Cover Page for Protocol

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Official title of study:	An Exploratory Trial investigating the Safety and Efficacy of Fast-acting Insulin Aspart in a Closed-loop Insulin Delivery System (bionic pancreas) in Adults with Type 1 Diabetes
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16.1.1 Protocol and protocol amendments

List of contents

Redacted protocol
Includes redaction of personal identifiable information only.

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Protocol

Protocol title: An Exploratory Trial investigating the Safety and Efficacy of Fast-acting Insulin Aspart in a Closed-loop Insulin Delivery System (bionic pancreas) in Adults with Type 1 Diabetes

Substance : insulin aspart

Universal Trial Number: U1111-1205-1788

Trial phase: 2

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1 Synopsis

Rationale:

Despite improvements in the treatment of diabetes mellitus in the last decade, reaching treatment targets remains challenging for many patients. A leap forward towards reaching treatment targets could be made with closed-loop medical devices that combine insulin delivery with glucose monitoring such as the bionic pancreas (iLet™). Using fast-acting insulin aspart which has a greater early glucose-lowering effect compared to insulin aspart may even allow the iLet™ to achieve better glycaemic control than what can be achieved with using insulin aspart. Identifying a safe t_{max} for Fiasp® is considered a pre-requisite for this to be explored. Therefore, the rationale for conducting this trial is to investigate the safety of the iLet™ in an insulin-only configuration using fast-acting insulin aspart when the control algorithm is modified in terms of changing the t_{max} settings.

1.1 Objectives and endpoints

1.1.1 Primary objective

To investigate the safety of selected t_{max} settings in the insulin-only configuration of the iLet™ bionic pancreas using fast-acting insulin aspart in adults with type 1 diabetes mellitus in a short-term, outpatient clinical trial.

1.1.2 Secondary objective

To investigate the glycaemic control under non-default t_{max} settings compared to that under default t_{max} settings for the iLet™ using fast-acting insulin aspart in adults with type 1 diabetes mellitus in a short term, outpatient clinical trial.

1.1.3 Primary endpoint

Time in low interstitial glucose (defined as < 54 mg/dL; 3 mmol/L) from initiation of treatment (day 1) to end of treatment (day 7) (percentage) (for each of the two treatment periods)

1.2 Overall design:

This trial will be a single-centre, sequential-cohort, randomised, single blind, consisting of three individual cohorts in adult subjects with type 1 diabetes mellitus, each investigating a non-default t_{max} setting of the bionic pancreas to a default t_{max} setting in a two-period cross-over design. The different t_{max} settings will be escalating for each cohort.

At randomisation (visit 2), subjects will be randomised in a 1:1 manner to two different treatment sequences consisting of the default t_{max} setting (t_{65} = 65 minutes) and the non-default t_{max} setting (t_{50} = 50 minutes, t_{40} = 40 minutes or t_{30} = 30 minutes) within their respective cohort both in combination with fast-acting insulin aspart. The total treatment duration within each cohort will be 14 days with each cross-over period of treatment being 7 days. Continuation to the next cohort will

only occur if the stopping criteria on a cohort level are not met, see section 8.1.1. For each cohort, eight new subjects will be recruited and randomised. This will be a single blinded clinical trial where the participating subjects will be blinded towards the order of their t_{max} setting.

1.2.1 Key inclusion criteria

- 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
- Male or female, age ≥ 18 years and ≤ 75 years at the time of signing informed consent
- Diagnosed with type 1 diabetes mellitus ≥ 1 year prior to the day of screening
- Treated with continuous subcutaneous insulin infusion ≥1 year prior to the day of screening
- Have a mean total daily dose of insulin ≥ 20 units
- Familiar with continuous glucose monitoring as judged by the investigator
- Has someone over 18 years of age who (i) lives with them, (ii) has access to where they sleep, (iii) is willing to be in the house when the subject is sleeping, and (iv) is willing to receive calls from the study staff and check the welfare of the study subject
- BMI ≤ 35.0 kg/m^2 at screening
- HbA_{1c} equal to or below 8.5% (69 mmol/mol) at screening
- Able and willing to remain in a designated place for the specified duration of the 'in-patient' periods
- Lives within a 120-minute drive away from the central monitoring location (site)

1.2.2 Key exclusion criteria

- Known or suspected hypersensitivity to trial product(s) or related products
- Previous participation in this trial. Participation is defined as signed informed consent
- Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using an adequate contraceptive method (adequate contraceptive measures as required by local regulation or practice)
- Participation in any clinical trial of an approved or non-approved investigational medicinal product within 30 days before screening
- Any disorder, except for conditions associated with diabetes mellitus, which in the investigator's opinion might jeopardise subject's safety or compliance with the protocol
- Anticipated initiation or change in concomitant medications known to affect weight or glucose metabolism during the trial
- Impaired liver function, defined as Alanine Aminotransferase (ALT) ≥ 2.5 times or Bilirubin >1.5 times upper normal limit at screening
- Renal impairment measured as estimated Glomerular Filtration Rate (eGFR) value of eGFR < 60 ml/min/1.73 m^2
- Any episodes of diabetic ketoacidosis within the past 90 days prior to the day of screening

- Known hypoglycaemic unawareness as indicated by the Investigator according to Clarke's questionnaire question 8
- Recurrent severe hypoglycaemic episodes within the last year as judged by the Investigator
- Any of the following: myocardial infarction, stroke, hospitalization for unstable angina pectoris or transient ischaemic attack within the past 180 days prior to the day of screening
- Subjects presently classified as being in New York Heart Association (NYHA) Class IV
- Planned coronary, carotid or peripheral artery revascularisation known on the day of screening
- Inadequately treated blood pressure defined as Grade 3 hypertension or higher (Systolic ≥180 mmHg or diastolic ≥110 mmHg) at screening

1.2.3 Number of subjects:

Approximately 32 subjects will be screened to achieve 24 randomised subjects.

1.2.4 Treatment groups and duration

The total duration in the trial for an individual subject will differ for the different cohorts, as additional time for screening has been included for cohort 2 and 3. For a subject in cohort 1 the trial duration will be a maximum of 5 weeks. For cohort 2 and cohort 3 the trial duration for a subject will be a maximum of 8 weeks. It consists of a screening period (for cohort 1 appx. 2 weeks, for cohort 2 and 3 appx. 5 weeks), 2 x 7 days treatment period and a follow-up period is 7 days.

This is a cross-over trial and each randomised subject will switch between the default t_{max} setting (t_{65}) and the non-default t_{max} setting (t_{50}, t_{40} or t_{30}) within their respective cohort, both in combination with fast-acting insulin aspart.

1.2.5 Trial Products

Investigational medicinal product:

- Trial product: fast-acting insulin aspart, 100 U/mL, 1.6 mL cartridge (PumpCart®)

Investigational medical device:

- Bionic pancreas (iLet™), used in insulin-only configuration

2 Flowchart

		Treatment period			Follow up period
Visit Name (Week)	Screening (Week -2)	Randomisation (Week 0)	Cross-over (Week 1)	End of treatment (Week 2)	Phone Contact (Week 3)
Visit	V1	V2	V3	V4	P5
Timing of Visit (Days)	-14[a]	0	7[b]	7[b]	7[b]
Visit Window (Days)	0/13[i]	±0	-1/0	-1/0	+0/5
SUBJECT RELATED INFORMATION AND ASSESSMENTS					
Informed consent	X				
Demography[c]	X				
In/exclusion criteria	X				
Child bearing potential	X				
Concomitant illness/medical history	X				
Concomitant medication	X	X	X	X	
Diagnosis of diabetes	X				
Tobacco use[d]	X				
Body measurements	X	X	X		
Randomisation		X			
Discontinuation criteria		X	X	X	
Withdrawal of informed consent		X	X	X	
SAFETY					
Adverse event	X	X	X	X	X
Technical Complaints		X	X	X	
Infusion site reaction		X	X	X	
Medication error		X	X	X	
Hypoglycaemic episodes		X	X	X	
Haematology	X				
Biochemistry	X				
Lipids	X				
Pregnancy test[e]	X	X			
Vital signs	X				
Physical examination	X				
Parameters transferred from iLet™		X	X	X	
OTHER ASSESSMENTS					
Change of infusion set and PumpCart®		X	X	X	

		Treatment period			Follow up period
Visit Name (Week)	Screening (Week -2)	Randomisation (Week 0)	Cross-over (Week 1)	End of treatment (Week 2)	Phone Contact (Week 3)
Visit	V1	V2	V3	V4	P5
Timing of Visit (Days)	-14[a]	0	7[b]	7[b]	7[b]
Visit Window (Days)	0/13[i]	±0	-1/0	-1/0	+0/5
HbA_{1c}	X				
Start date and time of iLet™		X	X		
Stop date and time of iLet™			X	X	
CGM calibration value[f]			X	X	
Site contact to subject during remote monitoring			X	X	
Discharge at the end of in-patient period		X	X		
Escalation decision				X	
Escalation stopping criteria			X	X	
TRIAL MATERIAL					
Dispensing visit		X	X		
Drug accountability		X	X	X	
REMINDERS					
Hand-out ID card	X				
Hand out and instruct in diary		X			
Training in trial product		X	X		
Supply and instruct in use of backup kit		X			
Hand out and instruct in use of BG meter, iLet™ and CGM		X	X		
CGM sensor fitting		X	X[g]		
CGM data review via Remote Monitoring Unit		X[h]	X[h]	X	
Collect diary			X	X	
End of treatment				X	
End of trial					X
Affirmation statement					X

Footnote
a) Screening period for Cohort 1 will be up-to 14 days and for Cohort 2 and Cohort 3 will be up-to 5 weeks
b) Visit 3, visit 4 and phone contact (P5) are calculated as 7 days from the last visit date to ensure the required number of days per t_{max} setting and the follow-up period respectively.
c) Demography consists of date of birth, sex, ethnicity and race (according to local regulation).

Footnote
d) Smoking is defined as smoking at least one cigarette or equivalent daily.
e) Urine test for pregnancy to be done only in females of childbearing potential
f) CGM sensor should be calibrated as per manufacturer's instructions
g) CGM sensor should be changed as per manufacturer's instructions (every 7 days) and must be changed during the scheduled site visits
h) Subject will spend the 1st night at a hotel for close observation during each treatment period and each cross-over visit
i) Visit window for Cohort 1 will be 0/13 and for Cohort 2 and Cohort 3 will be 0/34

3 Introduction

3.1 Trial rationale

Despite improvements in the treatment of diabetes mellitus in the last decade, reaching treatment targets remains challenging for many patients[1]. A leap forward towards reaching treatment targets could be made with closed-loop medical devices that combine insulin delivery with glucose monitoring such as bionic pancreas (iLet™). Using fast-acting insulin aspart which has a greater early glucose-lowering effect compared to insulin aspart may even allow the iLet™ to achieve better glycaemic control than what can be achieved with using insulin aspart. Identifying a safe t_{max} for Fiasp® is considered a pre-requisite for this to be explored. Therefore, the rationale for conducting this trial is to investigate the safety of the iLet™ in an insulin-only configuration using fast-acting insulin aspart when the control algorithm is modified in terms of changing the t_{max} settings.

3.2 Background

3.2.1 Therapeutic area and the iLet™

The bionic pancreas consists of a combination of an insulin pump, a continuous glucose monitoring system, and mathematical dosing algorithms developed at Boston University and the Massachusetts General Hospital. Based on the individual subject's continuous glucose measurement (CGM) readings, the device autonomously delivers insulin and/or glucagon and manages the patients' blood sugar levels. The mathematical dosing algorithm determines dosing requirements in steps every five minutes adapting continually to each individual's ever-changing insulin needs. The adaptive meal-announcement algorithm eliminates the need for the user to set or know their carbohydrate-to-insulin ratios, as it makes automatic adjustments based on dosing history for similar past meal announcements, and customizes its doses to the individual and time of day to meet a target of 75% of the insulin needs for that size and mealtime. Previous trials with the bionic pancreas have shown an improved mean glucose and reduced time in hypoglycaemia and hyperglycaemia compared to the current standard of treatment[2, 3]. The bionic pancreas device, hereafter referred as the iLet™,

developed by Beta Bionics, integrates all the components of the Boston University–Massachusetts General Hospital bionic pancreas into a single hand-held medical device.

Better outcomes with the iLet™ are possible partly because the dosing algorithms compute an estimate of the cumulative insulin on board from past doses behind the current online step. It uses a bi-exponential function to model each dose's evolution, from its time of administration onwards until the dose is deemed cleared. At every step, the algorithm responds to the glucose level and its trend while taking into account the cumulative insulin on board. The more cumulative insulin deemed to be on board, the more it would reduce its dosing or refrain altogether and wait (it would be relatively less responsive in terms of additional insulin dosing). In this respect, the setting of model parameters in the dosing algorithm may play an important role. The parameter controlling the responsiveness of the algorithm is referred to as t_{max} and reflects the pharmacokinetic parameter t_{max} in a model based setting. As the t_{max} is decreased, the algorithm's bi-exponential rises and decays sooner for each dose and so past doses will be effectively declared cleared and "out of the dosing calculation" sooner. This implies that the algorithm would then sooner be less restrained in its response (insulin dosing) to a given glucose level and/or a trend. Conversely, when the t_{max} is increased, accumulation/pending effect of past doses will remain a stronger factor for a longer period in the dosing calculations, and the algorithm would remain relatively restrained (less responsive in terms of insulin dosing) for a longer period in its dosing response to a given glucose level and/or a trend.

