakfast bolus, or 3) subjects deviated from their typical breakfast.

For the postprandial glucose analysis (Table 2) there were limited observations available, but the estimated average glucose excursion was less for hyaluronidase compared to standard weeks on Day 1 of infusion set life (12-24 hours after the first hyaluronidase infusion) and Day 3 of infusion set life (immediately after second hyaluronidase infusion). This effect was lost on Day 2 of infusion set life (36-48 hours after the first hyaluronidase infusion) and Day 4 of infusion set life (24 hours after the second hyaluronidase infusion). The study was not powered to show a difference in glucodynamic parameters, but Cmax and tmax tended to be lower immediately after hyaluronidase infusions. Postprandial profiles obtained from CGM glucose values are presented in mean ± standard error for meals analyzed on Days 1-4 of infusion set life in Figure 3. There were too few meals available for analysis beyond Day 4 of infusion set life to allow postprandial analysis.

Table 2: Postprandial glucodynamic parameters following hyaluronidase injection

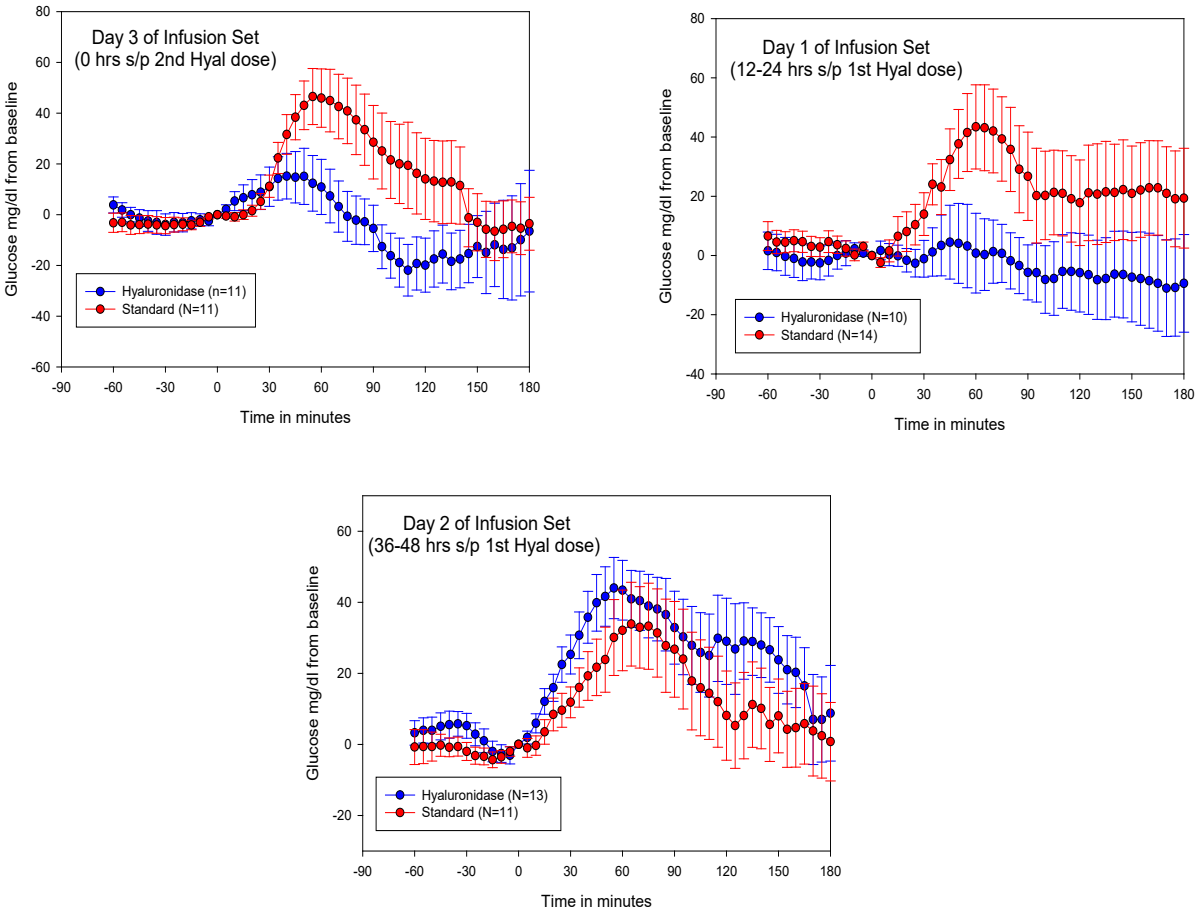
	0 hours post Hyaluronidase		12-24 hours post Hyaluronidase		36-48 hours post Hyaluronidase	
	Standard (N=11)	Hyal (N=11)	Standard (N=14)	Hyal (N=10)	Standard (N=11)	Hyal (N=13)
Estimated glycemic excursion⁺	24.8	-6.7	20.7	-5.4	14	26.9
P-value	<0.001*		<0.001*		<0.001*	
Cmax°						
Mean ± SD	69.5 ± 47.4	43.5 ± 44.5	72.0 ± 48.8	36.9 ± 35.1	51.6 ± 32.0	56.4 ± 25.9
Median, IQR	63 (31,80)	34 (7,68)	77.5 (19,117)	29 (17,48)	46 (33,76)	52 (42,69)
P-value	0.296		0.167		0.681	
tmax‡						
Mean ± SD	84.5 ± 49.3	69.1 ± 67.2	92.9 ± 58.9	76.5 ± 55.8	65.4 ± 32.6	73.8 ± 40.2
Median, IQR	65 (50,105)	50 (10,240)	82.5 (60,130)	60 (45,120)	65 (50,95)	55 (45,90)
P-value	0.3		0.5		0.591	

