An Exploratory, Single-center, Randomized, Open Label, Active-control, Cross-over Trial Comparing the Efficacy and Safety of Continuous Subcutaneous Insulin Infusion of Faster-acting Insulin Aspart (Fiasp®) compared to NovoLog® used in the Medtronic 670G closed loop system in Adults with Type 1 Diabetes

Investigator – Sponsored Study Protocol

UTN: U1111-1213-9104

Trial Phase: IIIb

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1 Background and Significance

Hybrid closed-loop (HCL) systems have been shown to improve glycemic control and reduce hypoglycemia by adjusting basal rates with the input of glucose data from continuous glucose monitoring to proprietary algorithms.(1)

The Minimed 670G HCL (670G HCL) system has been shown to be associated with less glycemic variability, more time in target glucose range, low rates of hypoglycemia, and reductions in A1c. (2,3)

The 670G HCL system has been studied using the rapid acting insulin analogues insulin lispro and insulin aspart (NovoLog®) The Minimed 670G System User Guide states that "Only use rapid acting U100 insulin (Humalog® (insulin lispro) and NovoLog® (IAsp) that has been prescribed by your healthcare professional for use with an infusion pump." (4)

The HCL system adjusts and controls basal insulin delivery. Mealtime bolus insulin is the responsibility of the user who must enter the amount of carbohydrates into a program in the insulin pump that calculates the amount of insulin to be delivered. The timing of the pre-meal bolus is determined by the user as well. (4)

One of the challenges of optimizing postprandial glucose control in an HCL system is slower than physiologic absorption of analog mealtime insulin (insulin lispro, insulin aspart, insulin glulisine). Patients with type 1 diabetes often comment that the bolus insulin doesn't take effect fast enough to control mealtime carbohydrate or to lower the glucose when elevated (personal communication with numerous patients with Type 1 Diabetes using the insulin pump). Faster acting insulin aspart (Fiasp®) with more rapid onset of action and peak than NovoLog® might help address this challenge. (5)

Fiasp® is a new formulation which contains two additional excipients niacinamide and L-arginine. Niacinamide is responsible for faster initial absorption of insulin aspart after subcutaneous administration and L-arginine serves as a stabilizing agent. These additions result in earlier absorption of NovoLog® following subcutaneous injection. Fiasp® given by SC injection has been shown to have greater early glucose-lowering effect compared to NovoLog®.(6)

The A1c lowering effect of mealtime Fiasp® has been shown to be non-inferior to NovoLog® in subjects with Type 1 diabetes on MDI regimens. In an active controlled randomized parallel-group trial, the Fiasp® arm had a statistically greater reduction in A1c compared to mealtime NovoLog®, and mealtime Fiasp® was shown to lead to superior postprandial glucose control relative to NovoLog®.

In this trial, Fiasp® had a safety profile that was similar to NovoLog® and the most common adverse event was hypoglycemia,-rate similar to NovoLog® (7)

Fiasp® has been studied in a non HCL insulin pump. A randomized, double blinded study comparing Fiasp® to NovoLog® in patients using the MiniMed Paradigm Veo™754 insulin pump showed the following:

1. Fiasp® had an early glucose-lowering effect (area under the curve for glucose infusion rate [GIR]0-30min) that was 2-fold higher than NovoLog®
2. Fiasp® had an onset of glucose-lowering effect (time to early 50% of maximum GIR) that was 11.1 minutes earlier (41.1 vs 52.3 minutes)
3. Offset of glucose-lowering effect occurred 24.0 minutes earlier (214.7 vs 238.7)
4. Fiasp® and NovoLog® were both well tolerated. (5)

In another double blinded crossover study comparing Fiasp® to NovoLog® in the MiniMed Paradigm_ pump (515/715, 522/722 or 523/723, Fiasp® led to significantly greater PPG lowering after a standardized meal test when compared to NovoLog®. In this trial, the one hour post meal test, PG levels were -29.47 mg/dL lower with Fiasp® versus NovoLog®. Continuous glucose monitoring (CGM) interstitial glucoses supported these findings with the largest differences being observed after breakfast: 163.57 vs. 172.19 mg/dL. CGM date showed that the duration of low SMBG levels <70mg/dL per 24 h) was shorter for Fiasp® versus NovoLog®. (8)

In a study investigating the compatibility of Fiasp® with the insulin pump, it was shown that over 6 weeks of treatment, no microscopically confirmed infusion-set occlusions were observed for Fiasp® or NovoLog®, indicating similar compatibility with insulin pump use. (9)

It is possible that Fiasp® with its earlier onset and earlier offset of insulin effect will lead to improved postprandial readings in patients on the Medtronic 670G HCL system. This might lead to increased glucose time in range

2 Flow chart

	Screening	Randomization	Treatment Period 1 (7 weeks)					Treatment Period 2 (7 weeks)						End of treatment	Follow-up
Visit (V) **Phone contact (P)**	V 1	V 2	P 3	P 4	V 5	P 6	V 7	V 8	P 9	P 10	V 11	P 12	V 13	V 14	P 15
Time of visit	-2	0	1 day after V2	7 days after V2	2 weeks after V2	4 weeks after V2	6 weeks after V2	7 weeks after V2	1 day after V8	7 days after V8	2 weeks after V8	4 weeks after V8	6 weeks after V8	7 weeks after V8	30 days after V14
Visit window (days)[1]		+3			±1	±1	+3	±3			±1	±1	+3	±3	+7
Informed consent	X														
Inclusion/exclusion criteria	X														
Randomization criteria		X													
Criteria for discontinuation			X	X	X	X	X	X	X	X	X	X			
Demography	X														
Medical history	X														
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Daily 4-point profile (SMPG)		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hypoglycemic episodes		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Unexplained Hyperglycemic episodes		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Meal Test[2]							X						X		
Infusion site reactions		X	X	X	X	X	X	X	X	X	X	X	X	X	
Occlusion events		X	X	X	X	X	X	X	X	X	X	X	X	X	
Height	X														
Body weight	X						X						X		
BMI	X														
Vital signs	X						X						X		
HbA_{1c}	X						X						X		

Visit (V) **Phone contact (P)**	V 1	V 2	P 3	P 4	V 5	P 6	V 7	V 8	P 9	P 10	V 11	P 12	V 13	V 14	P 15
Time of visit	-2	0	1 day after V2	1 week after V2	2 weeks after V2	4 weeks after V2	6 weeks after V2	7 weeks after V2	1 day after V8	1 week after V8	2 weeks after V8	4 weeks after V8	6 weeks after V8	7 weeks after V8	30 days after V14
Visit window (days)[1]		+3			±1	±1	+3	±3			±1	±1	+3	±3	+7
Chemistry, Hematology	X												X		
1,5-anhydroglucitol		X					X						X		
Fructosamine		X					X						X		
Urine Pregnancy testing[3]	X													X	
Infusion site exam		X			X		X	X			X		X	X	
Pairing of Subjects Pump and Subject Number in Carelink	X														
Instruct in use of BG meter	X														
Hand out and instruct in use of diary	X	X	X	X	X	X	X		X	X	X	X	X		
Training in diabetes and carbohydrate counting[4]	X	X													
Training in pump use[4]	X	X													
Remind Subjects to bring BG meter to site visit	X			X		X	X			X		X	X		
Upload pump/ BG meter data into Carelink		X	X	X	X	X	X	X	X	X	X	X	X	X	
Dose adjustments/Pump Setting Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Instruct in use of trial product[5]		X	X	X	X	X	X	X	X	X	X	X	X		
Drug Accountability[5]		X					**X**	X					X	X	
Drug Dispensing[5]		X						X							
End of treatment														X	
Attend visit fasting[6]							X						X		
Remind subject to change sensor prior to meal test visit						X						X			

[1] Visit windows are relative to randomization (Visit 2) and Treatment Period 2 Start (Visit 8) and End of Treatment

[2] Meal tests should not be performed on days of the CGM sensor insertion or on Day 7 of the current sensor session. Meal test will consist of blood draws at the following time points: -2 min, 0 min, 30 min, 60 min, 120 min, and 180 min

[3] Urine pregnancy testing to be performed on women of child bearing potential only

[4] To be performed by qualified site staff

[5] At Visit 2 (Randomization) study medication will be dispensed.. At visit 8 (Treatment period 2) study medication will be dispensed.