It is hypothesized that using a rapid acting insulin analog such as fast-acting insulin aspart will allow the iLet™ to achieve better glycaemic control compared to what can be achieved using NovoLog® in the iLet™. Identifying a safe t_{max} for fast-acting insulin aspart is considered a pre-requisite for this to be explored.

3.2.2 Fast-acting insulin aspart

Fast-acting insulin aspart is an innovative formulation of insulin aspart which is currently approved for Multiple Daily Injection (MDI) insulin therapy in US. Fast-acting insulin aspart is currently not approved for use in insulin pumps in US. Fast-acting insulin aspart aims at approaching the physiological prandial insulin secretion pattern better than currently available treatments and thereby more effectively controlling the postprandial glucose (PPG) excursions and achieving a better PPG control compared with NovoLog®.

Fast-acting insulin aspart includes two excipients which result in an increased early absorption of insulin aspart following subcutaneous injection. This leads to a greater early glucose-lowering effect compared to NovoLog® [4]. Results from clinical pharmacology trials in adults comparing pharmacokinetic and pharmacodynamics properties of fast-acting insulin aspart and NovoLog® have shown that fast-acting insulin aspart resulted in an earlier onset of appearance and a greater early exposure to insulin aspart than NovoLog® in subjects with type 1 diabetes mellitus (T1DM),

with the largest difference found within the first 15 minutes after injection. Fast-acting insulin aspart also resulted in a greater early glucose-lowering effect than NovoLog®[4, 5].

3.3 Benefit-risk assessment

The current trial will evaluate different settings of the algorithm in the iLet™ using fast-acting insulin aspart. The currently available data demonstrate that treatment with fast-acting insulin aspart results in an increased early absorption of fast-acting insulin aspart compared to NovoLog®, thereby providing a faster action. It is expected that this clinical trial will yield increased knowledge about using fast-acting insulin aspart in an automated closed-loop system to control the glucose level. The individual subject may not benefit from study participation.

For the individual subject, the anticipated risks include hypoglycaemia, hyperglycaemia, infusion site reactions, CGM related inconveniences, systemic allergic reactions and antibody development.

As in any other clinical trials with T1DM patients, hypoglycaemia and hyperglycaemia are a risk in subjects in this clinical trial as well. Hypoglycaemia could occur if the system delivers an inappropriate amount of insulin given the subject's underlying glycaemic state. This could occur if, for example, a sensor is functioning poorly and significantly over-reads glucose values. Over-delivery may be minimized if the sensor's trend data remains accurate despite inaccurate level values, or by the safety constraints of the closed loop system. However, there is a risk of having a low blood sugar (hypoglycaemia) that may exceed the risk present as part of normal daily living. Hypoglycaemia could also occur if the t_{max} setting of the control algorithm is set to a value that is too low relative to the actual t_{max} setting of the insulin being administered to a particular research subject, leading to insulin stacking. Symptoms of hypoglycaemia can include sweating, jitteriness, and not feeling well. Hyperglycaemia and ketonaemia could occur if insulin delivery is attenuated or suspended for an extended period or if the pump or infusion set is not working properly. A sensor which was functioning poorly and significantly under-reading glucose values could lead to inappropriate reduction of insulin delivery.

There is a potential risk of hypoglycaemia, hyperglycaemia and potentially diabetic ketoacidosis in case of technical problems with the iLet™.

Remote monitoring is implemented in this trial and should minimize these risks of hypoglycaemia and hyperglycaemia to the extent possible, see section 9.16.

Subjects using the continuous glucose sensor will be at low risk for developing a local skin infection at the site of the sensor insertion. On rare occasions, the continuous glucose sensor may break and leave a small portion of the sensor under the skin that may cause redness, swelling or pain at the insertion site.

Infusion site reactions can occur. The nature of the infusion site reactions is expected to be mild and transient. When wearing sensors and insulin infusion sets there is always a risk of skin rashes,

allergic reactions to the tape, or infections at the insertion site. All trial treatments are contraindicated in case of hypersensitivity to the active substance or any of the excipients'.

The blood samples taken during the trial might be inconvenient to the subjects. Blood draws can cause some common reactions like pain, bruising, or redness at the sampling site. Less common reactions include bleeding from the sampling site, formation of a small blood clot or swelling of the vein and surrounding tissues, and fainting.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of fast-acting insulin aspart may be found in the latest version of the investigator's brochure. And the information related to the iLet™ may be found in System Risk Analysis document.

4 Objectives and endpoints

4.1 Primary, secondary and exploratory objective(s)

4.1.1 Primary objective

To investigate the safety of selected t_{max} settings in the insulin-only configuration of the iLet™ bionic pancreas using fast-acting insulin aspart in adults with type 1 diabetes mellitus in a short-term, outpatient clinical trial.

4.1.2 Secondary objective

To investigate the glycaemic control under non-default t_{max} settings compared to that under default t_{max} settings for the iLet™ using fast-acting insulin aspart in adults with type 1 diabetes mellitus in a short term, outpatient clinical trial.

4.2 Primary, secondary and exploratory endpoint(s)

4.2.1 Primary endpoint

- Time in low interstitial glucose (defined as < 54 mg/dL; 3 mmol/L) from initiation of treatment (day 1) to end of treatment (day 7) (percentage) (for each of the two treatment periods)

4.2.2 Confirmatory secondary endpoints

Not applicable for this trial.

4.2.3 Supportive secondary endpoints

- Number of treatment emergent severe hypoglycaemic episodes from initiation of treatment (day 1) to end of treatment (day 7) (count)

- Number of self-manageable (able to self-treat) treatment emergent hypoglycaemic episodes that require oral carbohydrate intervention per day from initiation of treatment (day 1) to end of treatment (day 7) (count)
- Number of treatment emergent hypoglycaemic episodes classified both according to the ADA definition and Novo Nordisk classification from initiation of treatment (day 1) to end of treatment (day 7) (count)
    - Overall
    - Daytime hypoglycaemic episodes
    - Nocturnal hypoglycaemic episodes (00:01-05:59 both inclusive)
- Time in interstitial glucose range defined as 70–180 mg/dL (3.9-10 mmol/L) from initiation of treatment (day 1) to end of treatment (day 7) (percentage)
- Mean interstitial-glucose level from initiation of treatment (day 1) to end of treatment (day 7) (mg/dL)
- Number of treatment emergent adverse events from initiation of treatment (day 1) to end of treatment (day 7) (count)
    -
- Number of treatment emergent infusion site reactions from initiation of treatment (day 1) to end of treatment (day 7) (count)
- Total insulin dose (U/kg) per day from initiation of treatment (day 1) to end of treatment (day 7) (U/Kg/day)

4.2.4 Exploratory endpoint(s)

- Mean interstitial glucose increment from time of announcement of a "typical meal" to 2 hours after announcement from initiation of treatment (day 1) to end of treatment (day 7) (mg/dL)

5 Trial design

5.1 Overall design

This trial is an escalation trial with the aim to investigate whether the selected t_{max} in the algorithm settings will allow safe use of the insulin only bionic pancreas with fast-acting insulin aspart. This trial is a single-centre, sequential-cohort, randomised, single blind, cross-over escalation trial over three cohorts.

For each cohort, eight new subjects will be recruited and randomised. Subjects will be randomised in a 1:1 manner to two treatment sequences i.e. the default t_{max} setting (t_{65} = 65 minutes) followed by the non-default t_{max} setting (t_{50} = 50 minutes, t_{40} = 40 minutes or t_{30} = 30 minutes) or the non-default t_{max} setting followed by the default t_{max} setting, all in combination with fast-acting insulin aspart. The treatment duration is 7 days for each treatment period, (see Figure 5–1). The subjects will be blinded towards the order of their t_{max} setting. There are no restrictions of any kind on diet,

exercise, or other activities. Subjects will be asked to keep their diet and activity as normal as possible throughout the trial.

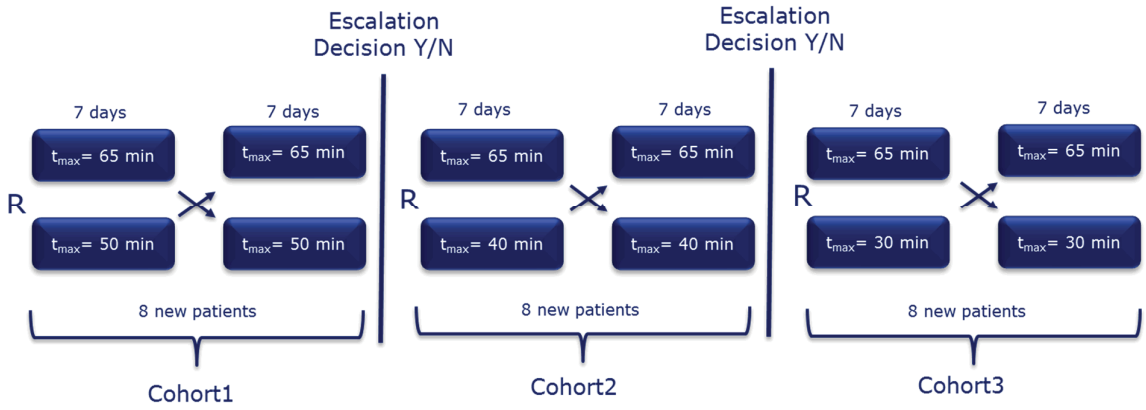


Figure 5–1 Trial design

The treatment in this trial is defined as the combination of selected t_{max} setting on the iLet™ with fast-acting insulin aspart. The total treatment duration within each cohort will be 14 days with each cross-over period of treatment being 7 days. No wash-out is implemented between the cross-over periods. Continuation to the next cohort will occur only if the stopping criteria on a cohort level are not met (see section 8.1.1 for stopping criteria).

For each subject, an 'in-patient' period is implemented for the first 1 day (24 hours ± 3 hours) following treatment initiation, i.e. at visit 2 and at cross-over visit (visit 3). This entails that subjects will stay at a designated place (such as a hotel) for the specified duration and will be discharged as per PI's discretion, see section 9.15. This period is included in the 7 days treatment period. The 'out-patient' period is defined as the period after the discharge from the designated place where the subject stays during the 'in-patient' period and until the end of treatment.

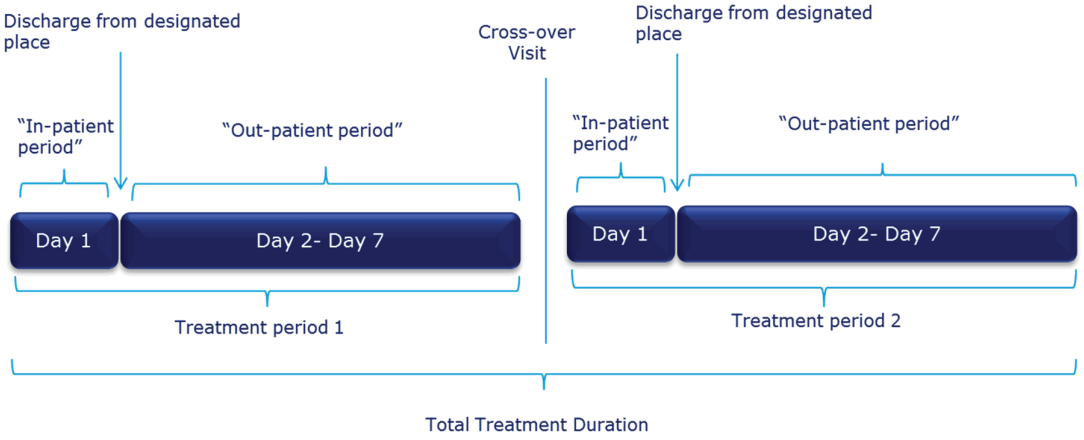


Figure 5–2 In-patient and Out-patient period

Each treatment period will have 1 day of "in-patient" period and 6 days of "out-patient" period, see Figure 5–2.The period between visit 2 and visit 3 is called treatment period 1 and the period between visit 3 and visit 4 is called treatment period 2, see Figure 5–3.

Each cohort of the trial will have 5 visits: a screening visit (visit 1), an initiation of treatment i.e. randomisation visit (visit 2), a mid-period cross-over visit (visit 3), an end of treatment visit (visit 4) and a phone contact (P 5), 7 days after end of treatment visit, see Figure 5–3.

The total duration in the trial for a subject will differ for the different cohorts, as additional time for screening has been included for cohort 2 and 3. This has been included in order to give possibility to the site of screening the subjects for cohort 2 and 3 during the treatment of the first cohort, thereby enabling the site to have the subjects ready for randomisation soon after the escalation decision on previous cohort is made. For subjects in cohort 1 the trial duration will be a maximum of 5 weeks. For cohort 2 and cohort 3 the trial duration will be a maximum of 8 weeks. It consists of a screening period (for cohort 1 app. 2 weeks, for cohort 2 and 3 app. 5 weeks), 2 x 7 days treatment period and a follow-up period is 7 days.