P-values were obtained using a mixed-effects model accounting for crossover study design of the study with the sequence of treatment nested within the patient, and this was the random effect.

⁺AUC=Area under the Curve (mg/dL)

°Cmax=Peak glucose concentration (mg/dL)
‡Tmax=Time to peak glucose concentration (minutes)
*represents statistical significance (i.e. P<0.05)

Figure 1-5: Postprandial glucose profiles by Day of infusion set wear (and hours following hyaluronidase infusion)



1.3 Study Overview

Use of Fiasp®: Fiasp® insulin has been approved for sale in the USA, and has been available since February 7th 2018. Although it is not approved for pumps, it will be used in pumps off-label because of it has a more rapid onset of action. The 670G closed-loop system automatically adjusts basal rates throughout the day and night to minimize hyper and hypoglycemia. Use of the 670G provides a unique opportunity to assess how Fiasp® works in a closed-loop system and to determine if any changes need to be made to the 670G pump to optimize the use of Fiasp®.

According to the FDA guidelines we do not think this study requires an IND since we meet all of the following six conditions:

i. it is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug;

ii. it is not intended to support a significant change in the advertising for the product;

iii. it does not involve a route of administration (it is still being given subcutaneously) or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

iv. it is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively];

v. it is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR 312.7]; and

vi. it does not intend to invoke 21 CFR 50.24."

1.4 Protocol Synopsis:

This is a pilot outpatient study conducted at Stanford to obtain preliminary data on how Fiasp® works in a closed-loop system. The plan will be to enroll up to 20 subjects for each part of the study. Part 1 is a blinded cross-over study to assess how well Fiasp® insulin works when used with the 670G pump compared to aspart insulin and will take 6 weeks for a subject to complete. Part 2 is a Fiasp® optimization phase to assess if making changes to meal coverage with the knowledge that Fiasp® is being used can optimize the advantages of the 670G pump with Fiasp® use, and to observe longer term use of Fiasp® in the 670G pump. This will be a 6 week study.

Part 1: Randomized cross-over, blinded study which includes assessment of meal pharmacodynamics.
Part 1 will be a randomized cross-over blinded study and will also test to see how the 670G pump responds to the introduction of Fiasp® insulin. Subjects enrolled in

the study will have a 2 week period of optimization with weekly assessments of their Carelink download before entering the blinded phase of the study. They will use their usual home insulin during the optimization phase. They will then been started on their first blinded insulin (aspart or Fiasp®) which they will use for 2 weeks, before they cross-over to the other insulin. During the second week of each arm we will:

1) Assess CGM measurements of:
    a) time in range (70-180 mg/dl)
    b) percent time <70 mg/dl,
    c) mean glucose,
    d) glucose CV,
2) Pump data for:
    a) CHO:I ratios at Breakfast, Lunch and Dinner,
    b) total daily insulin dose,
    c) total daily basal insulin,
    d) insulin delivery form MN to 6AM, and 6AM to MN
3) We will test to see if there is any difference in pharmacodynamics when using Fiasp® in the home environment when they are eating their usual breakfast.
4) We will also assess their glucose levels following a high fat meal at dinner of at least 30 grams of fat.