[6] Fasting is considered 8 hours with no food or drink, other than water

3 Rationale

The Medtronic 670G HCL system offers closer to physiologic algorithm based insulin delivery with variable basal insulin administration which interacts with CGM derived, glucose levels.

Slower than physiologic insulin effect at mealtime limits the ability to control the postprandial excursions in patients on insulin pumps including HCL systems. It is expected that Fiasp® in the 670G HCL system would lead to better postprandial control with more rapid insulin onset of effect. More rapid offset of insulin action might lead to less post meal hypoglycemia. Using Fiasp® in the 670G HCL might lead to improved % of time in range with its more rapid effect with pulses of insulin in the basal algorithm and lower post prandial glucose.

Fiasp® has not been studied in the 670G HCL system to date and its potential for optimizing glycemic control in the 670G HCL system needs to be evaluated.

The purpose of this study is to compare the efficacy and safety of Fiasp® versus NovoLog® in the Minimed 670G HCL system in T1DM subjects.

Both CGM and a standardized meal test will be used to evaluate the effect of Fiasp® vs. NovoLog® on postprandial glucose excursions in subjects on "Auto Mode" (active use of the HCL feature of the 670G). Time in range will be based on data downloaded from Medtronic Carelink data management software. The meal test will compare the physiological effect on post-prandial glucose of Fiasp® vs. NovoLog® at the end of each treatment period. The use of a weight-based insulin dose calculation for the meal test aims to minimize inter-subject variability in insulin sensitivity. This will allow us to study insulin effect in a more direct manner, and gain insight into postprandial physiology.

7 week treatment periods during each crossover period will allow time for adjustment of the settings (I:CR and active insulin time) at appropriate intervals such as might be done in a clinical practice and then allow for 2-3 weeks of stable dosing to determine time in range during stable dosing (recognizing that the only settings that can be adjusted are I:CR and active insulin time). The 3 weeks after the dose adjustment period of stable dosing will compare the "time in range" in the Fiasp® vs. NovoLog® group in the 670G Hybrid Closed Loop System. The measurement of time in range during the post dose adjustment period makes this a more clinical, real world study as it compares efficacy over a period of weeks.

4 Research Design

Our hypothesis is that post prandial glucoses will be lower and time in range will be greater during the Fiasp® treatment period.

Objectives

Primary objective

To compare Fiasp® in terms of glycemic control with a focus on post-prandial 1-hour plasma glucose level and system-based outcomes to NovoLog® insulin when used in the Medtronic mini Med 670G HCL system (operating in auto-mode) in patients with type 1 diabetes.

Secondary objectives

- Assessment of post-prandial glucose regulation (Continuous glucose monitor data, and 1,5 anhydroglucitol levels)
- Evaluation of cumulative glycemic control (HbA1c)
- Measurement of HCL parameters
- Reporting of Fructosamine levels

Endpoints

Primary Endpoint

- Post-prandial 1-hour plasma glucose levels at 6 weeks into start of therapy in each arm

Secondary Endpoints

- Post- prandial 2- hour plasma glucose levels at 6 weeks into start of therapy in each arm
- HbA1c and 1, 5 AG levels prior to cross-over, and at end of study
- Glycemic excursion parameters: Time spent within glycemic ranges as below will be reported and analyzed. Time spent in specific ranges will be expressed as a percentage of total time on treatment.
    - Time spent (%) within 70-180 mg/dl
    - Time spent (%) < 70 mg/dl
    - Time spent (%) >200 mg/dl
    - Hypoglycemia (differentiated as level 1 or level 2) (Reference 11)
    - Severe hypoglycemia

- Insulin related parameters

    - Total daily dose
    - change in %bolus and %basal from baseline
    - Auto basal / basal amount (per day)
    - Change in insulin : carbohydrate ratio from baseline
    - Active insulin time
- Pump related parameters
    - Time spent (%) in auto mode
    - Time spent (%) in manual mode
    - Auto mode exits (with reasons for exit)
    - Infusion site reactions reported by patient
    - Occlusion events reported by patient

This is an exploratory, single-center, randomized, open label, active-controlled, complete cross-over trial comparing safety and efficacy of Fiasp® versus NovoLog® when used in the Medtronic MiniMed 670G system in subjects with T1DM.

Study timeline:

FPV expected to be April 2019 with LPV in January 2020.The total duration of the trial participation for subjects is approximately 20 weeks as shown below:

Visit 1: Screening

Visit 2: Randomization /Treatment Period 1 Start / Day 0

Visit 3: Phone visit / 1 day after randomization

Visit 4: Phone visit / 1 week after randomization

Visit 5: Office visit / Week 2

Visit 6: Phone visit / Week 4

Visit 7: Office visit / Week 6 / Meal test

Visit 8: Office visit / Week 7/ Treatment Period 2 Start

Visit 9: Phone follow-up / 1 day after Visit 8

Visit 10: Phone follow-up / 1 week after Visit 8

Visit 11: Office visit / Week 9

Visit 12: Phone follow-up / Week 11

Visit 13: Office visit / Week 13 / Meal test

Visit 14: Office visit Week 14

Visit 15: 30-day follow-up after EOT (phone)

The screening visit assesses subjects' eligibility. Eligible subjects will enter a two-week screening period. The screening period will provide subjects with an opportunity to become more familiar with the HCL, and will give the investigator opportunities to focus on pump use review, and review and training in study procedures as needed.

After the screening period, the subjects will be randomized (visit 2) to NovoLog® or Fiasp®. After 7 weeks on the initially assigned regimen, a cross-over will occur at Visit 8.

Rationale for study design

The screening period has been included to optimize HCL use, and assure adequate training of subjects in study procedures.

The 7-week randomized treatment period is needed to collect valid and adequate data to analyze safety and efficacy. A cross-over design will provide adequate control data.

The 6-week post-prandial readings and 1,5-AG levels will provide data on post-prandial glycemic control, and time-in-range and HbA1c measurements will provide data on cumulative glycemic control.

Fructosamine levels indicate the average level of blood glucose control over the past 2-3 weeks. These levels may be a more accurate measure of average blood glucose control after a 6 weeks treatment period than A1c which measures average glucose control over 2-3 months.

Safety will be assessed via hypoglycemia records, patient logs, and HCL parameters.

Treatment principles

During the screening period, the main focus will be ensuring all subjects are familiar with the HCL system, trouble-shooting potential problems, and reviewing study procedures. If the Investigator feels the subject should extend the screening period to further ensure familiarity with the HCL system, this will be allowed once.

In the treatment period, the investigators will strive to achieve glycemic targets of fasting and pre-prandial levels of 70-110 mg/dL in a treat-to-target fashion. All subjects must perform glucose calibration measurements as dictated by the 670G system CGM requirements.