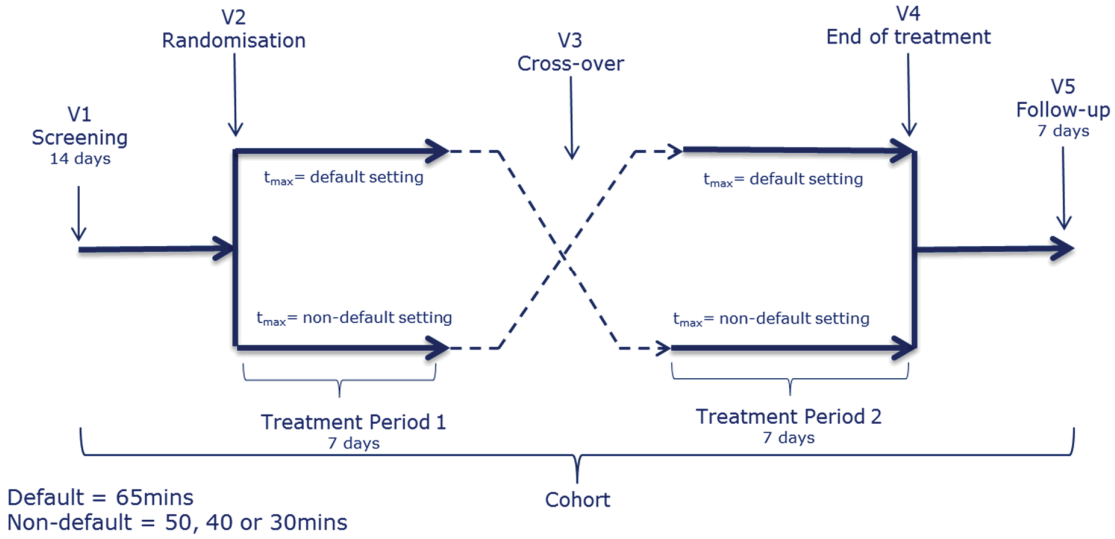


Figure 5–3 Visit structure for a single cohort

5.2 Subject and trial completion

Approximately 32 subjects will be screened to achieve 24 subjects randomly assigned to two treatment sequences i.e. the default t_{max} setting followed by the non-default t_{max} setting or the non-default t_{max} setting followed by the default t_{max} setting all in combination with fast-acting insulin aspart.

Each subject will have at-least 1 designated contact as per the inclusion criteria 7.

Treatment period completion for a subject:

Treatment period completion is defined as when the randomised subject has received the required treatment as per treatment period 1 and 2 and attended the 'end of treatment' visit according to the flowchart (See section 2).

Trial period completion for a subject:

Trial period completion is defined as when the randomised subject has completed the final scheduled visit ('end of trial' according to the flowchart, see section 2). 'Date of trial completion' is the date the subject completed the final scheduled visit.

5.3 End of trial definition

The end of the trial is defined as the date of the last visit of the last subject in the trial.

5.4 Scientific rationale for trial design

The medical need for using closed-loop medical devices that combine insulin delivery with glucose monitoring is anticipated to be the highest in subjects with T1DM. This is also the patient population with the highest percentage of usage of continuous subcutaneous insulin infusion. For these reasons, this trial will include subjects with T1DM. An escalation trial is chosen since the default t_{max} setting is going to be investigated along with three non-default t_{max} settings. A cross-over design is used to enable glycaemic control under non-default t_{max} settings to be evaluated in a within-subject setting, reducing the impact of between-subject variability.

5.5 Justification for t_{max} setting

The t_{max} settings for the trial have been chosen to reflect the default t_{max} investigated in earlier clinical trials with insulin aspart (t_{65}) and three values below (t_{50}, t_{40} and t_{30}). These values span a range that is expected to include a more optimal t_{max} setting for the iLet™ using the fast-acting insulin aspart, considering its pharmacokinetic profile[4].

6 Trial population

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1 Inclusion criteria

Subjects are eligible to be included in the trial only if all of the following criteria apply:

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 and ≤ 75 years at the time of signing informed consent.
3. Diagnosed with type 1 diabetes mellitus ≥ 1 year prior to the day of screening.
4. Treated with continuous subcutaneous insulin infusion ≥ 1 year prior to the day of screening.
5. Have a mean total daily dose of insulin ≥ 20 units
6. Familiar with continuous glucose monitoring as judged by the investigator.
7. Has someone over 18 years of age who (i) lives with them, (ii) has access to where they sleep, (iii) is willing to be in the house when the subject is sleeping, and (iv) is willing to receive calls from the study staff and check the welfare of the study subject .
8. BMI ≤ 35.0 kg/m^2 at screening.
9. HbA_{1c} equal to or below 8.5% (69 mmol/mol) at screening.

10. Able and willing to remain in a designated place for the specified duration of the 'in-patient' periods.
11. Lives within a 120-minute drive away from the central monitoring location (site).

6.2 Exclusion criteria

Subjects are excluded from the trial if any of the following criteria apply:

1. Known or suspected hypersensitivity to trial product or related products
2. Previous participation in this trial. Participation is defined as signed informed consent
3. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using an adequate contraceptive method (adequate contraceptive measures as required by local regulation or practice)
4. Participation in any clinical trial of an approved or non-approved investigational medicinal product within 30 days before screening
5. Any disorder, except for conditions associated with diabetes mellitus, which in the investigator's opinion might jeopardise subject's safety or compliance with the protocol
6. Anticipated initiation or change in concomitant medications known to affect weight or glucose metabolism during the trial
7. Impaired liver function, defined as Alanine Aminotransferase (ALT) ≥ 2.5 times or Bilirubin >1.5 times upper normal limit at screening
8. Renal impairment measured as estimated Glomerular Filtration Rate (eGFR) value of eGFR < 60 ml/min/1.73 m^2
9. Any episodes of diabetic ketoacidosis within the past 90 days prior to the day of screening
10. Known hypoglycaemic unawareness as indicated by the Investigator according to Clarke's questionnaire question 8[a]
11. Recurrent severe hypoglycaemic episodes within the last year as judged by the Investigator
12. Any of the following: myocardial infarction, stroke, hospitalization for unstable angina pectoris or transient ischaemic attack within the past 180 days prior to the day of screening
13. Subjects presently classified as being in New York Heart Association (NYHA) Class IV
14. Planned coronary, carotid or peripheral artery revascularisation known on the day of screening
15. Inadequately treated blood pressure defined as Grade 3 hypertension or higher (Systolic ≥180 mmHg or diastolic ≥110 mmHg) at screening

[a]Information on hypoglycaemia unawareness will be recorded according to Clarke's questionnaire, question 8[6]. The investigator must ask the subject in the following way: "To what extent can you

tell by your symptoms that your blood glucose is low? Never, Rarely, Sometimes, Often or Always." Subjects answering 'never, rarely or sometimes' are considered to have impaired awareness of hypoglycaemia.

6.3 Lifestyle restrictions

Not applicable for this trial.

6.4 Screen failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are not eligible for participation according to in/exclusion criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet requirements from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial may not be rescreened. Re-sampling is not allowed if the subject has failed one of the inclusion criteria or fulfilled one of the exclusion criteria related to laboratory parameters. However, in case of technical issues (e.g. haemolysed or lost), re-sampling is allowed for the affected parameters.

6.5 Randomisation criteria and dosing day exclusion criteria and run-in exclusion criteria

Not applicable for this trial.

7 Treatments

7.1 Treatments administered

7.1.1 Investigational and non-investigational medicinal products

Trial product must only be used, if it appears clear and colourless.

Table 7–1 Trial products provided by Novo Nordisk A/S

Trial product name:	Fast-acting insulin aspart , 100 U/ml (Investigational medicinal product (IMP), test product)	Fiasp® , 100 U/ml (Non- Investigational medicinal product (NIMP))
Dosage form:	Solution for injection	Solution for injection
Route of administration:	Subcutaneous	Subcutaneous
Dosing instructions:	Dosing is handled by iLet™ autonomously	Dosing as per PI's discretion
Packaging	1.6 mL cartridge (PumpCart®)	3-mL prefilled insulin pen

		(Fiasp® FlexTouch®)

7.1.2 Medical devices

Investigational medical device(s):

- iLet™*: The bionic pancreas including pigtail adapters, used in insulin-only configuration

*For technical complaints (medical device incidents) related to iLet™ it must be evaluated by the investigator if the technical complaint could have led to an SAE (serious medical device incident) according to Section 9.2.8 and Appendix 6.

Information related to the instructions for use of the iLet™ can be found in the iLet™ instructional manual.

Beta Bionics will provide the iLet™ and the StudyPhone with CGM application (app). For complaints related to the iLet™, the investigator should report it to both Novo Nordisk and Beta Bionics, see Appendix 6. And for complaints related to the Study phone, the investigator must contact Beta Bionics directly.

Non-investigational medical device(s):

- CGM device (Dexcom G5®) and its auxiliaries
- StudyPhone with CGM app**
- BG meter (Contour® Next One) and its auxiliaries
- Infusion set with 60 cm tube (Contact™ detach)

Novo Nordisk will provide the aforementioned non-investigational medical devices (except StudyPhone with CGM app) to the subjects along with the paper diary.

For complaints related to the BG meter, infusion set or CGM device, the investigator must contact the device manufacturer's technical support according to Operator's Manuals provided with the BG meter, infusion set and the CGM device.

**StudyPhone with CGM app is an iPhone installed with a CGM app which is used to display the CGM values and to record the SMPGs values for sensor calibration.

Training in the medical devices

At visit 2, investigator should ensure that subjects know how to use the medical devices and perform appropriate training using relevant manuals (as specified in flowchart section 2). The investigator will, as necessary, repeat the trainings at visit 3. The investigator must document all the

trainings in the subject's medical record (such as site record, research record or any other similar document).

The investigator should ensure that the subject knows the following as the minimum:

iLet™

- How to replace the PumpCart®
- How and when to replace the batteries
- Troubleshooting in case of iLet™ failure or any technical problems

CGM – Dexcom G5®

- How and when to change the sensor
- How and when to calibrate the sensor
- How to use the CGM app on StudyPhone

BG Measurement - Contour® Next One

- When to perform self-measured plasma glucose (SMPG) measurements
- How and where to report the SMPG measurements
- How and when to perform ketone measurement

Infusion set – Contact™ detach

- How and when to perform infusion set change
- How to report infusion set change in the diary

7.2 Dose modification

Dose modification is handled autonomously by the iLet™ based on the CGM sensor readings and the user interaction with the iLet™ e.g. meal announcements. Therefore, there is no standard insulin titration algorithm in this trial.

7.3 Method of treatment assignment

Interactive Web Response System (IWRS) will not be used in this trial. All subjects will be assigned a unique number (randomisation number) in ascending numerical order at the trial site. The randomisation number encodes the subject's assignment to one of the treatment sequences of the trial, according to the randomisation schedule generated before the trial.

7.4 Blinding

A single trial product is used in this trial. This is packed open-label; however, the specific treatment sequence for a subject will be assigned using a randomisation list. This will be a single blinded

clinical trial where the participating subjects will be blinded towards the order of their t_{max} setting as this information will not be visible to them.

7.5 Preparation/Handling/Storage/Accountability

Only subjects enrolled in the trial may receive trial product and only authorised site staff may supply or administer trial product.

Table 7–2 Trial product storage conditions

Trial product name	Storage conditions (not-in-use)	In-use conditions	In-use time[a]
Fast-acting insulin aspart, 100 U/ml	Store in refrigerator (2°C-8°C) Protect from light Do not freeze	Store below 37°C Protect from light Do not refrigerate Do not freeze	Use within 2 days

[a]In-use time starts when the PumpCart® is connected to the iLet™

The trial site will be supplied with sufficient trial products for the trial on an on-going basis.

The investigator must confirm that appropriate temperature conditions have been maintained during transit for all trial products received and any discrepancies are reported and resolved before use of the trial products.

All trial products must be stored in a secure, controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.

The investigator must inform Novo Nordisk immediately if any trial product has been stored outside specified conditions. Additional details regarding handling of temperature deviations can be found in the Trial Materials Manual (TMM).

Trial product that has been stored improperly must not be dispensed to any subject before it has been evaluated and approved for further use by Novo Nordisk.

The investigator is responsible for drug accountability and record maintenance (i.e. receipt, accountability and final disposition records). Drug accountability should be performed at PumpCart® level. Destruction of trial products can be performed on an ongoing basis and will be

done according to local procedures after accountability is finalised by the site and reconciled by the monitor. Destruction of trial products must be documented via site normal procedures.

All returned, expired or damaged trial products (for technical complaint samples see Appendix 6) must be stored separately from non-allocated trial products. No temperature monitoring is required.

Non-allocated trial products including expired or damaged products must be accounted as unused, at the latest at closure of the trial site.

The CGM sensors distributed to site will have to be stored according to Table 7–3 and temperature monitoring is required.