Part II: Extended Use Observational Study.

This study will consist of 6 weeks of closely monitored home use of the 670G pump with review of their pump and sensor downloads every 2 weeks by clinicians who are experienced in using the 670G pump. The goals of this phase of the study are to:

1) Assess how Fiasp® changes meal bolusing, i.e. do adjustments need to be made in their carbohydrate to insulin ratios or timing of their boluses when they are using Fiasp® I
2) Assess how Fiasp® works with the higher fat meals that may occur with dinner, i.e. will the dinner dose need to be divided into early and late boluses
3) Assess how Fiasp® affects infusion sites under usual care conditions, i.e are there any local reactions to Fiasp®
4) Assess if Fiasp® becomes less effective over the life an infusion set (are sets changed more frequently)
5) Assess how the 670G performs when Fiasp® is used:
    a. Do insulin-to-carbohydrate ratios need to be modified
    b. Does duration of insulin action need to be modified
    c. Is more or less basal insulin delivered
    d. Does the total daily dose change
    e. Does the performance of the 670G change overnight (MN to 6AM) and during the day (6AM to MN) in terms of time in range, mean glucose and % of readings <70 mg/dL.

will include both males and females and an enrollment goal will be to achieve an

approximately equal sex distribution. Their total daily insulin dose should be at least 0.3 units/kg/day and they should be eating at least 60 grams of carbohydrate each day.

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: Randomized cross-over, blinded study with assessment of meal pharmacodynamics: up to 20 subjects will be studied and the studies for each subject will last 6 weeks.

Part 2: Long term use of Fiasp®. We will recruit up to 20 subjects who are using Fiasp® insulin, they are not excluded if they were in Part 1, in fact subjects in part 1 will be encouraged to continue into part 2 of the study. Duration is up to 6 weeks, or until subject decides to stop using Fiasp®.

Eligibility and Exclusion Criteria

Eligibility Criteria

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

1. Clinical diagnosis of type 1 diabetes and using 670G pump for at least 1 month, and willing to have the 670G pump downloaded into a Carelink Clinical research database.
2. The diagnosis of type 1 diabetes is based on the investigator's judgment; C-peptide level and antibody determinations are not needed.
3. Age ≥18 years
4. Using Novolog or Fiasp® insulin at time of enrollment
5. Willing to use Fiasp® insulin
6. Total daily insulin dose is at least 0.3 units/kg/day
7. Usual carbohydrate intake is at least 60 grams a day, and willing to have at least 25 grams of carbohydrates for breakfast
8. For females, not currently known to be pregnant
9. An understanding of and willingness to follow the protocol and sign the informed consent
10. Willing to have photographs taken of their infusion sites
11. Willing to download their 670G pump every 1-2 weeks to a research Carelink account
12. Willingness to answer a brief online questionnaire every 2 weeks
13. Must be able to understand spoken or written English
14. For subjects participating in Part 2 of this study they will need to be using Fiasp® as part of their usual care
15. Hemoglobin A1c between 6 and 10% at the time of enrollment

Exclusion Criteria

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

1. Pregnant or lactating females
2. No hypoglycemic seizure or loss of consciousness in the past 6 months
3. Severe episode of DKA in the 6 months prior to study enrollment that was unrelated to an infusion set failure
4. No known cardiovascular events in the last 6 months
5. No active proliferative diabetic retinopathy

6. Known tape allergies
7. Current treatment for a seizure disorder
8. Cystic fibrosis
9. Active infection
10. A known medical condition that in the judgment of the investigator might interfere with the completion of the protocol
11. Inpatient psychiatric treatment in the past 6 months
12. Presence of a known adrenal disorder
13. If on antihypertensive, thyroid, anti-depressant or lipid lowering medication, with lack of stability on the medication for the past 2 months prior to enrollment in the study
14. Abuse of alcohol
15. Dialysis or renal failure
16. Known eGFR <60%

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

Recruitment Plan:

We will contact subjects at our clinic who are using the 670G system and are using Novolog or Fiasp® insulin. A short description of the present study will be given to them via email, phone or in-person. If the subject expresses interest, then the study will be presented in detail. The goal will be to enroll four subjects each week to establish cohorts of 4 subjects.