At end of the treatment period, subjects will be switched to suitable approved regimen at the discretion of the investigator.

5 Study population

5.1 Number of Subjects

Number of Subjects planned to be screened: 45

Number of Subjects planned to be randomized: 40

5.2 Inclusion criteria

For an eligible Subject, all inclusion criteria must be answered "Yes".

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial
2. Male or female, age ≥18 years at the time of signing informed consent
3. Documented diagnoses of T1DM ≥1 year prior to the day of screening
4. Using the Medtronic pump Minimed 670G for CSII in a basal-bolus regimen with a rapid acting insulin analogue for at least 30 days prior to screening and willing to continue using their personal Medtronic Minimed 670G and CSII for insulin treatment throughout the trial.
5. Ability and willingness to use the same insulin infusion sets throughout the trial
6. Using the same insulin for at least 30 days prior to screening
7. $HbA_{1c} \leq 8.5\%$ as assessed by local laboratory at screening
8. BMI ≤ 35.0 kg/m^2 at screening
9. Ability and willingness to adhere to the protocol including performing SMPG profiles, attending visits, utilizing the auto mode feature of the pump for at least 80 % of the time during the study, and completing meal tests

5.3 Exclusion criteria

For an eligible Subject, all exclusion criteria must be answered "No".

1. Known or suspected hypersensitivity to trial products or related products

2. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using adequate contraceptive methods (adequate contraceptive measures as required by local regulation or practice)

3. Participation in another clinical trial within 28 days before the screening visit. Note: clinical trials do not include non-interventional studies

4. Anticipated significant change in lifestyle (e.g. eating, exercise or sleeping pattern) throughout the trial

5. Any of the following: myocardial infarction, stroke, hospitalization for unstable angina or transient ischemic attack within the past 180 days prior to the day of screening

6. Subjects classified as being in New York Heart Association (NYHA) Class IV at screening

7. Planned coronary, carotid or peripheral artery revascularization known on the day of screening.

8. Inadequately treated blood pressure defined as Grade 3 hypertension or higher (Systolic ≥180 mmHg or diastolic ≥110 mmHg) at screening

9. Impaired liver function, defined as ALT ≥ 2.5 times upper normal limit at screening

10. Renal impairment measured as estimated Glomerular Filtration Rate (eGFR) value of < 45 ml/min/1.73 m^2

11. Anticipated initiation or change in concomitant medications (for more than 14 consecutive days) known to affect weight or glucose metabolism in the opinion of the Investigator

12. Proliferative retinopathy or maculopathy requiring acute treatment at the time of screening

13. History of hospitalization for ketoacidosis ≤180 days prior to the day of screening

14. Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria within 30 days before screening

15. Presence of malignant neoplasms at the time of screening. Basal and squamous cell skin cancer and any carcinoma in-situ is allowed.

16. Reoccurring Severe hypoglycemia while on the Medtronic Minimed 670G in the investigators opinion

17. Any condition which, in the opinion of the Investigator, might jeopardize Subject's safety or compliance with the protocol

5.4 Randomization criteria

To be randomized, the below randomization criteria must be answered "Yes".

1. Subjects ability and willingness to adhere to the protocol and satisfactory handling of the pump, including regular changes of the infusion sets, utilization of the auto mode feature of the pump for at least 80 % of the time, and adequate bolus dosing based on the Investigator's judgment.

5.5 Criteria for premature withdrawal from trial

Efforts should be made to ensure Subjects attend and complete all scheduled visits and procedures.

5.5.1 Withdrawal from trial

The Subject may withdraw at will at any time. The Subject's request to discontinue from the trial must always be respected. The investigator may withdraw the subject at any time due to safety or non- compliance.

If a Subject decides to withdraw consent or the Investigator withdraws the Subject, the Subject should be asked to undergo procedures described in Section 2.

A Subject will be considered "lost to follow up" if the Subject repeatedly fails to attend the scheduled visits and the site is unable to establish contact to the Subject. The following actions must be taken by the site in relation to a Subject who fails to attend the site for a scheduled visit:

- The site should attempt to contact the Subject and to reschedule the missed visit as soon as possible
- The site should re-train the Subject in the importance of maintaining the scheduled visits

- In cases where a Subject is deemed lost to follow up the Investigator must make every effort to regain contact to the Subject

5.6 Subject replacement

Subjects who are withdrawn after randomization (Visit 2) will not be replaced.

5.7 Rationale for trial population

40 patients, accounting for 10% dropout rate, to achieve 80% power to detect 32 mg/dl treatment difference

6 Methods and Assessments

6.1 Visit procedures

The following sections describe the assessments and procedures. Timing of the different assessments and procedures including type of visit and the visit windows are also described in the flowchart in section 2.

6.1.1 Informed Consent

Before any screening activities take place, the Subjects must be provided with written and oral information about the trial, the procedures involved and their responsibilities and rights while participating in the trial, in accordance with ICH-GCP and local requirements. The Subjects will also be informed about possible advantages/disadvantages when being treated with trial products. The Subjects will have the opportunity to ask questions and will have ample time to consider participation.

Subjects who wish to participate in the trial will sign and date the Subject Informed Consent before any trial-related procedures commence. Trial-related activities are any procedures that would not have been performed during the normal management of the Subject. All Subjects must be provided with a copy of their own signed and dated Informed Consent.

6.1.2 Screening visit

At screening (Visit 1), each Subject's will be assigned a unique 3-digit Subject number which will remain the same throughout the trial.

Any abnormal and clinically significant findings at Visit 1 must be recorded on the medical history/concomitant illness form in the source documentation

For screening (Visit 1) procedures, please see flowchart in section 2.

6.1.2.2 Re-screening

Re-screening is allowed once if the subject has failed one of the inclusion or exclusion criteria related to laboratory parameters.

6.1.3 Randomization

Randomization (Visit 2) should occur after the screening period has been completed.

Randomization can take place as soon as the Subject has been found eligible and should take place no later than 30 days after screening (Visit 1). The results of all the screening assessments must be available (including central laboratory results) and must have been reviewed by the Investigator before the Subject can randomize.

If the Subject meets the randomization criterion at Visit 2, the Subject will be randomized into one of the two treatment arms for the first cross-over period. Subjects will change their pumps to manual mode for 1 week post- randomization. After the 7 day manual mode wear, the subject will turn the pumps on auto mode for the remainder of the treatment period.

For randomization (Visit 2) procedures, please see flowchart in section 2.

6.1.4 Site visits

If a visit to the site is not performed as scheduled for any reason, then the Investigator should arrange for the visit to be performed as soon as possible and within the visit windows specified in section 2.

Scheduled dispensing of trial product should be performed at the visits indicated in the flowchart in section 2. Drug accountability should be performed at each dispensing visit from start of randomization (Visit 2) until end of treatment (Visit 14).

For assessments performed at the site visits, please see flowchart in section 2.

6.1.5 Phone contacts

Before any phone contact, both the Investigator and Subject should agree on the date, timing and direction of the call. The Investigator remains responsible for ensuring that the phone contacts occur even if it is agreed that the Subject should call the site.

If a planned phone contact is, for some reason, not performed at the agreed time point, the Investigator must arrange for the phone contact to be performed as soon as possible and within the scheduled visit windows specified in section 2. A phone contact visit may be converted to a site visit if needed.

The withdrawal criteria should be reviewed during the phone contact to ensure the Subject is eligible to continue in the trial.

For assessments performed at the phone contacts please refer to the flowchart in section 2.