Table 7–3 Dexcom G5 R CGM sensor storage conditions

Device name	Storage conditions (not-in-use)	In-use conditions	In-use time [b]
Dexcom G5R sensor	Store (2°C – 25°C / 36°F – 77°F) Do not freeze	-	Up to 7 days

[b]In-use time starts when sensor has been fitted

7.6 Treatment 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.

7.7 Concomitant medication

Any medication other than the trial product that the subject is receiving at the time of screening visit or receives during the trial must be recorded along with:

- Trade name or generic name
- Indication
- Dates of administration including start and stop dates

Changes in concomitant medication must be recorded at each visit. If a change is due to an AE/SAE, then this must be reported according to Section 9.2.

7.7.1 Rescue medication

In case of hypoglycaemia, please refer to the section 9.3 for treatment of overdose.

In case of hyperglycaemia (e.g. due to pump failure) the subject should be instructed to call the site immediately.

The trial site will supply glucagon (as a part of back-up kit) that will be provided by Novo Nordisk.

The following rescue medications may be used for hypoglycaemia:

1. Ingestion of carbohydrates (e.g. juice)
2. Dextrose
3. Glucagon
4. Parenteral glucose

The rescue medication for hyperglycaemia should be used as per investigator's discretion.

7.8 Treatment after the end of the trial

When discontinuing trial product, the subject should be transferred to a suitable marketed product at the discretion of the investigator.

8 Discontinuation/Withdrawal criteria

The subject may be discontinued at any time during the trial at the discretion of the investigator for safety, behavioural, compliance or administrative reasons. A subject may also withdraw consent at any time at his/her own request.

If a subject is discontinued due to the criteria listed in section 8.1, the investigator must ask the subject if he/she is willing, as soon as possible, to have assessment performed according to visit 4 and a phone contact (P 5) after 7 days.

See the flowchart section 2 for data to be collected at the time of treatment discontinuation, and follow-up, and for any further evaluations that need to be completed.

8.1 Discontinuation of trial treatment

The subject must be discontinued from trial treatment, if the following applies:

1. Included in the trial in violation of the inclusion and/or exclusion criteria
2. Pregnancy
3. Intention of becoming pregnant
4. Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product.

The primary reason for discontinuation of trial product must be specified in the end-of-trial-form in the case report form (CRF), and final drug accountability must be performed.

8.1.1 Escalation stopping criteria

After all subjects have completed Visit 4 in a given cohort, the PI will evaluate if any of the following have occurred in individual subjects:

- Time in low interstitial glucose (defined as below 54 mg/dL (3.0 mmol/L)) is higher than 2% of the total time from initiation of treatment (day 1) to end of treatment (day 7) on the same t_{max}, or,
- One or more episodes of treatment emergent severe hypoglycaemia (see Appendix 7 for definition) have occurred from initiation of treatment (day 1) to end of treatment (day 7) on the same t_{max}

For each subject and for each treatment period, the time in low interstitial glucose (percentage) and number of treatment emergent severe hypoglycaemia episodes as per the above evaluation must be recorded in the CRF.

Escalation decision

If any of the above specified events occur in two or more subjects on the same t_{max} setting within a cohort, continuation to the next cohort with a lower t_{max} setting will not occur. Concretely, continuation to the next cohort with a lower t_{max} setting will not occur in the following scenarios:

- Time in low interstitial glucose (defined as below 54 mg/dL (3.0 mmol/L)) is higher than 2% of the total time from initiation of treatment (day 1) to end of treatment (day 7) on the same t_{max} in two or more subjects,

- One or more episodes of treatment emergent severe hypoglycaemia (see Appendix 7 for definition) have occurred from initiation of treatment (day 1) to end of treatment (day 7) on the same t_{max} in each of two or more subjects,

- Time in low interstitial glucose (defined as below 54 mg/dL (3.0 mmol/L)) higher than 2% of the total time from initiation of treatment (day 1) to end of treatment (day 7) on the same t_{max} in one or more subjects and one or more episodes of treatment emergent severe hypoglycaemia (see Appendix 7 for definition) have occurred from initiation of treatment (day 1) to end of treatment (day 7) on the same t_{max} in one or more subjects.

The escalation decision at the end of the cohort must be documented by the PI. If the escalation decision is to not open the next cohort, then the subjects who are in screening will be registered as withdrawn and an end-of-trial form must be completed.

8.1.2 Temporary discontinuation of trial treatment

During the temporary discontinuation of trial treatment, subject should be treated as per PI's discretion and the Fiasp® pen included in the back-up kit may be used. In a scenario where the iLet™ is replaced or restarted due to any technical reasons, subject will not be required to have an "in-patient" period again.

8.1.3 Rescue criteria

The criteria for the use of rescue medication should be as per investigator's discretion. Please see section 7.7.1 for the description of rescue medication.

8.2 Withdrawal from the trial

Final drug accountability must be performed even if the subject is not able to come to the trial site.

If a subject withdraws from the trial, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the medical record.

If the subject withdraws consent, Novo Nordisk may retain and continue to use any data collected before such a withdrawal of consent.

Although a subject is not obliged to give his/her reason(s) for withdrawing, 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 withdrawal must be specified in the end of trial form in the CRF.

8.2.1 Replacement of subjects

Subjects who discontinue trial treatment or withdraw from trial will not be replaced.

8.3 Lost to follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the trial site.

The following actions must be taken if a subject fails to return to the trial site for a required visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the trial.
- Before a subject is deemed lost to follow-up, the investigator must make every effort to regain contact with the subject (where possible, at least three telephone calls and, if

necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's source document.

- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the trial with a primary reason of lost to 'follow-up'.

9 Trial assessments and procedures

- Trial procedures and their timing are summarised in the flowchart, see section 2.
- Informed consent must be obtained before any trial related activity, see Appendix 3.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria.
- The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reason for screen failure, as applicable.
- At screening, subjects will be provided with a card stating that they are participating in a trial and giving contact details of relevant trial site staff.
- Adherence to the trial design requirements, including those specified in the flowchart, is essential and required for trial conduct.
- Review of completed diaries must be documented either on the documents or in the subject's source documents. If clarification of entries or discrepancies in the diary is needed, the subject must be questioned and a conclusion made in the subject's source documents. Care must be taken not to bias the subject.
- Repeat samples may be taken for technical issues and unscheduled samples or assessments may be taken for safety reasons. Please refer to Appendix 2 for further details on laboratory samples.

9.1 Efficacy assessments

The endpoints and derivations calculated based on the interstitial glucose profiles will be assessed using the data collected on the iLet™, see section 9.12.

9.1.1 Clinical efficacy laboratory assessments

There are no laboratory assessments related to clinical efficacy.

9.2 Adverse events

The definitions of AEs and SAEs can be found in Appendix 4.

The investigator is responsible for detecting, documenting, recording and following up on events that meet the definition of an AE or SAE.

9.2.1 Time period and frequency for collecting AE and SAE information

All AEs will be collected from the first trial-related activity after obtaining informed consent and until the follow up visit, at the time points specified in the flowchart.

All SAEs will be recorded and reported to Novo Nordisk or designee within 24 hours, as indicated in Appendix 4. The investigator must submit any updated SAE data to Novo Nordisk within 24 hours of it being available.

Investigator is not obligated to actively seek for AE or SAE in former trial subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discontinued from/completed the trial, and the investigator considers the event to be possibly/probably related to the investigational trial product or trial participation, the investigator must promptly notify Novo Nordisk.

The method of recording, evaluating and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

In order for Novo Nordisk to perform a complete investigation of reported SAEs, Novo Nordisk might ask the investigator to complete a technical complaint form. For reporting of technical complaints, see Appendix 6 .

Timelines for reporting of AEs are listed in Figure 9–1.

Some AEs require additional data collection via a specific event form. This includes medication errors observed during the trial. The relevant specific events are listed in Table 9–1 and the reporting timelines in Figure 9–1.

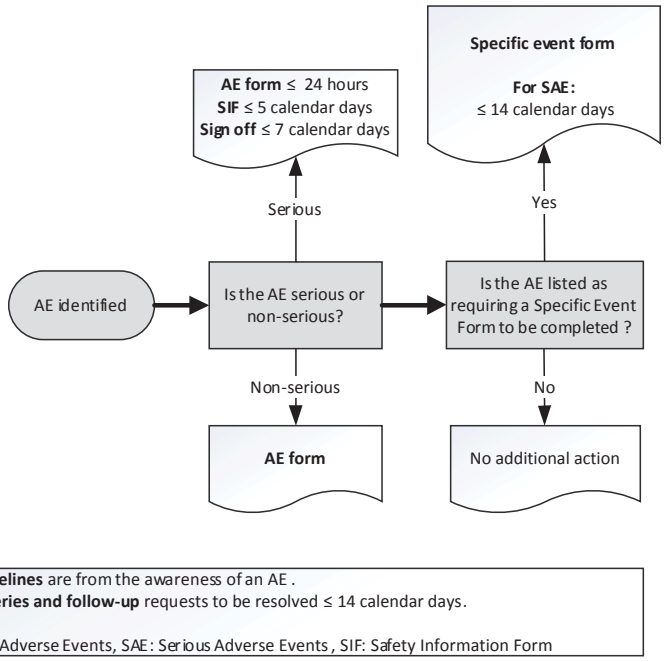


Figure 9–1 Decision tree for determining the event type and the respective forms to complete with associated timelines

Table 9–1 AEs requiring additional data collection (via specific event form)

Event type	AE requiring additional event form
Hypoglycaemic episode[a]	X
Infusion site reaction[b]	X
Medication error[c]	X

[a] Non-serious hypoglycaemic episode should only be reported on the hypoglycaemic episode form. Hypoglycaemic episode qualifying as a SAE should be reported on the AE form, SIF and Hypoglycaemic episode form. Refer to Section 9.2.6 and Appendix 4 for reporting details
[b]Refer to Section 9.4.3 and Appendix 4 for reporting details
[c]Refer to Appendix 4for reporting details

9.2.2 Method of detecting AEs and SAEs

Care should be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about events.

9.2.3 Follow-up on AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, or if the event is otherwise explained (e.g. chronic condition) or the subject is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

9.2.4 Regulatory reporting requirements for SAEs

Prompt notification by the investigator to Novo Nordisk of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a trial product under clinical investigation are met.

Novo Nordisk has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a trial product under clinical investigation. Novo Nordisk will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institution review board (IRB), independent ethics committee (IEC), and investigators.

Investigator safety reports must be prepared for Suspected Unexpected Serious Adverse Reaction (SUSARs) according to local regulatory requirements and Novo Nordisk policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g. summary or listing of SAEs), from Novo Nordisk will review and then file it along with the investigator's brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.5 Cardiovascular and death events

Cardiovascular and death events will be handled and reported according to AE/SAEs description in Section 9.2.1.

9.2.6 Disease-related events and/or disease-related outcomes not qualifying as an AE or SAE

The following Disease-Related Event (DRE) is common in subjects with T1DM and can be serious/life threatening:

- Hypoglycaemic episodes

Definitions, classification and reporting requirements are described in Appendix 7.

Hypoglycaemia

Non-serious hypoglycaemia must be reported on a hypoglycaemic episode form.

If the hypoglycaemic episode fulfils the criteria for an SAE then in addition to the above, an AE form and a safety information form must also be filled in. One AE form and safety information form can cover several hypoglycaemic episode forms, if the subject has not recovered between the episodes.

9.2.7 Pregnancies and associated adverse events

Details of pregnancies in female subjects after the first exposure to trial product at visit 2 and until pregnancy's outcome and the new born infant is one month of age.

If a pregnancy is reported in female subjects, the investigator should inform Novo Nordisk within 14 calendar days of learning of the pregnancy and should follow the procedures outlined in Figure 5–2 and Appendix 5.

Pregnancy outcome should be documented in the subject's medical record. Abnormal pregnancy outcome (e.g. spontaneous abortion, foetal death, stillbirth, congenital anomalies and ectopic pregnancy) is considered an SAE.

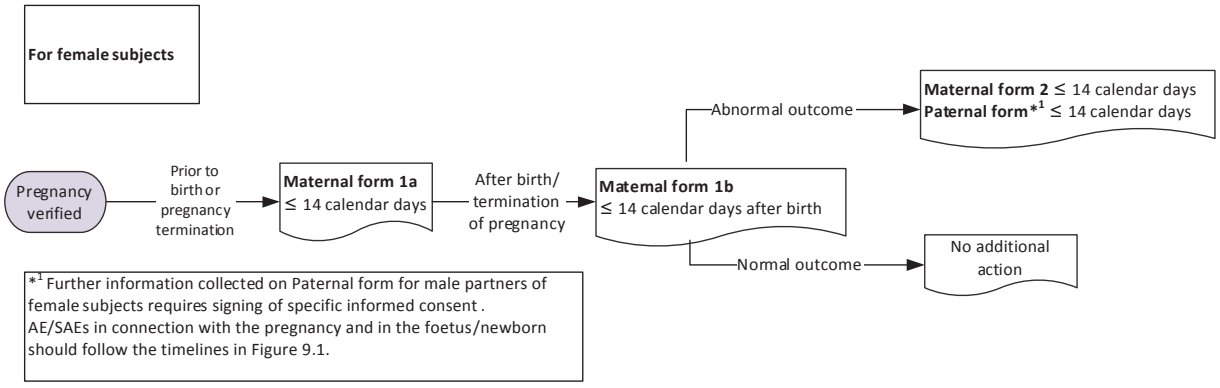


Figure 9–2 Decision tree for determining the forms to complete with associated timelines for pregnancy.