Informed Consent Plan and HIPAA Authorizations:

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. The subject 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.

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.

Historical Information and Physical Exam

A history will be elicited from the subject and/or extracted from available medical

records with regard to the subject's diabetes history, current diabetes management, other past and current medical problems, past and current medications, and drug allergies. A study focused physical exam (including height, weight measurements and infusion site assessments) will be performed by the study investigator or designee (an attending physician, fellow, nurse practitioner or a physician assistant).

HbA1c

A point of care HbA1c level will be obtained at the time of enrollment, at the start of the 3 month observational study and at the end of the observational study.

Authorization Procedures

As part of the informed consent process, each subject 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, questions will be answered about the details regarding authorization.

CHAPTER 3: PROTOCOL PROCEDURES

Visit 1: Informed consent process:

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.

History and physical exam: Including age at diagnosis of diabetes, duration of diabetes, any retinal, renal or cardiac conditions. Height, weight, and examination of skin where infusion sets are inserted.

Laboratory tests: Point of care A1c will be obtained and urine pregnancy test will be obtained on all women who are pre-menopausal.

Training on home procedures:

Blood glucose monitoring: Subjects will test blood glucose using a Bayer Contour Next Link home glucose meter at least 3 times daily. Subjects will be instructed to check blood ketones using a blood ketone meter if there is unexplained sensor hyperglcyemia and the blood glucose meter reading is greater than 250 mg/dL.

Calibration of Guardian Sensor: They will be instructed to calibrate the Guardian sensor before breakfast and before dinner each day when there are no rate of change arrows and after washing their hands or using the second drop of blood. They will also be instructed to calibrate if the Guardian is showing more than a 20% error when compared to their Contour Next blood glucose reading and the Guardian is not showing a rapid rate of change.

Replacement of Guardian Sensor: If the Guardian sensor stops functioning during the study, the subjects will insert a new sensor.

Determination of an infusion set failure:

They will be instructed to replace the infusion set if:

1. Their ketone level is greater than 0.6 mmol/L,
2. There is evidence of infection at the infusion site
3. Their blood glucose (meter) does not decrease by at least 50 mg/dL within 1 hour of a correction bolus for unexplained hyperglycemia with a blood glucose greater than 250 mg/dL.
4. There is a pump occlusion alarm.

Documentation of infusion site reactions: At home they will exam the infusion set site at time of infusion set failure for signs of infection. They will record bleeding, 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 measurments into a text to the study

coordinator or submit the information directly into RedCap.

The goal will be to have sensor wear at least 80% of the time and in automode at least 70% of the time. There pump will be uploaded to a research Carelink account each week. While in the blinded phase of the study the clinical staff will refrain from making changes to 670G pump settings unless requested by the subject or for safety reasons such as an episode of severe hypoglcyemia (unconscousness or seizure), >10% time <70 mg/dl, or >20% of the time over 250 mg/dl.

Part 1: Randomized, cross-over, blinded study to assess any adaptations of the 670G pump to Fiasp® and to assess meal pharmacodynamics of Fiasp® compared to aspart with a typical breakfast in the home environment

Participants will have a 2 week run-in on their usual home insulin (aspart of Fiasp®). During the run-in, there pump will be downloaded weekly, reviewed by the clinical staff and adjustments will be made to their settings as needed to optimize their glycemic control. Participants will then be randomly assigned to 2 sequences of testing starting with either aspart or Fiasp®. They will use each insulin for two weeks. The participants and the investigators will be blinded to the insulin. During the second week of using a blinded insulin they will have the meal pharmacodynamics testing. They will then cross-over to the other insulin and during the second week they will repeat meal pharmacodynamics testing. At the end of each week they will upload their 670G pump to a Carelink clinical (research) account and it will be reviewed by the research staff for safety purposes.