6.1.6 Fasting visits

Fasting is defined as no intake of drink or food for at least 8 hours prior to blood sampling (only water is allowed). The Subjects must attend the visits specified in section 2 in a fasting condition. Correction boluses are allowed until four hours before the measurement of the FPG.

Bolus insulin dosing and medication which should be taken with or after a meal should be withheld until blood sampling has been performed. Any other concomitant medication can be taken as usual.

If the Subject attends the fasting visits in a non-fasting condition, all blood samples and meal test must be rescheduled within the visit window.

6.1.7 Withdrawal procedures

6.1.7.1 Withdrawal from trial

If a Subject withdraws consent from the trial after randomization (Visit 2), the Investigator must ensure every possible effort is made to undertake procedures same as those for end of treatment (Visit 14) including the meal test, as soon as possible after decision of ending trial. The meal test should be performed with trial product according to randomization unless this is not feasible due to safety reasons as judged by the Investigator.

The Subject should also complete the follow-up visit (Visit 15). Final drug accountability must be performed even if the Subject is not able to come to the trial site.

Although a Subject is not obliged to give his/her reason(s) for withdrawing from a trial, the Investigator must make a reasonable effort to ascertain the reason(s), while fully respecting the Subject's rights. Where the reasons are obtained, the primary reason for not completing the trial must be specified within the source documentation.

6.1.8 Crossover (Visit 8)

At Visit 8 cross over the subject's will be dispensed study medication and switched to the comparative trial product . The Subject's will be instructed to change their pumps to manual mode for 1 week after the start of the crossover period. After 7 days of manual mode then subject will turn on auto mode for the duration of the treatment period.

6.1.9 End of treatment (Visit 14)

At end of treatment (Visit 14), the trial product should be discontinued and a stop date of trial product must be recorded in the source documentation.
The Subject should be switched to a suitable marketed product at the discretion of the Investigator and this product should be recorded on the source documentation. For procedures to be performed at end of treatment (Visit 14), please see flowchart in section 2.

6.1.10 Follow-up

The follow-up period is a 30-day follow-up (Visit 15) relative to the end of treatment visit (Visit 14).

6.1.10.1 Follow-up (Visit 15)

During the 30-day follow-up period (Visit 15) the following information will be collected:

- AEs
- Concomitant medication
- Concomitant diabetes medication
- Hypoglycemic events
- Unexplained hyperglycemic events

6.2 Subject related information

6.2.1 Demography

The following demographic data will be obtained by the Investigator:

- Date of birth
- Age at screening
- Ethnicity

- Race
- Sex

6.2.2 Diagnosis of Type 1 Diabetes Mellitus

At screening (Visit 1) the date of diagnosis of T1DM, as part of the medical history intake, will be obtained.

6.2.3 Concomitant illness and medical history

A **concomitant illness** is any illness, except T1DM, that is present at the start of the trial (i.e. at screening (Visit 1) or found as a result of the screening procedures.

Any change to a concomitant illness should be recorded in the source documentation. A clinically significant worsening of a concomitant illness must be reported as an AE as described in section 12.

Medical history is a medical event that the Subject has experienced in the past. Only relevant medical history, as judged by the Investigator, should be reported.

The information collected for concomitant illness and medical history should include diagnosis, date of onset, date of resolution, or continuation, as applicable.

6.2.4 Childbearing potential

It must be recorded in the source documentation whether female Subjects are of childbearing potential.

Female of non-childbearing potential is defined as, but not limited to:

- A female who has undergone a hysterectomy, bilateral oophorectomy, uterine ablation or bilateral tubal ligation
- Postmenopausal defined as no menses for 12 months without an alternative medical cause
- Other medical reasons preventing childbearing potential

Pregnancy testing must be performed on females with childbearing potential, as described in Section 2.

The Subjects must be instructed to use approved contraceptive methods, throughout the trial and until 1 week after end of treatment.

6.3 Clinical assessments

6.3.1 Concomitant medication

A concomitant medication is any medication, other than trial products and diabetes medication which is taken during the trial, including in the screening, treatment, and follow-up periods.

Details of any concomitant medication must be recorded in the source documentation at screening (Visit 1). Any changes in concomitant medication must be recorded at each visit or phone contact as they occur. The information collected for each concomitant medication includes (at a minimum) trade name or generic name, indication, start date, and stop date (or continuation).

If a change is due to an AE, then this must be recorded and reported according to section 09.

6.3.2 Use of Pumps and BG meters

During the trial, from start of the randomization period (Visit 2) until end of treatment (Visit 14), each time the Subjects attends a site visit the following data will be uploaded to Medtronic CareLink (a web based database):

- All BG meter data transferred to the pump
- All pump data

Data uploaded from the insulin pump include SMPG values, insulin doses, dose calculation related data (e.g. carbohydrates, carbohydrate ratio and insulin sensitivity), primes and rewinds, alarms and other pump settings. Once data has been uploaded to Medtronic CareLink the Investigator will use the reports generated to:

- Check Subject treatment and compliance
- Make adjustments to the Subject's treatment
- Reconcile data entered in the Subjects diary

6.3.2.1 Insulin dose

It is recommended that the bolus dose should be established by Subjects using the Bolus Wizard® according to their usual practice based on instructions from the Investigator.

6.3.2.2 Self-measured plasma glucose

At Screening (Visit 1) the Subject will be required to use their personal BG Contour® meter and supplies during the study. If the subject is not able to use their own supplies, they will be provided with a BG Contour® meter, including lancets and test strips for BG meters. The Subject will be instructed verbally on how to use the device according to the

manufacturer's instructions, as needed. The Subject will also be provided with written instructions as needed. Sites will, as necessary, go through the instructions of use with the Subject during visits to the site.

Throughout the trial, only the BG Contour® meter specifically designed to pair with the Medronic 670G pump must be used to measure the plasma glucose values.

The BG Contour® meter and the pump should be confirmed to be linked by the site personnel at Screening (Visit 1) by review and/or entering the BG Contour® meters Identifications number into the pump to ensure SMPGs are automatically transferred to the pump. The BG Contour® meter must be set to transfer all SMPG values automatically.

The Subjects must be instructed to bring their BG Contour® meter to the site at every visit. The site personnel must upload the data from the BG Contour® meter into Medtronic CareLink at every site visit.

The Investigator will be able to review the SMPG profiles in Medtronic CareLink reports and use them to evaluate the Subject's glycemic control and make adjustments to the pump settings in order to optimize insulin titration.

For the following episodes additional information needs to be recorded in the diary:

- If a SMPG value is ≤ 70 mg/dL, the Subject should record the hypoglycemic episode.
- If a SMPG value is > 70 mg/dL, but the Subject feels typical symptoms of hypoglycemia and interprets those as indicative of hypoglycemia, the subject should record symptoms and glucose level.

- If an SMPG value is ≥ 300 mg/dL, the Subject should record only the unexplained hyperglycemic episodes.

The Investigator should check whether the Subject has recorded the episodes in the hypoglycemia and unexplained hyperglycemia section of the diary, by comparing the diary with the Medtronic CareLink report. If not, the missing information needs to be filled in by the Subject during the visit.

4-point self-measured plasma glucose profile

Subjects will be instructed to perform 4-point profiles every day during the conduct of the trial (from Visit 1 to Visit) mainly for titration purposes. The SMPGs should be measured at the following time points:

- Before breakfast

- Before lunch
- Before main evening meal
- At bedtime

SMPG measurements before breakfast should be performed in a fasting condition. SMPG measurements before lunch, main evening meal, and at bedtime should be performed before any bolus insulin infusion.