9.2.8 Medical device incidents (including malfunctions)

Medical devices are provided for use in this trial for the administration of fast-acting insulin aspart, blood glucose measurement and continuous glucose measurement. In order to fulfil regulatory reporting obligations, the investigator is responsible for the detection and documentation of events meeting the definition of medical device incident that occur during the trial with such medical devices.

Medical device incidents are considered a subset of technical complaints. The definition and reporting process can be found in section 9.2.9 ,Appendix 4 and Appendix 6.

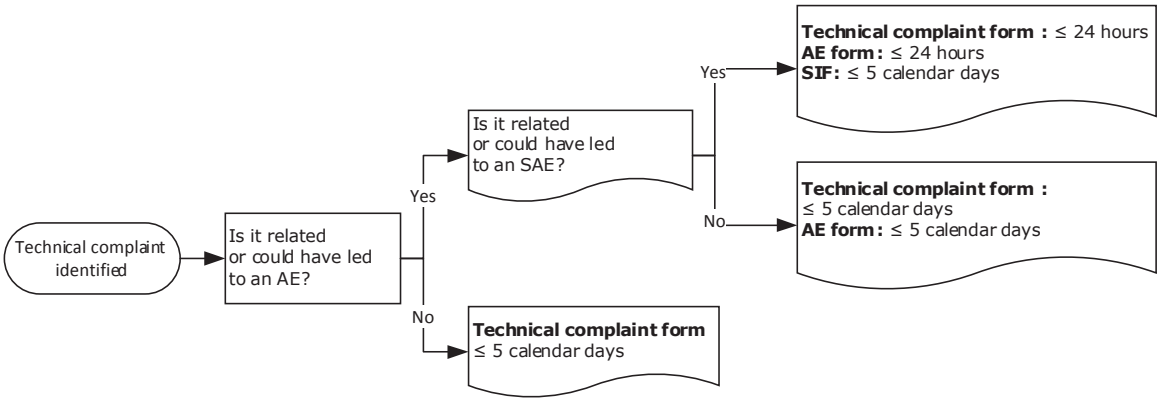
9.2.9 Technical complaints

The investigator must assess whether a technical complaint is related to an AE.

For the iLet™ the investigator must assess if the technical complaint could have led to SAE.

The definitions and reporting process for technical complaints can be found in Appendix 6.

Timelines for reporting technical complaints are listed in Figure 9–3.



AE: Adverse Event, SAE: Serious Adverse Event, SIF: Safety Information Form

Figure 9–3 Decision tree for determining the forms to complete with associated timelines for technical complaints.

9.3 Treatment of overdose

During treatment with insulin delivered by the iLet™, there is a risk of hypoglycaemia (see section 3.3). Symptoms of hypoglycaemia may occur suddenly and may include cold sweat, nervousness or tremor, anxious feelings, unusual tiredness, confusion, difficulty in concentration, excessive hunger, temporary vision changes, headache, nausea and palpitation. Prolonged or severe hypoglycaemia can lead to a loss of self-control, seizures, and/or unconsciousness and, in extreme cases, death.

Hypoglycaemic episodes should be treated according to local standard practice. Mild to moderate symptoms may be treated by ingestion of carbohydrate (for example, juice). Severe hypoglycaemia resulting in the loss of consciousness may be treated with dextrose, glucagon or parenteral glucose.

In the event of an overdose, the investigator should closely monitor the subject for overdose-related AE/SAE and laboratory abnormalities.

For more information on overdose, consult the current version of the fast-acting insulin aspart investigator's brochure and the iLet™'s System Risk Analysis document.

9.4 Safety assessments

Planned time points for all safety assessments are provided in the flowchart, see section 2.

A **concomitant illness** is any illness that is present at the start of the trial *(i.e. at the first visit)* or found as a result of a screening procedure or other trial procedures performed before exposure to trial product. ***Medical history*** *is a medical event that the subject has experienced in the past.*

Only relevant concomitant illness and medical history as judged by the investigator should be reported. Diabetes history and related complications should be reported in the Medical history/Concomitant Illness form. The information collected for concomitant illness and medical history should include diagnosis, date of onset and date of resolution or continuation, as applicable.

In case of an abnormal and clinically significant finding, the investigator must record the finding on the Medical History/Concomitant Illness form if it is present at screening. Any new finding fulfilling the AE definition (see Appendix 4) during the trial and any clinically significant worsening from baseline (Visit 2) must be reported as an AE (see Section 9.2).

9.4.1 Physical examinations

A physical examination will include assessments of following:

- Head, Ears, Eyes, Nose, Throat and Neck
- Cardiovascular System
- Respiratory System
- Gastrointestinal system including mouth
- Musculoskeletal system
- Central and Peripheral Nervous system
- Skin
- General appearance
- Abdomen

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Body measurements (e.g. height and weight) will also be measured and recorded as specified in the flowchart.

- Body weight (BW) should be measured in kilogram (kg) or pounds (lb) without coat and shoes wearing only light clothing. BW measured at visit 1 will be recorded to one decimal in the CRF. BW measured at visit 2 and visit 3 for the initialisation of iLet™ will be recorded directly on the iLet™

- Height should be assessed without shoes. Height is measured in inches or centimetres at visit 1 and recorded to the nearest whole number in the CRF
- Investigator should calculate the BMI using the BW (measured at visit 1) and the height information and record it in CRF.

9.4.2 Vital signs

- Pulse rate, as well as diastolic and systolic blood pressure will be assessed.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions (e.g. television, cell phones).
- Blood pressure at screening (visit 1) will consist of 3 diastolic and systolic blood pressure measurements with intervals of at least 1 minute. All three readings must be entered in the CRF and the average of the 3 blood pressure readings will be recorded on the CRF.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

9.4.3 Infusion site reaction

The investigator should evaluate the skin for any local skin irritation or skin infection at every visit to the trial site. Any abnormal clinically significant findings should be recorded as an infusion site reaction in the CRF. If the 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 administration must be recorded as an AE and on an infusion site reaction form in the CRF throughout the trial from randomisation (Visit 2) to end of treatment visit (visit 4). Please refer to section 9.2.1 for the reporting timelines and Appendix 4 for the information on data to be collected.

The investigator should evaluate whether further actions are needed (e.g. extra visits, discontinuation of trial product, dermatologist consultation).

9.4.4 Clinical safety laboratory assessments

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the local laboratory procedures and manual and the flowchart in Section 2.

9.5 Other assessments

9.5.1 Change of infusion set

Infusion sets will be dispensed at site visits indicated in the flowchart in section 2.

The subjects should be instructed to routinely change infusion set in intervals not exceeding 2 days. Fast-acting insulin aspart PumpCart® should also be replaced with every change of infusion set. 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 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 at the site (visit 2 and visit 3) under the supervision of investigator to ensure that the subject is trained in changing the infusion set.

Infusion sets must be replaced if any change in the insulin solution or occlusion is perceived by the subject, e.g. because of an iLet™ alarm indicating an occlusion or other observations pointing towards obstruction of the insulin flow. Infusion set changes can be considered as a 'non-routine change' or 'routine change'.

Non-routine change

An infusion set or reservoir change that is due to any problem with the pump, the infusion set or glucose values is defined as a non-routine change.

Routine change

A routine change is defined as any change of infusion set and reservoir not fulfilling the criteria for a non-routine change. In addition to this, the following will be considered as routine change:

- Infusion set insertion at the site during visit 2
- Infusion set change at site during visit 3 unless an issue fulfilling the definition for a non-routine change is detected.

Collection of infusion set change information

All infusion set changes from Visit 2 to Visit 4 will be collected in the subjects' diary. Investigator should ensure that the instructions for change are being followed by reviewing the change of infusion set information in the subject's diary. For all infusion set and PumpCart® changes the subject must record the following in the diary:

- The date and time of insertion of infusion set and PumpCart®
- The date and time of removal of infusion set and PumpCart®
- Was the infusion set and PumpCart® change considered a routine change (Yes/No)?
    - If yes, and the infusion set is changed prior to the 2 days, the subject should enter the reason in the paper diary.

- If no, the subject must enter the reason in the paper diary.

9.5.2 HbA_{1c}

HbA_{1c} will be measured at screening to assess inclusion criterion 9, see section 2.

9.6 Pharmacokinetics

Not applicable for this trial.

9.7 Pharmacodynamics

Not applicable for this trial.

9.8 Genetics

Not applicable for this trial.

9.9 Biomarkers

Not applicable for this trial.

9.10 Continuous glucose measurement

The CGM sensor has an in-use period of 7 days. The sensor will automatically stop recording data exactly 7 days after sensor insertion and start. This should be taken into account when scheduling the subjects' visits.

It is of utmost importance that the CGM sensor is calibrated regularly to ensure accuracy and for continuous reception of sensor glucose data. CGM sensor should be calibrated twice daily as per the manufacturer's instructions. Investigator or delegated staff should review the subject's diary to ensure that the CGM sensor is calibrated as required otherwise the subject should be re-trained.

Subjects should be instructed to avoid medications with acetaminophen/paracetamol while wearing the CGM sensor. These medications may affect the performance and readings of the CGM sensor (e.g. false high CGM readings) [7-9]. Also, subject should be instructed to remove the Dexcom G5 sensor, transmitter, and receiver before x-ray, Magnetic Resonance Imaging (MRI), Computed Tomography (CT) scan, or high-frequency electrical heat (diathermy)[9].

9.11 Self-measured plasma glucose

Subjects will be provided with a BG meter including auxiliaries as well as instructions for use. The subjects will be instructed in how to use the device and the instruction should be repeated, if needed

The BG meters use test strips calibrated to plasma values. Therefore, all measurements performed with capillary blood are automatically calibrated to plasma equivalent glucose values, which will be shown on the display.

The BG meter provided by Novo Nordisk should be used for the measurements required in the protocol. SMPGs must be performed to calibrate the CGM sensor (section 9.10) and in the event of hypoglycaemic episode (Appendix 7) and should be reported in the diary, see section 9.14.

All SMPGs values must be recorded in the paper diary. In addition to paper diary, SMPGs performed for the calibration of the CGM sensor must also be recorded on the StudyPhone with CGM app. The record of each SMPG value on paper diary should include date, time and value. All data from the diary must be transcribed into the CRF during or following the contact.

9.12 iLet™ settings

The glucose target for the iLet™ will be set to 120 mg/dL (6.6 mmol/L). Subjects must be instructed not to change any settings related to BW and glucose target on the iLet™. Temporary targets are not allowed.

Initialisation of iLet™

The iLet™ should be initialised by entering the subject's current BW at visit 2 and visit 3. See section 9.4.1 for reporting of BW.

The date and time when the site staff starts the iLet™ at visit 2 and visit 3 will be considered as the time-point for initiation of treatment. This start date and time must be recorded in the CRF.

Stopping of iLet™

The date and time when the site staff stops the iLet™ at visit 3 and visit 4 will be considered as time-point for end of treatment. These stop date and time must be recorded in the CRF.

t_{max} setting

The t_{max} setting in the iLet™ should be set by the site staff at visit 2 and visit 3 as per the subject's randomisation sequence.

Meal announcements

Meal announcements can be entered via a user interface that runs on the iLet™. The user interface allows optional meal announcements, designated as "start of the day", "middle of the day", or "end of the day" or "sleeping", of size "tiny", "small", "typical for me" or "large". Subjects will be recommended to use this feature immediately before eating the main meals of the day, but not snacks.

Parameters transferred from iLet™

Following parameters will be transferred from the iLet™ to the NN database:

- Date and time of records from the iLet™ parameters
- Body weight (Visit 2 and Visit 3)

- t_{max} setting
- Interstitial glucose from CGM
- Plasma glucose measurements entered in iLet™
- Infusion set change announcement
- Target glucose value
- Target glucose settings
- Insulin delivery status (delivery channel available)
- Calculated insulin dose
- Delivered insulin dose (combined basal, bolus and meal insulin dose component)
- Basal insulin dose component
- Bolus insulin dose component
- Meal announcement (meal size and time point of meal)
- Calculated meal insulin dose component
- Delivered meal insulin dose component
- Notifications

9.13 Back-up Kits

The investigator must instruct the subjects to always to carry a back-up kit containing medication and spare supplies to be used in case of pump failure. The subjects must be trained in how to use the back-up kit and what to bring when leaving home. The back-up kit consists of the following:

- Participation ID card with relevant phone numbers and contact details
- Fiasp® pen-injector
- Needles (to be used with Fiasp® pen-injector)
- Extra infusion set
- Fast acting glucose preparation (e.g. tablets or powder)
- Glucagon for injection (supplied by Novo Nordisk)
- Extra battery for the iLet™
- CGM sensor (including Sensor Applicator)
- Urine sticks for ketone monitoring

Subjects will also be encouraged to always carry the BG - meter and test strips.

9.14 Diary

Diaries will be used in this trial and handed out to the subjects as specified in section 2. At end of treatment visit (visit 4) the subjects have to return their last diaries. The investigator must carefully instruct the subjects in how to fill out the diary. The subjects should bring their diary to each site visit. At each site visit, the investigator or delegated site personnel must review the diary together with the subject to ensure consistency/compliance. The information in the diary must be transferred

into the CRF by the trial personnel. The review of diaries must be documented either on the front page of the diary and/or in the subject's medical record. If clarification of entries is needed or discrepancies in the diary are found, the subject must be questioned and a conclusion must be made in the subject's medical record. Care must be taken not to bias the subject.