Procedure for meal testing. For each week of meal testing they will be asked to have 3 days with a consistent breakfast that is the same for all 6 days they are doing a meal test (3 days on each insulin). The breakfast studies should ideally occur on standard work days (not holidays or weekends). On these three days they will be asked to have a dinner with at least 30 grams of fat and no additional food in the evening (unless they are treating hypoglycemia). They will be asked to take a picture of the dinner meal and identify their food and portion sizes. If they have a smart phone (Android or Apple), they may download Calorie Mamma® or Calorie King® to help them in calculating carbohydrates, protein and fat from the meal. They will do this for each of their dinner meals on each of the days they are doing the breakfast study, and for the breakfast meals they are eating each morning as part of the pharmacodynamic testing. They will change their infusion set before dinner prior to the first day of starting a standard breakfast, i.e., if they work from Monday to Friday, this could be done on Sunday.

They are blinded to the insulin and the insulin dose decisions for these meals is also not under their control since: 1) The overnight insulin delivery is not under their control, 2) The timing of the meal bolus will be the same for all mornings, the dose will be given immediately before eating, 3) They dose of insulin will be determined by their pump using their preset insulin-to-carbohydrate ratio and they will be eating the same amount of carbohydrates each morning. They also will not be getting a

correction dose of insulin in the morning because they are using the closed-loop controller overnight. If they required a correction dose of insulin, we will not use the data from that morning in our data analysis. We will assess during each of these four weeks the time in-range (70-180 mg/dl), mean glucose, CV, and time <70 mg/dl.

At the end of each two week period of blinded insulin use the participants and the health care providers will be given a questionnaire asking them which insulin they thought they were using, and if they had noticed any advantages to disadvantages while they were using this insulin, and whether they would have wanted to make any changes to their insulin delivery settings while using the insulin.

Part 2: Extended Use Optimization Study

To be eligible for Part 2 one of the inclusion criteria will be that the subject is currently using Fiasp® insulin under their usual care. Subjects for Part 1 may participate in part 2, and we will also recruit subjects outside of part 2 who are currently using a 670G pump and taking Fiasp insulin. They will download their 670G pump to a research Carelink account every 2 weeks. Their data will be reviewed within 3 days by the clinicians managing the study at each research clinical site. An email, text or phone call will be made to the subject after reviewing their pump/sensor data. Recommendations for dosage changes will be recorded on a case report form or directly into RedCap. The study investigators will meet every 2 to 4 weeks during the study to review clinical issues and insights that have been observed.

To assess the long term effect of using Fiasp® on infusion sites and insulin action, they will be asked to use Fiasp® as long as they see benefit in using it after the initial meal boluses testing is completed. Each time they change their infusion set, we will ask them to examine the site for any bleeding, redness or induration, and measure these changes and take a picture if there are any findings. (See Documentation of infusion site reactions). We will have them download to a CareLink research data base every two weeks to look at their total daily insulin requirements, glucose values, and basal insulin requirements with extended use of Fiasp®. They will have an email sent to them every 2 weeks by RedCap to assess for issues they have observed while using Fiasp®.

Documentation of infusion site reactions: At home subjects will exam their infusion set site when they are changing an infusion set and assess for bleeding, signs of a 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 or submit the information directly into RedCap.

They will be instructed to replace the infusion set if:

1. Their ketone level is greater than 0.6 mmol/L,
2. There is evidence of infection at the infusion site
3. Their blood glucose (meter) does not decrease by at least 50 mg/dL within 1 hour of a correction bolus for unexplained hyperglycemia with a blood glucose greater than 250 mg/dL.
4. There is a pump occlusion alarm.

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 (DKA), 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.

Dr. Buckingham will inform the IRB of serious study-related adverse events and abide by any other reporting requirements specific to their IRB.

Potential Risks and Side Effects

There may be a higher frequency of hypoglycemia immediately following a meal bolus. There may be prolonged hyperglycemia following a high fat meal. There may be local tissue

reactions at the FIASP® infusion sites. Infusion sites may need to be changed more frequently than usual when infusing FIASP®. As with any insulin, there is a risk for both high and low blood glucose levels occurring if there is a mismatch between your insulin needs and the insulin levels provided by the insulin. See hypoglycemia and hyperglycemia risks below. It is very rare, but allergic reactions to insulin may occur.