6.3.2.3 Change of infusion set and reservoir

Infusion sets will not be provided by the study. The subjects should be able to continue to afford and use their own personal infusion sets throughout the entire study period. The type of infusion set should be recorded in the source documentation at screening and the subjects should remain on the same type of sets throughout the duration of the entire study period.

The Subjects should be instructed to routinely change infusion set in intervals not exceeding 3 days (2 days for SureT® (Easy-set®)). Infusion set and reservoir should be changed at the same time. The trial products should preferably be administered in the abdominal wall. The Investigator should ensure that the Subject is instructed in the following:

- The infusion region chosen should remain unchanged throughout the trial
- The infusion site should be rotated within the same region
- The infusion set should preferably be inserted in the same way

The Subject should change infusion set and reservoir at the site under supervision by the Investigator at randomization (Visit 2) and at end of treatment (Visit 14) due to the change from pre-trial insulin to trial product. The Investigator should evaluate the skin for any local skin irritation or skin infection at every office visit. Any abnormal clinically significant findings should be recorded as an infusion site reaction, as detailed in Section 7.

6.3.2.4 Training in pump use

At start of the screening period (Visit 1), the Investigator should ensure that the Subject knows how to use the insulin pump and perform appropriate training. The Investigator will repeat the training at the randomization visit. The Investigator should ensure that the Subjects know about the following:

- How to set the time and date on their pump
    - Importance of maintaining the correct time and date (e.g. when traveling or entering time changes due to daylight savings)
- How to ensure the SMPG values are recorded in the pump
- Pump settings including settings for basal rates and bolus doses

- Dose adjustment of insulin and use of Bolus Wizard®
- When to perform a routine and non-routine change of infusion set and reservoir
- How to report infusion set change information
- Filling reservoir from vials including priming of infusion set and checking for air in the infusion set before insertion of reservoir
- Carbohydrate counting
- Troubleshooting in case of hypoglycemia and hyperglycemia
- When and how to measure ketones
- Troubleshooting in case of pump failure or any technical problems with the pump
- Proper sensor change techniques and timing
- Auto mode features and use
- Use of acetaminophen in conjunction with sensor use
- Standard 3 hour active insulin time will be used. This may be changed at the investigators discretion
- Standard bolus speeds will used
- Standard target of 120 mg/dL will be used during auto mode

The Subjects should be instructed to call the site in case of any episodes of pump failures (e.g. technical problems or software problems) as well as to contact the pump manufacturer's technical support. The Investigators should record this pump failure incident in the Subject medical record.

6.3.2.5 Training in diabetes and carbohydrate counting

All Subjects should have reinforced diabetes training including carbohydrate counting e.g. sessions with a diabetes educator, dietician or qualified site staff (i.e. diabetes specialized nurse) according to local practice.

It is the Investigators responsibility to ensure that the Subject is adequately trained during the trial and has a satisfactory knowledge in:

- Recognition of carbohydrates in commonly eaten foods
- Ability to count the carbohydrate content in typical portions of simple foods
- Ability to interpret a nutrition label for carbohydrate content
- Glycemic targets
- Preventing and treating hypoglycemia using carbohydrate foods
- Ability to sum up the carbohydrate content of a meal

6.3.3 Body measurements

Height (without shoes) will be measured at screening (Visit 1) only and recorded rounded to the nearest centimeter (cm).

Body weight should be measured in kilograms (kg) without overcoat and shoes, and wearing only light clothing. Body weight will be recorded to one decimal place.

The body weight should be assessed on the same calibrated weighing scale equipment throughout the trial, if possible.

BMI will be calculated by kg/m^2 .

6.3.4 Meal test

The Subject will undergo a standardized liquid meal test at certain visits (see section 2).

During that time 5 blood samples will be drawn, as specified in section 2. The samples will be analyzed by the local laboratory. The Subject must attend the meal test visits in a fasting condition. Bolus infusion and other medication which should be taken before, in a relation to or after a meal should be withheld until the meal test has been performed.

The Subject should before the meal test be instructed to:

- Follow normal routine regarding eating and exercise habits on the day prior to the meal test
- Refrain from intake of alcohol on the day prior to the meal test
- Change infusion set and reservoir prior to the visit so that the meal test is not completed on the day of a sensor change or on day 7 of the current sensor wear
- Take a correction bolus according to guidance from Bolus Wizard® if the PG value above the target level. There should be a minimum of four hours between any correction bolus dose and the start of the meal test.

Any hypoglycemic episodes from midnight before the meal test should be treated and the hypoglycemic episode should be recorded in the diary. At the investigator's discretion, the meal test should be re-scheduled within the visit window.

The Subject should have SMPG values within a range of 71-180 mg/dL before beginning the meal test and bolus insulin dosing. The SMPG values should be verified and recorded at the site before starting the meal test. If the Subject is not fasting or the SMPG value is outside the range, at the Investigators discretion, the meal test should be rescheduled within the visit window.. The Subject's body weight must be measured and a blood sample must be drawn two minutes before intake of the standardized liquid meal. The bolus insulin dose should be calculated by the Investigator based on the dose level of 0.1 unit/Kg body weight. The calculated dose should be

rounded to the nearest whole unit. The 0.1 unit/kg dose is chosen as an approximation of a clinically relevant bolus dose needed for the given size of a standardized meal for T1DM. The use of a weight-based insulin dose calculation for the meal test was specifically chosen to be used in the study in order to minimize inter-subject variability. Only a normal bolus type is allowed. The start of bolus infusion will be defined as time point 0. The Subject will have a carbohydrate-rich standardized meal served immediately after bolus infusion and must consume this as quickly as possible (within 15 minutes). The Investigator should confirm that the Subject consumed the required volume of the standardized liquid meal and actual clock time of start of infusion and meal consumption should be noted. The standardized meal will be provided by the site. The volume of the standardized meal to be consumed should be measured out by the Investigator to be the equivalent to 78 grams of carbohydrate.

Time points of blood glucose obtained during the meal test will be as follows: -2 min, 0 min, 30 min, 60 min, 120 min and 180 min.

No smoking or intake of meals and liquids will be allowed during the meal test, except for water.

If SMPG values ≤ 70 mg/dL are measured then the hypoglycemia should be treated according to site practice and the meal test should continue according to the Investigator's discretion. The hypoglycemic episode must be reported.

After the meal test, the Investigator should make sure that the Subject is safe to leave the site confirmed by an additional SMPG value.

6.3.5 Site insertion examination

The site insertion examination will be performed as outlined in the flow chart (section 2). Site insertion examination will include a skin examination of the subjects preferred infusion set site insertion.

Any abnormal and/or clinically significant findings must be recorded in the Subject's medical record or reviewed for an adverse event.

Any clinically significant worsening from screening, as well as any new abnormal and clinically significant findings, must be reported as an AE in accordance with section 9.

6.3.6 Vital signs

Diastolic blood pressure, systolic blood pressure and pulse should be assessed while the Subject is in a sitting position after five minutes of rest. If the Subject is using antihypertensive medication to control the blood pressure, then the medication should be taken as usual prior to assessing vital signs.

Vital signs will be assessed according to the flow chart, please see section 2.

Any abnormal and/or clinically significant findings at screening (Visit 1) must be recorded in the Subject's medical record.

Any clinically significant deterioration of a pre-existing condition, as well as any new clinically significant signs or symptoms, should be reported as an AE in accordance with section 09.

6.4 Laboratory assessments

Except for urine pregnancy testing, all laboratory analyses will be performed by a local laboratory contracted by the Investigator. The local laboratory will provide all laboratory supplies for the sampling and transportation of all blood and urine samples taken during the trial.