The following data will be captured by the subject in the diary:

- Hypoglycaemic episodes
- Change of infusion set
- Calibration of CGM sensor

It is the investigator's responsibility to ensure that relevant information from the diary and the medical record is transcribed into the CRF.

9.15 Discharge criteria

The discharge of subjects from the "in-patient" period (during which subjects will be at a designated place such as a hotel) is at the discretion of the PI. In order to make the evaluation whether it is safe for the subjects to continue to the "out-patient" period of the trial, the PI may rely on data that include but are not limited to: hypoglycaemic episodes, the number of times carbohydrates are taken by subjects to prevent or treat hypoglycaemic episodes and time in low interstitial glucose (defined as < 54 mg/dL; 3 mmol/L).

The date and time of discharge (end of "in-patient" period) must be recorded in CRF.

9.16 Remote Monitoring

Real-time remote telemetric monitoring for hypoglycaemia or persistent hyperglycaemia will be performed by the site staff 24 hours a day, using a remote-monitoring system provided by Beta Bionics. There will be at least one of the following – Medical Doctor, Nurse Practitioner or Physician's Assistant and at least one additional site staff member on call in addition to the site staff member monitoring for alarms. A site staff member will make contact with the subjects or the designated contact as necessary and help them troubleshoot any issues that may arise.

When an alert comes in, a site staff member will call the subject. If staff remains unable to contact the subject, they will call the designated contact. Depending on the circumstances, they may call locations the subject is known to frequent (e.g. usual work location) or they may be dispatched to make contact with the subject (if the location is nearby and reaching the location would be no risk to the safety of the staff member or violate employment rules).

An alert will be generated if remote monitoring for a subject goes offline. Site staff will call the subject every 2 hours to check on safety and device function until remote monitoring is restored. If there are no indications of device malfunction as the cause for lost connectivity, the glucose level is

in safe range, and a subject chooses to remain in an area with poor network coverage, site staff will instruct the subject to check the iLet™ display or the CGM app on the study phone at least every 20 minutes for alert icons and to be aware that we are unable to monitor for severe lows or highs at this time.

The date, time and the reason for site staff contact with subjects should be recorded in the CRF.

9.16.1 Remote Monitoring for Hypoglycaemia

The remote monitoring system will generate an alarm if the interstitial glucose < 50 mg/dL (2.8 mmol/L) for 15 minutes. Subjects will also be alerted as the Study Phone with CGM app will generate an alarm if the interstitial glucose is < 55 mg/dl (3.05 mmol/L) and a reminder alarm in 15 minutes if it is still < 55 mg/dL (3.05 mmol/L). iLet™ will also alert the subjects if the interstitial glucose is < 50 mg/dL (2.8 mmol/L).

Site staff will verify that the subjects, or their designated contacts, are aware of the hypoglycaemia and are taking action to treat it. Subjects will be reminded of the procedures to follow in case of hypoglycaemia and the site staff will ensure they understand and will follow the procedures. Subjects will be encouraged to follow up with any questions or concerns. All contact with the subjects in response to hypoglycaemia alarms will be documented in the subjects' medical records.

In the case of a low threshold alarm with no response from the subjects and no success in locating them, the site PI will be immediately informed. If remote monitoring shows ongoing hypoglycaemia, a decision may be made to dispatch emergency medical services to the locations the subject is known to frequent.

9.16.2 Remote Monitoring for Hyperglycaemia

The remote monitoring system will generate an alarm if the interstitial glucose is > 300 mg/dl (16.6 mmol/L) for 90 minutes. Subjects will also be alerted as the StudyPhone with CGM app will generate an alarm if the interstitial glucose is > 300 mg/dl (16.6 mmol/L) and a reminder alarm in 1 hour if it is still > 300 mg/dl (16.6 mmol/L).

Subjects will be reminded to contact the site immediately in case they have been hyperglycaemic for ≥ 2 hours. Site staff will recommend the subjects to measure BG and ketones every hour until the BG is < 180 mg/dl (10 mmol/L) and the ketones measurement is negative. Subjects will be encouraged to follow up with any questions or concerns. All contact with the subjects in response to a hyperglycaemia alarms will be documented in the subjects' medical records.

10 Statistical considerations

10.1 Sample size determination

The primary objective of the trial is to investigate the safety of selected t_{max} settings in the insulin-only configuration of the iLet™ bionic pancreas using fast-acting insulin aspart in adults with T1DM in a short-term, outpatient clinical trial for the endpoint percentage of time in low interstitial glucose (< 54 mg/dL; 3 mmol/L). No formal sample size calculations are made for the safety endpoints. Eight (8) subjects per cohort (24 subjects in total) have been deemed adequate to give an assessment of the primary objective. In case of subjects discontinuing treatment or withdrawing from trial, no replacement will occur.

10.2 Definition of analysis sets

The following analysis sets are defined in accordance with the ICH-E9 guideline[10]:

- Full analysis set (FAS): includes all randomised subjects receiving treatment. In exceptional cases subjects from the FAS may be excluded. In such cases the exclusion will be justified and documented. Subjects in the FAS will contribute to the evaluation 'as treated'.
- Safety analysis set: includes all subjects receiving treatment. Subjects in the safety analysis set will contribute to the evaluation 'as treated'.

One observation period, "on-treatment", is defined.

- On-treatment: the observation period from time of initiation of treatment to end of treatment. The on-treatment observation period will be defined separately for each treatment period.

10.3 Statistical analyses

If necessary, a statistical analysis plan (SAP) may be written in addition to the protocol, including a more technical and detailed elaboration of the statistical analyses. The SAP will be finalised before database lock.

Endpoints and derivations based on the interstitial glucose profiles will be summarised and analysed using the FAS, unless otherwise stated. The other endpoints will be summarised using the safety analysis set and analysed using the FAS.

10.3.1 Primary endpoint

The primary objective of the trial is to investigate the safety of selected t_{max} settings in the insulin-only configuration of the iLet™ bionic pancreas using fast-acting insulin aspart in adults with T1DM in a short-term, outpatient clinical trial. The primary endpoint to address this objective is:

- Time in low interstitial glucose (defined as below 54 mg/dL [3 mmol/L]) from initiation of treatment (day 1) to end of treatment (day 7) (percentage)

This will be derived as the percentage of available interstitial glucose values below 54 mg/dL (3 mmol/L)

The assessment of the primary endpoint will be based on descriptive summaries presenting mean, median, minimum and maximum values by cohort and treatment.

Supplementary analysis for the primary analysis

The default t_{max} setting (t_{65}) will be compared to each of the non-default t_{max} settings (t_{50}, t_{40} and t_{30}) separately by cohort for time spent in low interstitial glucose (defined as below 54 mg/dL [3mmol/L]) using a linear mixed effect model with treatment and period as fixed effects and subject as random effect. This is done to investigate the treatment differences from a within-subject perspective.

10.3.2 Secondary endpoints

10.3.2.1 Supportive secondary endpoints

Time in interstitial glucose range defined as 70-180 mg/dL (3.9-10 mmol/L) from initiation of treatment (day 1) to end of treatment (day 7) (percentages)

Time in interstitial glucose range defined as 70-180 mg/dL (3.9-10 mmol/L) will be derived as the percentage of available interstitial glucose values above or equal to 70 mg/dL (3.9 mmol/L) and below or equal to 180 mg/dL (10 mmol/L).

It will be presented using descriptive statistics made by cohort and treatment, and analysed using a model similar to the supplementary analysis for the primary analysis.

Mean interstitial glucose level from initiation of treatment (day 1) to end of treatment (day 7) (mg/dL)

The mean interstitial glucose level will be derived as the average of the available interstitial glucose values.

The mean interstitial glucose level will be presented using descriptive statistics made by cohort and treatment, and analysed using a model similar to the supplementary analysis for the primary analysis.

Number of treatment-emergent severe hypoglycaemic episodes from initiation of treatment (day 1) to end of treatment (day 7) (count)

Severe hypoglycaemic episodes are classified according to the ADA definition as described in Appendix 7.Treatment emergent severe hypoglycaemic episodes will be presented in terms of the

number of subjects with at least one episode (N), the percentage of subjects with at least one episode (%), the number of episodes (E) and the episode rate per 100 years of exposure (R) made by cohort and treatment.

Number of treatment emergent hypoglycaemic episodes classified both according to the ADA definition and Novo Nordisk classification from initiation of treatment (day 1) to end of treatment (day 7) (count)

Hypoglycaemic episodes classified both according to the ADA definition and Novo Nordisk classification as described in Appendix 7. Treatment emergent hypoglycaemic episodes will be presented in terms of the number of subjects with at least one episode (N), the percentage of subjects with at least one episode (%), the number of episodes (E) and the episode rate per 100 years of exposure (R) made by cohort and treatment. Separate summaries are made by severity considering all episodes, daytime and nocturnal episodes using Novo Nordisk and ADA classified episodes.

Number of self-manageable (able to self-treat) treatment-emergent hypoglycaemic episodes that require oral carbohydrate intervention per day from initiation of treatment (day 1) to end of treatment (day 7) (count)

Treatment emergent self-manageable (able to self-treat) hypoglycaemic episodes that require oral carbohydrate intervention per day will be calculated as the sum of all treatment-emergent hypoglycaemic episodes where the subject is able to self-treat and that require oral carbohydrate intervention divided by the actual duration of the treatment period in days. It will be presented using descriptive statistics made by cohort and treatment.

Number of treatment-emergent adverse events from initiation of treatment (day 1) to end of treatment (day 7) (count)

Adverse events will coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be presented based on system organ class and preferred terms.

Treatment-emergent: adverse events will be defined as treatment-emergent, if the onset of the event occurs in the on-treatment period

Treatment-emergent adverse events will be presented in terms of the number of subjects with at least one event (N), the percentage of subjects with at least one event (%), the number of events (E) and the event rate per 100 years of exposure (R) made by cohort and treatment. These summaries are done by seriousness, severity, relation to trial product, adverse events leading to discontinuation of trial treatment and outcome.

Furthermore, summary tables based on system organ class and preferred terms are made for:

- All treatment-emergent adverse events
- Serious treatment-emergent adverse events

- Possibly and probably related treatment-emergent adverse events
- Severe treatment-emergent adverse events

All adverse events will be listed with information on when it occurred.

Number of treatment-emergent infusion site reactions from initiation of treatment (day 1) to end of treatment (day 7) (count)

Treatment-emergent infusion site reactions will be summarised by cohort and treatment.

Total insulin dose (U/kg) per day from initiation of treatment (day 1) to end of treatment (day 7) (U/Kg/day)

Total daily insulin dose will be calculated as the sum of all insulin doses delivered by the iLet™ divided by the actual duration of the treatment period in days. It will be presented using descriptive statistics made by cohort and treatment.

10.3.3 Exploratory endpoints

Mean interstitial glucose increment from time of announcement of a "typical meal" to 2 hours after announcement from initiation of treatment (day 1) to end of treatment (day 7) (mg/dL)

The mean interstitial glucose increment from time of announcement of a "typical meal" to 2 hours after announcement will be derived as an average over all available interstitial glucose increments for each subject.

The interstitial glucose increment from time of announcement of a "typical meal" to 2 hours after announcement is calculated as the average of the available interstitial glucose from time of announcement of a "typical meal" and during 2 hours after announcement and subtracting an average of the interstitial glucose immediately before the announcement.

The mean interstitial glucose increment from time of announcement of a "typical meal" to 2 hours after announcement will be presented using descriptive statistics made by cohort and treatment.

10.3.4 Other analyses

10.3.4.1 Derivations based on the interstitial glucose profile

The definition and calculation of derivations based on the interstitial glucose profile are described in Table 10–1.

Table 10–1 Definition and calculation of derivations based on the interstitial glucose profile

Derivation	Calculation
Time in low interstitial glucose (defined as	Percentage of available interstitial glucose

Derivation	Calculation
below 60 and 70 mg/dL [3.3 and 3.9 mmol/L]) from initiation of treatment (day 1) to end of treatment (day 7) (percentage)	values below 60 and 70 mg/dL (3.3 and 3.9 mmol/L) respectively.
Time in high interstitial glucose (defined as above 180, 250 and 300 mg/dL [10.0, 13.9 and 16.7 mmol/L]) from initiation of treatment (day 1) to end of treatment (day 7) (percentage)	Percentage of available interstitial glucose values above 180, 250 and 300 mg/dL (10.0, 13.9 and 16.7 mmol/L) respectively.
Number of episodes with low interstitial glucose (defined as below 54, 60 and 70 mg/dL [3.0, 3.3 and 3.9 mmol/L]) from initiation of treatment (day 1) to end of treatment (day 7) (count)	Count of all periods spend with interstitial glucose below 54, 60 and 70 mg/dL (3.0, 3.3 and 3.9 mmol/L) respectively.
Number of episodes with high interstitial glucose (defined as above 180, 250 and 300 mg/dL [10.0, 13.9 and 16.7 mmol/L]) from initiation of treatment (day 1) to end of treatment (day 7) (count)	Count of all periods spend with interstitial glucose above 180, 250 and 300 mg/dL (10.0, 13.9 and 16.7 mmol/L) respectively.
Coefficient of variation in the interstitial glucose profile from initiation of treatment (day 1) to end of treatment (day 7) (percentage)	The coefficient of variation of the available interstitial glucose values.
Time in interstitial glucose range defined as 70-140 mg/dL (3.9-7.8 mmol/L) from initiation of treatment (day 1) to end of treatment (day 7) (percentages)	Percentages of available interstitial glucose values above or equal to 70 mg/dL (3.9 mmol/L) and below or equal to 140 mg/dL (7.8 mmol/L).