Risk of 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.

Risk of Hyperglycemia

As with any person having insulin-dependent diabetes, there is always a risk of having a high blood sugar (hyperglycemia). The frequency should be no more than it would be as part of daily living with diabetes.

Protection Against Risks and Treatment of Side Effects:

Subjects will be given descriptions of possible side effects from wearing an infusion set, and local side effects with insulin infusion sets or Guardian 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).

Other Risks

Some subjects may develop skin irritation or allergic reactions to the adhesives used to secure the CGM sensor, or to secure the insulin infusion sets for the Continuous Subcutaneous Insulin Infusion (CSII). 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 very infrequently, but, if an infection was to occur, oral and/or topical antibiotics can be used. 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

Fiasp® may provide a more rapid onset of insulin action and improved post-prandial glycemic control.

Subject Compensation

For Part 1, participants will be compensated $50 for each visit, $15 for completing weekly uploads to Carelink for a maximum payment of $245. For part 2, subject will receive $50 for each visit, and $20 for uploading to Carelink and contact with the investigators every two weeks they are in the extension phase. Maximum payment of $160. 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 also be provided to Medtronic Diabetes.

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 6 months.

CHAPTER 6: STATISTICAL CONSIDERATIONS

This is a pilot study to determine if there are any clinical issues with using Fiasp® in the 670G hybrid closed-loop system. These studies are not statistically powered.

In the blinded cross-over studies (Part I) we will use data obtained during the second week of each arm to compare the following measurements using a mixed-effects model accounting for crossover study design of the study with the sequence of treatment nested within the patient:

a) time in range (70-180 mg/dl)
b) percent time <70 mg/dl,
c) mean glucose,
d) glucose CV,
e) total daily insulin dose,
f) total daily basal insulin,
g) insulin delivery form MN to 6AM, and 6AM to MN

We will test to see if there is any difference in pharmacodynamics when using Fiasp® in the home environment when they are eating their usual breakfast. Insulin pharmacodynamics following the standard breakfast will be assessed by measuring the peak glucose concentration (C_{max}), time to C_{max} (t_{max}), and estimated average glucose excursions were assessed using sensor glucose values at a time interval of 0 to 180 minutes after breakfast bolus. If a bolus was given between 120-180 minutes following the breakfast bolus, CGM values were only used up to the time of the bolus. The glucose at the time of the breakfast bolus (Time 0) will be set to 0 mg/dL for each meal, and the remaining CGM values were adjusted proportionally to allow analysis of postprandial glucodynamic parameters. We will utilize a mixed-effects model accounting for crossover study design of the study with the sequence of treatment nested within the patient. Breakfast meals are excluded from postprandial analysis if: 1) the rate of change was greater than 0.3mg/dL/min in the 1 hour prior to breakfast, 2) subjects gave a subsequent bolus prior to 120 minutes following the breakfast bolus, or 3) subjects deviated from their typical breakfast. Dinner meals will be assessed when there has been no additional food intake after dinner. The duration of insulin delivery to cover the meal will be determined by the time it takes the post prandial glucose to reach 160 mg/dL beyond 1 hour of eating. The peak glucose will also be recorded.

During the 6 week optimization study (Part II) we will use data obtained during the first two weeks of the study (before data was reviewed and changes made by the investigators) to data obtained during the last two weeks of the 3 month optimization period. We will compare the following measurements using paired t-tests for data with a normal distribution and a Mann-Whitney rank sum test for data that is not normally distributed:

a) time in range (70-180 mg/dl)
b) percent time <70 mg/dl,
c) mean glucose,

d) glucose CV,
e) total daily insulin dose,
f) total daily basal insulin,
g) insulin delivery form MN to 6AM, and 6AM to MN
h) CHO:I ratios at breakfast, lunch and dinner
i) Active insulin time
j) Number of days between infusion set changes
k) Erythema (mm) and induration (mm) at infusion sites when they are changed
l) Average daily insulin, and mean glucose for each day of infusion set wear
m) Number of episodes of unexplained hyperglycemia in the first month vrs the last month

CHAPTER 7: REFERENCES

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