Laboratory samples can be drawn on another day than on the day of the actual visit, as long as it is within the visit window, as stated in the flowchart in section 2.

If laboratory samples need to be retaken due to missing result(s) (e.g. hemolyzed, sample leaked during transit, sample not being conclusive, lost in transit, etc.), the Subject should be called in for resampling.

6.4.1 1,5-anhydroglucitol

1,5 –anhydroglucitol is measured in order to evaluate post prandial glucose control. Please see section 2.

6.4.2 HbA_{1c}

Blood samples will be drawn as specified in the flow chart (section 2) to determine the HbA_{1c} level in order to evaluate glycemic control.

6.4.3 Pregnancy testing

For females of childbearing potential, a urine pregnancy test will be performed at the visits, as detailed in the flowchart in section 2. In addition, urine pregnancy tests will be performed locally during the trial if a menstrual period is missed or if deemed necessary by the Investigator or required by local law. A positive urine pregnancy test should be followed by a confirmatory serum-hCG (local laboratory).

6.4.4 Fructosamine

Fructosamine levels indicate the average level of blood glucose control over the past 2-3 weeks Please see section 2.

6.5 Other assessments and procedures

6.5.1 Diary

Diaries will be used in this trial and handed out to the Subjects as specified in section 2.
At End of treatment the Subjects have to return their last diaries.

The Investigator must carefully instruct the Subject in how to fill out the diary. The Subject should bring the diary at each visit to the site and there the Investigator or delegated site personnel must review the diary together with the Subject to ensure consistency/compliance. If clarification of entries is needed or discrepancies in the diary are found, the Subject must be questioned and a conclusion made in the Subject's medical record.
The following data will be captured by the Subject in the diary:

- Hypoglycemic episodes
- Unexplained hyperglycemic episodes (including any urine/blood ketone values measured, if available)

6.5.1.1 Hypoglycemic episodes

All plasma glucose values:

- ≤ 70 mg/dL
- > 70 mg/dL occurring in conjunction with hypoglycemic symptoms

Plasma glucose should always be measured and recorded by the Subject in the diary, when a hypoglycemic episode is suspected. Hypoglycemic episodes should be reported in the diary according to the instructions below throughout the trial from Visit 1 to End of treatment.

In case of several low SMPG values within the 60 minutes interval, the first value taken is the one that will be reported as the SMPG value for the hypoglycemic episode.

6.5.2 Occlusion event reporting

Starting from randomization (Visit 2) until the end of treatment (Visit 14) the subjects will be questioned at each visit on the occurrence of infusion set occlusions. Occlusion events, for this trial, are defined as a premature change of an infusion set prompted by suspicion of occlusion, leakage, or unexplained hyperglycemia. Subjects will be asked to return any infusion sets to the site, that are thought to have been occluded, for the site to view.

6.6 Subject compliance

Throughout the trial, the Investigator will remind the Subjects to follow the trial procedures and requirements to ensure Subject compliance. If a Subject is found to be non-compliant, the Investigator will remind the Subject of the importance of following the instructions given including taking the trial products as prescribed.

Treatment compliance: To ensure treatment compliance, the Investigator will at each visit assess the Subject's compliance by evaluating the drug accountability, glycemic control, amount of time in auto mode, adherence to the visit schedule, completion of the Subject's diary, and the SMPG values in the CareLink Clinical Report. If a Subject is being non-compliant with the treatment, then the Investigator must discuss this with the Subject and emphasize the importance of being in compliance.

7 Trial supplies

Trial supplies comprise trial products and auxiliary supplies.

Trial products must not be dispensed to any person not included in the trial. Trial product must

not be used if it does not appear clear and colorless.

7.1 Trial products

Table 7–1 The following will be provided by Novo Nordisk

Trial product	Strength	Dosage form	Route of administration
Faster aspart (Fiasp®) (IMP)	100 U/mL	Solution for injection in vial, 10 mL	s.c.
Insulin aspart (NovoLog®) (IMP)	100 U/mL	Solution for injection in vial, 10 mL	s.c.

7.2 Labelling

Labelling of the trial products will be in accordance with local regulations and trial requirements. Labelling will include the product related requirements and precautions.

7.3 Storage

Table 7–2 Storage of trial products

Trial product	Storage conditions (not-in-use)	In-use conditions	In-use time*
Faster aspart (Fiasp®)	Store in refrigerator (2°C – 8°C) Do not freeze Protect from light	Store below 30°C Do not refrigerate Do not freeze Protect from light	Use within 4 weeks
Insulin aspart (NovoLog®)	Store in refrigerator (2°C – 8°C) Do not freeze Protect from light	Store below 30°C Do not refrigerate Do not freeze Protect from light	Use within 4 weeks

* In-use time starts when vial is removed from refrigerator (dispensing at site).

When the trial product is in the pump reservoir the in-use condition is to keep it below 37°C for a maximum of 6 days. Therefore the trial products in the pump reservoir should be discarded after no more than 6 days of use or after exposure to temperatures that exceeds 37°C.

The Investigator must ensure the availability of proper storage conditions, and also record and evaluate the temperature.

7.4 Drug accountability and destruction

Drug accountability is the responsibility of the Investigator. The Investigator or designee will perform the drug accountability at each dispensing visit and will destroy the investigational product onsite according to site SOPs.

Subjects are instructed to return all used, partly used and unused trial product at each dispensing visit, and then finally at end of treatment.

7.5 Auxiliary supplies

The Subject will use their own insulin pump, insulin infusion sets, reservoirs and sensors during the trial.

7.5.1 Auxiliaries supplied by the site

- Bayer Contour® Next Link meters, and strips, lancets and control solution for BG meters for subjects who do not have a personal meter
- Syringes for injection of insulin (for use with vial)

8 Randomization Procedure

At randomization (Visit 2) the Subject will be randomized to either Fiasp® or NovoLog® in a 1:1 manner at the first cross over period to the two different treatment arms described below. At the second cross over period (Visit 8) the Subject will be given the comparative treatment.

- Fiasp®
- NovoLog®

9 Adverse events, hypoglycemia, hyperglycemia, infusion site reactions, technical complaints and pregnancies

9.1 Definitions

9.1.1 Adverse events

An AE is any untoward medical occurrence in a Subject administered a product, and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a product,

whether or not considered related to the product. AE collection will begin after the Subject signs the Informed Consent.

The current version of our local Summary of Product Characteristics (US Product Information) or any updates thereof will be used for assessment of expectedness for adverse events.