The derivations based on the interstitial glucose profile will be presented using descriptive statistics made by cohort and treatment.

10.3.4.2 Derivations based on the 'out-patient' period

To further investigate the safety and glycaemic control of the selected t_{max} settings using fast-acting insulin aspart further derivations will be done similar to the endpoints and derivations above but using data collected during the 'out-patient' period.

10.3.4.3 Escalation decision

For each of the two escalation stopping criteria defined in section 8.1.1 , the number and percentage of subjects fulfilling the criteria will be presented separately by cohort and treatment.

10.4 Pharmacokinetic and/or pharmacodynamic modelling

Not applicable for this trial

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12 Appendices

Appendix 1 Abbreviations and Trademarks

ADA	American Diabetes Association
AE	adverse event
ALT	alanine aminotransferase
App	application
AST	aspartate aminotransferase
BG	blood glucose
BMI	body mass index
CGM	continuous glucose monitoring
CFR	Code of Federal Regulations
CLAE	clinical laboratory adverse event
CRF	case report form
CTR	clinical trial report
CV	coefficient of variation
DCF	data clarification form
DM	diabetes mellitus
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DRE	disease related event
DUN	dispensing unit number
eGFR	estimated glomerular filtration rate
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FDAAA	FDA Amendments Act
Fiasp	fast-acting insulin aspart
FSFV	first subject first visit
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HbA_{1c}	glycated haemoglobin
HDL	high-density lipoproteins
HRT	hormone replacement therapy

ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee
IMD	investigational medical device
IMP	investigational medicinal product
IRB	institutional review board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IWRS	interactive web response system
LAR	legally acceptable representative
LSFT	last subject first treatment
LDL	low-density lipoprotein
LSLV	last subject last visit
MedDRA	Medical Dictionary for Regulatory Activities
MDI	multiple daily injection
MIDF	monitor-initiated discrepancy form
NIMD	non-investigational medical device
NIMP	non-investigational medical product
NYHA	New York Heart Association
PCD	primary completion date
PG	plasma glucose
PI	Principal Investigator
PPG	Prandial plasma glucose
SAE	serious adverse event
SAP	statistical analysis plan
SmPC	Summary of Product Characteristics
SMPG	self-measured plasma glucose
SUSAR	suspected unexpected serious adverse reaction
T1DM	Type-1 diabetes mellitus
TMM	trial materials manual
WOCBP	woman of child bearing potential

Appendix 2 Clinical laboratory tests

As this is a single centre trial, a local laboratory at the site will be used for all laboratory assessments. The tests detailed in will be performed by the local laboratory and the results must be entered into the CRF.

Additional tests may be performed at any time during the trial as determined necessary by the investigator or required by local regulations. And if additional laboratory sampling is needed, e.g. to follow up on AEs, this must be done at a local laboratory.

The laboratory equipment may provide analyses not requested in the protocol but produced automatically in connection with the requested analyses according to specifications in the laboratory standard operating procedures. Such data will not be transferred to the trial database, but abnormal values will be reported to the investigator. The investigator must review all laboratory results for concomitant illnesses and AEs. Laboratory samples will be destroyed after analysis on an ongoing basis.

Table 12–1 Protocol required safety laboratory assessments

Laboratory assessments	Parameters
Glucose metabolism	HbA1c
Haematology	Erythrocytes Haematocrit Haemoglobin Leucocytes Thrombocytes (platelets) Basophils Eosinophils Neutrophils Lymphocytes Monocytes
Biochemistry[1]	Alanine Aminotransferase (ALT) Albumin Alkaline phosphatase Aspartate Aminotransferase (AST) Creatinine Bilirubin
Lipids	Cholesterol High density lipoprotein (HDL) cholesterol Low density lipoprotein (LDL) cholesterol
Pregnancy Testing	Urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)
Other tests	eGFR calculated by the local laboratory based on the creatinine value using the CKD-EPI equation
Notes : [1]Details of required actions for increased liver parameters are given in Appendix 4 (Hy's Law)	

Appendix 3 Trial governance considerations

1) Regulatory and ethical considerations

- This trial will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki[11] and applicable ICH Good Clinical Practice (GCP) Guideline[12] and ISO 14155[13]
  - Applicable laws and regulations
- The protocol, informed consent form, investigator's brochure (as applicable) and other relevant documents (e.g. advertisements), must be submitted to an IRB/IEC and reviewed and approved by the IRB/IEC before the trial is initiated.
- Regulatory authorities will receive the clinical trial application, device related documents, protocol amendments, reports on SAEs, and the clinical trial report according to national requirements.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate safety hazard to trial subjects.
- Before a trial site is allowed to start screening subjects, written notification from Novo Nordisk must be received.
- The investigator will be responsible for:
  - providing written summaries of the status of the trial annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC and/or regulatory authorities
  - notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - providing oversight of the conduct of the trial at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations
  - ensuring submission of the clinical trial report (CTR) synopsis to the IRB/IEC.

2) Financial disclosure

Investigators and sub-investigators will provide Novo Nordisk with sufficient, accurate financial information as requested to allow Novo Nordisk to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the trial and one year after completion of the trial.
For US trial sites: verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest.

3) Informed consent process

- The investigator or his/her representative will explain the nature of the trial to the subject and answer all questions regarding the trial.
- The investigator must ensure the subject ample time to come to a decision whether or not to participate in the trial.
- Subjects must be informed that their participation is voluntary.
- Subjects will be required to sign and date a statement of informed consent that meets the requirements of local regulations, ICH guidelines [12], Declaration of Helsinki[11] and the IRB/IEC or trial site.
- The medical record must include a statement that written informed consent was obtained before any trial related activity and the date when the written consent was obtained. The authorised person obtaining the informed consent must also sign and date the informed consent form before any trial related activity.
- The responsibility of seeking informed consent must remain with the investigator, but the investigator may delegate the task of informing to a medically qualified person, in accordance with local requirements.
- Subjects must be re-consented to the most current version of the informed consent form(s) during their participation in the trial.
- A copy of the informed consent form(s) must be provided to the subject.

4) Information to subjects during trial

The site will be offered a communication package for the subject during the conduct of the trial. The package content is issued by Novo Nordisk. The communication package will contain written information intended for distribution to the subjects. The written information will be translated and adjusted to local requirements and distributed to the subject at the discretion of the investigator. The subject may receive a "welcome to the trial letter" and a "thank you for your participation letter" after completion of the trial. Further the subject may receive other written information during the trial.

All written information to subjects must be sent to IRB/IEC for approval/favourable opinion and to regulatory authorities for approval or notification according to local regulations.

5) Data protection

- Subjects will be assigned a 6-digit unique identifier, a subject number which will remain same throughout the trial. Site will be assigned a 3-digit number and all subject number will start the with the site number as its 1st 3 digits. Any subject records or datasets that are transferred to Novo Nordisk will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject and any biological material obtained from the subject will be identified by subject number, visit number and trial ID. Appropriate measures such as encryption or

leaving out certain identifiers will be enforced to protect the identity of subjects as required by local, regional and national requirements.

- The subject must be informed that his/her personal trial related data will be used by Novo Nordisk in accordance with local data protection law. The disclosure of the data must also be explained to the subject.
- The subject must be informed that his/her medical records may be examined by auditors or other authorised personnel appointed by Novo Nordisk, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

6) Committee structure

Novo Nordisk safety committee

Novo Nordisk will constitute an internal fast-acting insulin aspart safety committee to perform ongoing safety surveillance. The fast-acting insulin aspart safety committee may recommend un-blinding of any data for further analysis, and in this case an independent ad hoc group will be established in order to maintain the blinding of the trial personnel.

7) Publication policy

The information obtained during the conduct of this trial is considered confidential, and may be used by or on behalf of Novo Nordisk for regulatory purposes as well as for the general development of the trial product. All information supplied by Novo Nordisk in connection with this trial shall remain the sole property of Novo Nordisk and is to be considered confidential information.

No confidential information shall be disclosed to others without prior written consent from Novo Nordisk. Such information shall not be used except in the performance of this trial.
The information obtained during this trial may be made available to other investigators who are conducting other clinical trials with the trial product, if deemed necessary by Novo Nordisk. Provided that certain conditions are fulfilled, Novo Nordisk may grant access to information obtained during this trial to researchers who require access for research projects studying the same disease and/or trial product studied in this trial.

Novo Nordisk may publish on its clinical trials website a redacted clinical trial report for this trial.

Communication of results

Novo Nordisk commits to communicate and disclose results of trials regardless of outcome. Disclosure includes publication of a manuscript in a peer-reviewed scientific journal, abstract submission with a poster or oral presentation at a scientific meeting or disclosure by other means.

The results of this trial will be subject to public disclosure on external web sites according to international and national regulations. Novo Nordisk reserves the right to defer the release of data

until specified milestones are reached, for example when the clinical trial report is available. This includes the right not to release the results of interim analyses, because the release of such information may influence the results of the entire trial.

At the end of the trial, one or more scientific publications may be prepared collaboratively by the investigator(s) and Novo Nordisk. Novo Nordisk reserves the right to postpone publication and/or communication for up to 60 days to protect intellectual property.

In all cases the trial results will be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations. In the event of any disagreement on the content of any publication, both the investigators' and Novo Nordisk opinions will be fairly and sufficiently represented in the publication.

Authorship

Novo Nordisk will work with one or more investigator(s) and other experts who have contributed to the trial concept or design, acquisition, analysis or interpretation of data to report the results in one or more publications.

Authorship of publications should be in accordance with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals by the International Committee of Medical Journal Editors[14].

All authors will be provided with the relevant statistical tables, figures, and reports needed to evaluate the planned publication.

Where required by the journal, the investigator from each trial site will be named in an acknowledgement or in the supplementary material, as specified by the journal.

Investigator access to data and review of results

As owner of the trial database, Novo Nordisk has the discretion to determine who will have access to the database. Individual investigators will have their own research subjects' data, and will be provided with the randomisation code after results are available.

8) Dissemination of clinical trial data

Information of the trial will be disclosed at clinicaltrials.gov and novonordisk-trials.com. It will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE)[15], the Food and Drug Administration Amendment Act (FDAAA)[16], European Commission Requirements[17, 18] and other relevant recommendations or regulations. If a subject requests to be included in the trial via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the subject. As a

result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

The Primary Completion Date (PCD) is the last assessment of the primary endpoint, and is for this trial Last Subject First Treatment (LSFT) + 14 days, corresponding to visit 4 of the cohort 3. If the last subject is withdrawn early, the PCD is considered the date when the last subject would have completed visit 4. The PCD determines the deadline for results disclosure at clinicaltrials.gov according to FDAAA.

9) Data quality assurance

Case Report Forms (CRFs)

- Novo Nordisk or designee is responsible for the data management of this trial including quality checking of the data.
- All subject data relating to the trial will be recorded on paper CRFs unless transmitted electronically to Novo Nordisk or designee. The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must ensure that data is recorded in the CRF as soon as possible after the visit.
- If corrections are made by the investigator's delegated staff after the date of the investigator's signature on the affirmation statement, the affirmation statement must be signed and dated again by the investigator.
- Corrections necessary after the CRFs have been removed from the trial site must be documented on a Data Clarification Form (DCF) or a Monitor Initiated Discrepancy Form (MIDF). If the affirmation statement for the subject has not yet been signed, any corrections must be approved by the investigator or her/his delegated staff. If the affirmation statement for the subject has already been signed, the investigator must approve any correction.

Monitoring

- The investigator must permit trial-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents (original documents, data and records). Direct access includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are important to the evaluation of the trial. If the electronic medical record does not have a visible audit trail, the investigator must provide the monitor with signed and dated printouts. In addition the relevant trial site staff should be available for discussions at monitoring visits and between monitoring visits (e.g. by telephone).
- Trial monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are accurate, complete and verifiable from source documents; that the safety and rights of subjects are being protected, to monitor drug accountability and collect completed paper CRF pages, if applicable, and that the trial is

being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements.

- Monitoring will be conducted using a risk based approach including risk assessment, monitoring plans, centralised monitoring (remote assessment of data by Novo Nordisk) and visits to trial sites.
- Monitors will review the subject's medical records and other source data e.g. the diaries, to ensure consistency and/or identify omissions compared to the CRF.

Protocol compliance

Deviations from the protocol should be avoided. If deviations do occur, the investigator must inform the monitor and the implications of the deviation must be reviewed and discussed.

Deviations must be documented and explained in a protocol deviation by stating the reason, date, and the action(s) taken. Some deviations, for which corrections are not possible, can be acknowledged and confirmed via listings from the trial database.