An AE includes:

- A clinically significant worsening of a concomitant illness
- A clinical laboratory AE (CLAE): a clinical laboratory abnormality which is clinically significant, i.e. an abnormality that suggests a disease and/or organ toxicity and is of a severity that requires active management. Active management includes active treatment or further investigations, for example change of medicine dose or more frequent follow-up due to the abnormality

The following should **not** be reported as AEs:

- Pre-existing conditions, including those found as a result of screening procedures (pre- existing conditions should be reported as medical history or concomitant illness)
- Pre-planned procedures unless the condition for which the procedure was planned has worsened from signing the Informed Consent
- Non-serious hypoglycemia
- Non-serious unexplained hyperglycemia

The following three definitions are used when assessing an AE:

- **Severity**
    - **Mild** - no or transient symptoms, no interference with the Subject's daily activities
    - **Moderate** - marked symptoms, moderate interference with the Subject's daily activities
    - **Severe** - considerable interference with the Subject's daily activities; unacceptable
- **Causality**

The following terms are used when assessing the relationship between an AE and the relevant trial product(s):

- **Probable** - good reason and sufficient documentation to assume a causal relationship
- **Possible** - a causal relationship is conceivable and cannot be dismissed
- **Unlikely** - the event is most likely related to etiology other than the trial product

- **Final outcome:**

- **Recovered/resolved** - the Subject has fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity after the Subject signed the informed consent
- **Recovering /Resolving** - the condition is still recovering/resolving at the end of the trial
- **Recovered/resolved with sequelae** - the Subject has recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE
- **Not recovered/not resolved** - the condition of the Subject has not improved and the symptoms are unchanged, or the outcome is not known
- **Fatal** - this term is only applicable if the Subject died from a condition related to the reported AE. Outcomes of other reported AEs in a Subject before he/she died should be assessed as "recovered/resolved", "recovering/resolving", "recovered/resolved with sequelae" or "not recovered/not resolved". An AE with fatal outcome must be reported as an SAE
- **Unknown** - this term is only applicable if the Subject is lost to follow-up

9.1.2 Adverse reaction

An Adverse Reaction (AR) is an Adverse Event for which the causal relationship between the Product and the Adverse Event is suspected.

9.1.3 Serious Adverse Event

An SAE is an experience that at any dose results in any of the following:

- Death
- A life-threatening experience
- In-patient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability or incapacity
- A congenital anomaly or birth defect
- Important medical events that may not result in death, be life threatening or require hospitalization may be considered an SAE when - based on appropriate medical judgement they may jeopardize the Subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition of SAE
- Suspicion of transmission of infectious agents must always be considered an SAE

9.1.4 Serious Adverse Reaction

An Adverse event that will fulfill both the criteria for a Serious Adverse event and the criteria for an Adverse Reaction.

9.1.5 Non-serious adverse events

A non-serious AE is any AE which does not fulfill the definition of an SAE.

9.1.6 Hypoglycemic episodes

All plasma glucose values:

- ≤ 70 mg/dL
- > 70 mg/dL occurring in conjunction with hypoglycemic symptoms

Upon onset of a hypoglycemic episode the Subject is recommended to measure plasma glucose every 15 minutes until the SMPG value is > 70 mg/dL or symptoms have been resolved in accordance to current guidelines.

If the Subject experiences a severe hypoglycemic episode (i.e. if the subject was not able to treat themselves) the Subject should be instructed to contact the site staff as soon as possible after recovery for further guidance on titration.

9.1.7 Unexplained hyperglycemic episodes

Any unexplained hyperglycemic episode with SMPG values ≥ 300 mg/dL and no apparent explanation (i.e. no apparent medical, dietary, insulin dosage, or pump failure reason) must be recorded in the Subjects' diary. Symptoms should be treated in accordance with instructions from Investigator.

All hyperglycemic episodes that are not unexplained should be reported as AEs in accordance to section 09 if the Investigator judges that the hyperglycemic episode is clinically significant.

9.1.8 Infusion site reactions

If suspicion of an infusion site reaction occurs, the Subject should be instructed to call the site staff as soon as possible for further guidance.

Infusion site reactions at the site of trial product(s) administration must be recorded as an AE throughout the trial from start of screening (Visit 1) until the end of treatment visit (Visit 14).

9.2 Reporting of adverse events

The Investigator is responsible for reporting all adverse events, including SAE's to the competent authority and IRB based on federal regulations and IRB policies. All events meeting the definition of an AE must be collected and reported. This includes events from randomization until the last phone contact/site visit..

During each contact with the trial site staff, the Subject should be asked about AEs.

All AEs should be recorded by the Investigator on an AE Form. The Investigator should report the diagnosis, if available. If no diagnosis is available, the Investigator should record each sign and symptom as individual AEs using separate AE Forms.

9.2.1 Timelines for initial reporting of serious adverse events

The Investigator should complete the following within the specified timelines:

- **SAEs** - The AE Form and notification to the Novo Nordisk **within 24 hours** and to the IRB, according to the IRB guidelines. As a minimum, the following should be reported to NovoNordisk: Study name, Patient identification (e.g. subject number, initials, sex, age), Event (Preferably diagnosis), Trial drug, Reporter, Causality, Outcome.

9.2.2 Follow-up of adverse events

Follow-up information must be followed up according to the following:

- **SAEs** - All SAEs should be followed until the outcome of the event is "recovered/resolved", "recovered/resolved with sequelae" or "fatal", and until all queries have been resolved. Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome "recovering/resolving" or "not recovered/not resolved". Cases can be closed with the outcome of "recovering/resolving" when the Subject has completed the follow-up period and is expected by the Investigator to recover. The SAE follow-up information should only include new (e.g. corrections or additional) information and must be reported **within 24 hours** of the Investigator's first knowledge of the information. This is also the case for previously non-serious AEs which subsequently become SAEs
- **Non-serious AEs -** Non-serious AEs should be followed until the outcome of the event is"recovered/resolved" or "recovered/resolved with sequelae" or until the end of the follow-up period stated in the protocol, whichever comes first. Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome "recovering/resolving " or "not recovered/not resolved".

9.3 Pregnancies

9.3.1 Pregnancies in female Subjects

Female Subjects must be instructed to notify the Investigator immediately if they become pregnant during the trial until end of treatment. The Investigator must report any pregnancy in Subjects who have received trial product(s).

The Investigator should follow the pregnancy until the pregnancy outcome and the new-born infant is one month of age.

The Investigator should report information about the pregnancy, pregnancy outcome, and health of the new-born infant(s), as well as AEs in connection with the pregnancy and AEs in the fetus and new-born infant.

Investigator to report all pregnancies in trial subjects occurring during use of a Novo Nordisk Product to Novo Nordisk.

10 Quality Control Procedures

During the course of the trial, site staff will perform frequent quality checks through the duration of the study to ensure that the protocol is adhered to, that all issues have been recorded, and to monitor drug accountability. Data reviewed includes, but is not limited to, subject source charts, laboratory results, Medtronic Carelink reports, drug logs, and Subject diaries.

11 Data Handling and Record Keeping

Record keeping for this study will be handled by the Investigative site in accordance to the regulatory requirements.

Subject's data will be handled as follows:
Data already collected will be retained by the Investigator entered into the database and used for the trial report.
Safety events will be reported to Novo Nordisk and regulatory authorities according to regulatory requirements.
Data will be kept onsite at the Investigators location in a secure area through the duration of the trial and then moved offsite into a secure storage location for the required time post trial completion.

12 Statistical considerations

12.1 General considerations

All efficacy and safety endpoints will be summarized and analyzed using the full analysis set.

Estimated mean treatment differences (or ratios) will be presented together with two-sided 95% confidence interval (CI) for all endpoints analyzed. Data collected before randomization will only be summarized descriptively.

Recognizing that there may be more adjustment by the 670G software in the first two weeks of treatment in each crossover period, analyzation of data will be focused on week 3-7 of each cross over period.

12.2 Sample size calculation

The primary objective of the trial is to compare glycemic control with Fiasp® versus NovoLog® when used in the MiniMed 670G System in Auto Mode. The primary objective will be addressed by estimating the treatment difference (including 95% confidence intervals (CI)) for HbA1c and the PPG increment at 1 hour (meal test) after 6 weeks of treatment.

The trial population is assumed to be similar to that of a prior study with Fiasp® (reference 8) (exploratory, double-blind, randomized, 3×14-days, cross-over, single-center, active controlled trial evaluating external continuous subcutaneous infusion of insulin aspart in three different formulations in adult subjects with type 1 diabetes). In that trial, the within-subject standard deviation (SD) for 1-hour PPG increment (meal test) across all periods was 5.81, while the estimated treatment difference between Fiasp® and NovoLog® was -1.81 mmol/L (95% CI: -2.96 to -0.67).

Assuming that the treatment difference will be no less than that seen in that study, there is at least 80% power to detect a treatment difference with 36 subjects. Accounting for 10% dropouts, a total of 40 subjects should be randomized.

The subject population is furthermore in keeping with the treatment difference seen in the Onset 5 study (Reference 10), which was (ETD -0.91 mmol/L [95% CI -1.43; -0.39]; P = 0.001)

12.3 Primary endpoints

The primary endpoint is PPG increment at 1 hour (meal test) after 6 weeks of treatment (i.e. the difference in 1-hour PPG and PPG immediately prior to bolus administration). The primary endpoint will be used to address the primary objective of investigating postprandial glycemic control with Fiasp® compared to NovoLog® when used with the MiniMed 670G System in 'Auto Mode'.

The primary endpoint will be analyzed for subjects who perform the meal tests in both treatment periods, using the MiniMed 670G System in 'Auto Mode'. In other words, the treatment difference will be estimated in subjects who are able to manage 14 days of treatment with both Fiasp® and NovoLog® using the MiniMed 670G System in 'Auto Mode'.

The mean treatment difference stipulated by the estimand (including 95% CI), alongside treatment means, will be derived from a linear mixed model for repeated measurements. The model will include treatment, and period as factors, and subject as a random effect. Because the treatment difference is estimated in the population of subjects who are able to manage treatment with both Fiasp® and NovoLog®, i.e. subjects who contribute meal test data under both treatments, no special methods are needed to address missing data for the primary estimand.

12.4 Secondary endpoints

- Difference in HbA1c between periods will be assessed.
    - Glycemic excursion parameters. Time spent within glycemic ranges as below will be reported and analyzed. Time spent in specific ranges will be expressed as a percentage of total time on treatment.
        - Time spent (%) within 70-180 mg/dl
        - Time spent (%) < 70 mg/dl
        - Time spent (%) >200 mg/dl
        - Hypoglycemia
        - Severe hypoglycemia

The time spent within 70-180 mg/dL, <70 mg/dL, and >200 mg/dL, and hypoglycemia is defined for each subject as the accumulated time in hours spent within the above intervals as recorded by the continuous glucose monitoring component of the MiniMed 670G system. Comparison between the NovoLog® and Fiasp® groups will be analyzed by using linear mixed modeling for repeated measurements for each range. The models will include treatment and period as factors, and subject as a random effect.

- Insulin related parameters
    - Total daily dose
    - change in %bolus and %basal from baseline
    - Auto basal / basal amount (per day)
    - Change in insulin : carbohydrate ratio from baseline
    - Active insulin time

- Pump related parameters
    - Time spent (%) in auto mode
    - Time spent (%) in manual mode
    - Auto mode exits (with reasons for exit)
    - Infusion site reactions reported by patient
    - Occlusion events reported by patient

Secondary endpoints will be assessed through duration of follow-up in the study.

13 Ethics

The trial will be conducted in compliance with ICH GCP and applicable regulatory requirements, and in accordance with the Declaration of Helsinki.

All Subjects included in the trial will be randomized to either Fiasp® or NovoLog®.

The most common side effect of all available insulin preparations is hypoglycemia. The Investigator will explain to the Subject how they should check their BG meter and what precautions to take.

Subjects randomized in the trial will be transferred to a treatment regimen anticipated to be either better than or equal to the treatment they receive at the time they entered the trial.

At the end of treatment, the Subject and Investigator will decide on the best available treatment on the market.

13.1 Informed Consent

In seeking and documenting Informed Consent, the Investigator must comply with applicable regulatory requirement(s) and adhere to ICH GCP and the requirements in the Declaration of Helsinki.

Before any trial-related activity, the Investigator must give the Subject verbal and written information about the trial and the procedures involved in a form that the Subject can read and understand.

The Subjects must be fully informed of their rights and responsibilities while participating in the trial as well as possible disadvantages of being treated with the trial products.

The Investigator must ensure the Subject has ample time to come to a decision whether or not to participate in the trial. A voluntary, signed, and personally dated Informed Consent must be obtained from the Subject before any trial-related activity.

The responsibility for seeking Informed Consent must remain with the Investigator, but the task may be delegated by the Investigator to a medically qualified person, in accordance with local requirements. The Informed Consent must be signed and personally dated by the person who seeks the Informed Consent before any trial-related activity.

If information becomes available that may be relevant to the Subject's willingness to continue participating in the trial, the Investigator must inform the Subject in a timely

manner, and revised Informed Consent must be provided and a new Informed Consent must be obtained.

14 Protocol compliance

Deviations from the protocol should be avoided.

Deviations should be documented and explained in at minimum in the Subject's source chart.

15 Audits and inspections

The Investigator and the site staff have an obligation to cooperate and assist in audits and inspections from domestic or foreign regulatory authorities or from IRBs/IECs. This includes giving auditors and inspectors direct access to all source documents and other documents at the trial site relevant to the clinical trial.

16 Investigator Responsibilities

All staff will conduct the trial in compliance with ICH GCP, applicable regulatory requirements and the Declaration of Helsinki.

The Investigator is accountable for the conduct of the trial. If any tasks are delegated, the Investigator shall maintain a list of appropriately qualified persons to whom he/she has delegated specified significant trial-related duties. The Investigator shall ensure that there is adequate training for all staff participating in the conduct of the trial. It is the Investigator's responsibility to supervise the conduct of the trial and to protect the rights, safety, and well-being of the Subjects.

A qualified physician, who is an Investigator or a sub-Investigator for the trial, shall be responsible for all trial-related medical decisions.

The Investigator must ensure adequate supervision of the conduct of the trial at the trial site.

17 Institutional Review Boards and regulatory authorities

Institutional Review Boards

Written approval shall be obtained from an IRB prior to commencement of the trial.

During the trial, the Investigator should promptly report the following to the IRB in accordance with local requirements: updates to IB, unexpected SAEs as applicable to IRB guidelines, protocol amendments, deviations to the protocol according to the IRB guidelines, new information that may affect adversely the safety of the Subjects or the conduct of the trial (including new benefit-risk analysis in case it will have an impact on the planned follow-up of the Subjects), annually written summaries of the trial status, and other documents as required by the local IRB.

The Investigator should maintain an accurate and complete record of all submissions made to the IRB/IEC. The records must be filed in the Investigator trial master file and copies must be sent to Novo Nordisk.

Regulatory Authorities

Regulatory authorities will receive the clinical trial application, protocol amendments, and reports on SAEs, according to national requirements.

18 Publication Plan

Public disclosure of results will be published within 4 months of completion and will include a publication of a paper in at least one scientific journal and one presentation (poster or oral presentation) at a scientific meeting.

19 References

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5. Heise T, Zijlstra E, Nosek L, *et al*. Pharmacological properties of faster-acting insulin aspart vs insulin aspart in patients with type 1 diabetes receiving continuous subcutaneous insulin infusion: A randomized, double-blind,
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10. Klonoff DC, Evans ML, Lane W, et al. A randomized, multicentre trial evaluating the efficacy and safety of fast - acting insulin aspart in continuous subcutaneous insulin infusion in adults with type 1 diabetes (onset 5) *Diabetes Obes Metab. 2018 Dec 9. doi: 10.1111/dom.13610. [Epub ahead of print]*

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