10) Source documents

- All data entered in the CRF must be verifiable in source documentation other than the CRF. The data from the iLet™ is regarded as intermediate data until first permanent storage in supplier database where it is regarded as source.
- If source data is entered directly in a paper CRF, each data entry or clear series of data entries must be signed and dated separately by the trial staff making the entry.
- The original of the completed diaries must not be removed from the trial site, unless they form part of the CRF and a copy is kept at the site.
- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the trial site.
- Data reported on the paper CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records. Also, current medical records must be available.
- It must be possible to verify subject's medical history in source documents such as subject's medical record.
- The investigator must document any attempt to obtain external medical information by noting the date(s) when information was requested and who was contacted.
- Definition of what constitutes source data can be found in a source document agreement at the trial site. There will only be one source document defined at any time for any data element.

11) Retention of clinical trial documentation

- Records and documents, including signed informed consent forms, pertaining to the conduct of this trial must be retained by the investigator for 15 years after end of trial unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Novo Nordisk. No records may be transferred to another location or party without written notification to Novo Nordisk.

- The investigator must agree to archive the documentation (this includes both electronic and paper-based records) pertaining to the trial in an archive after completion or discontinuation of the trial if not otherwise notified. The investigator should not destroy any documents without prior permission from Novo Nordisk. If the investigator cannot archive the documents at the trial site, Novo Nordisk can refer the investigator to an independent archive provider that has a system in place to allow only the investigator to access the files. The investigator must be able to access his/her trial documents without involving Novo Nordisk in any way. A copy of all data will be stored by Novo Nordisk.

- Subject's medical records must be kept for the maximum period permitted by the hospital, institution or private practice

12) Trial and site closure

Novo Nordisk reserves the right to close the trial site or terminate the trial at any time for any reason at the sole discretion of Novo Nordisk. If the trial is suspended or terminated, the investigator must inform the subjects promptly and ensure appropriate therapy and follow-up. The investigator and/or Novo Nordisk must also promptly inform the regulatory authorities and IRBs/IECs and provide a detailed written explanation.

Trial sites will be closed upon trial completion. A trial site is considered closed when all required documents and trial supplies have been collected and a trial site closure visit has been performed.

The investigator may initiate trial site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a trial site by Novo Nordisk or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, Novo Nordisk procedures or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further trial product development.

In addition to above, the trial may close earlier if the stopping criteria for any cohort have been met, see section 8.1.1

13) Responsibilities

The investigator is accountable for the conduct of the trial at his/her site and must ensure adequate supervision of the conduct of the trial at the trial site. If any tasks are delegated, the investigator must maintain a log of appropriately qualified persons to whom he/she has delegated specified trial-related duties. The investigator must ensure that there is adequate and documented 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, must be responsible for all trial-related medical decisions.

The investigator is responsible for filing essential documents (i.e. those documents which individually and collectively permit evaluation of the conduct of a trial and the quality o f the data produced) in the investigator trial master file. The documents, including the subject identification code list must be kept in a secure locked facility so that no unauthorized persons can get access to the data.

The investigator will take all necessary technical and organisational safety measures to prevent accidental or wrongful destruction, loss or deterioration of data. The investigator will prevent any unauthorised access to data or any other processing of data against applicable law. The investigator must be able to provide the necessary information or otherwise demonstrate to Novo Nordisk that such technical and organisational safety measures have been taken.

During any period of unavailability, the investigator must delegate responsibility for medical care of subjects to a specific qualified physician who will be readily available to subjects during that time.

If the investigator is no longer able to fulfil the role as investigator (e.g. if he/she moves or retires) a new investigator will be appointed in consultation with Novo Nordisk.
The investigator and other site personnel must have sufficient English skills according to their assigned task(s).

14) Indemnity statement

Novo Nordisk carries product liability for its products, and liability as assumed under the special laws, acts and/or guidelines for conducting clinical trials in any country, unless others have shown negligence.

Novo Nordisk assumes no liability in the event of negligence or any other liability of the sites or investigators conducting the trial or by persons for whom the said site or investigator are responsible.

Appendix 4 Adverse events: definitions and procedures for recording, evaluation, follow-up, and reporting

AE definition
An AE is any untoward medical occurrence in a clinical trial subject administered or using a medicinal product, whether or not considered related to the medicinal product or usage. An AE can be any unfavourable and unintended sign, including an abnormal laboratory finding, symptom or disease (new or exacerbated) temporally associated with the use of a medicinal product. Note 1: This includes events related to the procedures involved (any procedure in the protocol). Note 2: For users or other persons this is restricted to events related to the investigational medical device.

Events meeting the AE definition
Any abnormal laboratory test results or safety assessments, including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. A CLAE: a clinical abnormal laboratory finding 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. Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. Signs, symptoms or the clinical sequelae of a suspected drug-drug interaction. Signs, symptoms or the clinical sequelae of a suspected overdose of trial product regardless of intent. A "lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition.
Events NOT meeting the AE definition
Pre-existing conditions, anticipated day-to-day fluctuations of pre-existing conditions, including those identified during screening or other trial procedures performed before exposure to trial product. Note: pre-existing conditions should be recorded as medical history/concomitant illness. Pre-planned procedures, unless the condition for which the procedure was planned has worsened from the first trial related activity after the subject has signed the informed consent.

Definition of an SAE
An SAE is an AE that fulfils at least one of the following criteria:
Results in death
Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalisation or prolongation of existing hospitalisation Hospitalisation signifies that the subject has been detained at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be

considered serious.

Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

Note:

- Hospitalisations for administrative, trial related and social purposes do not constitute AEs and should therefore not be reported as AEs or SAEs.
- Hospital admissions for surgical procedures, planned before trial inclusion, are not considered AEs or SAEs.

Results in persistent disability/incapacity

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experience of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Is a congenital anomaly/birth defect

Important medical event:

Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations. This includes important medical events that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious and reported as SAEs using the important medical event criterion.

The following adverse events must always be reported as SAEs using the important medical event criterion, if no other seriousness criteria are applicable:

- suspicion of transmission of infectious agents via the trial product.
- risk of liver injury defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 x UNL and total bilirubin >2 x UNL, where no alternative aetiology exists (Hy's law).

Note: This includes device deficiencies that might have led to an SAE if:
a) suitable action had not been taken
or
b) intervention had not been made
or
c) if circumstances had been less fortunate.

These are handled under the SAE reporting system.

Description of AEs requiring additional data collection (via specific event form)

Medication error:

- A medication error concerning trial products is defined as:
- Administration of wrong drug.

Note: Use of wrong DUN is not considered a medication error unless it results in a confirmed administration of wrong drug.

- Wrong route of administration, such as intramuscular instead of subcutaneous.

Infusion site reactions:

By questioning the subject the investigator should obtain the following information and record it in the CRF:

- Date and time of reaction
- Was the skin around the infusion site normal before the infusion? (Yes/No) If "No", specify
- Time of appearance of the reaction after the insertion of infusion set
- Associated local symptoms (burning, pain, numbness, itching etc.)
- The time and date of the last infusion set change prior to the episode
- Objective findings based on examination (redness, swelling, macula, haematoma, bleeding etc.)

- The anatomical site of reaction
- Size of the reaction at time of examination (widest diameter in cm/in)
- Was any treatment(s) given for this condition? (Yes/No, if Yes: antihistamines, corticosteroids, analgesics, other (specify))
  - Were symptoms relieved? (Yes/No)
- Were there any risk/confounding factors? (Yes/No)
- If yes, personal history of allergies or intolerance (specify), family history of allergies or intolerance (specify), other (specify)

Hypoglycaemic episodes: Please refer to Appendix 7

AE and SAE recording

The investigator will record all relevant AE/SAE information in the CRF.
The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory and diagnostics reports) related to the event.
There may be instances when copies of source documents (e.g. medical records) for certain cases are requested by Novo Nordisk. In such cases, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the source documents before submission to Novo Nordisk.
For all non-serious AEs the applicable forms should be signed when the event is resolved or at the end of the trial at the latest. For sign-off of SAE related forms refer to "SAE reporting via paper CRF" later in this section.
Novo Nordisk products used as concomitant medication: if an AE is considered to have a causal relationship with a Novo Nordisk marketed product used as concomitant medication in the trial, it is important that the suspected relationship is reported to Novo Nordisk, e.g. in the alternative aetiology section on the safety information form. Novo Nordisk may need to report this adverse event to relevant regulatory authorities.

Assessment of severity

The investigator will assess intensity for each event reported during the trial and assign it to one of the following categories:
Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
Severe: An event that prevents normal everyday activities.
Note: Severe is a category used for rating the intensity of an event; and both an AE and SAE can be assessed as severe. An event is defined as 'serious' when it meets at least one of the outcomes described in the definition of an SAE and not when it is rated as severe.

Assessment of causality

The investigator is obligated to assess the relationship between trial product and the occurrence of each AE/SAE.

Relationship between an AE/SAE and the relevant trial product(s) should be assessed as:

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 aetiology other than the trial product.

Alternative aetiology, such as underlying disease(s), concomitant medication, and other risk factors, as well as the

temporal relationship of the event to trial product administration will be considered and investigated.

The investigator should use the fast-acting insulin aspart investigator's brochure and iLet™ System Risk Analysis document for the assessment. For each AE/SAE, the investigator must document in the medical records that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, **it is important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data**.

The investigator may change his/her opinion of causality in light of follow-up information and send a follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Final outcome

The investigator will select the most appropriate 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 improving and the subject is expected to recover from the event. This term is only applicable if the subject has completed the trial or has died from another AE.

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 sequelae 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 a fatal outcome must be reported as an SAE.

Unknown: This term is only applicable if the subject is lost to follow-up.

Follow-up of AE and SAE

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Novo Nordisk to elucidate the nature and/or causality of the AE or SAE as fully as possible (e.g. severe hypersensitivity reactions). This may include additional laboratory tests (e.g. skin prick test) or investigations, histopathological examinations, or consultation with other health care professionals.

If a subject dies during participation in the trial or during a recognised follow-up period, the investigator should provide Novo Nordisk with a copy of autopsy report including histopathology.

New or updated information will be recorded in the CRF.

SAE reporting via paper CRF

Relevant CRF forms (AE and safety information form) must be forwarded to Novo Nordisk either by fax, encrypted e-mail or courier.

Initial notification via telephone is acceptable, although it does not replace the need for the investigator to complete the AE and safety information form within the designated reporting time frames (as illustrated in Figure 9–1):

AE form within 24 hours.

Safety information form within 5 calendar days.

Both forms must be signed within 7 calendar days. Contact details for SAE reporting can be found in the investigator trial master file.

Reporting of AEs for Non-investigational medical devices provided by Novo Nordisk for use in the trial
Reporting of AEs on Contour® Next One BG meter, Contact™ detach infusion set and Dexcom G5® CGM device: All complaints (including AEs) should be reported directly to the manufacturer.

Appendix 5 Contraceptive guidance and collection of pregnancy information

It must be recorded in the CRF whether female subjects are of childbearing potential.

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile.

Women in the following categories are not considered WOCBP

1. Premenarcheal
2. Premenopausal female with one of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

    Note: Documentation can come from the site personnel's review of subject's medical records, medical examination or medical history interview.
3. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high Follicle Stimulating Hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or Hormonal Replacement Therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the trial. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before trial enrolment.

Contraception guidance

Female subjects

- Female subjects of childbearing potential are eligible to participate if they agree to use methods of contraception consistently and correctly as described in table(s) below:

Table 12–2 Highly effective contraceptive methods

Highly effective contraceptive methods that are user dependent [a and c] Failure rate of <1% per year when used consistently and correctly.
Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation [b] • oral • intravaginal

• transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • oral • injectable
Highly effective methods that are user independent [a and c]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation • Intrauterine Device (IUD) • Intrauterine hormone-releasing System (IUS) • Bilateral tubal occlusion
Vasectomised partner A vasectomised partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial product. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject.
Notes: [a]Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical trials. [c]Contraception should be utilised during the treatment period and for at least 1 week after the last dose of trial product.

Table 12–3 Acceptable effective contraceptive methods

Acceptable effective contraceptive methods[a] Failure rate of >1% per year when used consistently and correctly
Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action.
Male or female condom with or without spermicide
Cap, diaphragm or sponge with spermicide
Note: [a]Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical trials.

Pregnancy testing

- WOCBP should only be included after a negative highly sensitive urine pregnancy test.
- Pregnancy testing should be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

Collection of pregnancy information: Female subjects who become pregnant

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this trial.
- Information will be recorded on the appropriate form and submitted to Novo Nordisk within 14 calendar days of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on subject and neonate, which will be forwarded to Novo Nordisk. Generally, follow-up will not be required for longer than 1 month beyond the delivery date.
- Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-trial pregnancy which is considered possibly/probably related to the trial product by the investigator will be reported to Novo Nordisk as described in Appendix 4. While the investigator is not obligated to actively seek this information in former subjects, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating in the trial will discontinue from trial treatment.

Appendix 6 Technical complaints (including medical device incidents): Definition and procedures for recording, evaluation, follow-up and reporting

Technical complaint definition and medical device incident
A technical complaint (including medical device incidents) is any written, electronic or oral communication that alleges product (medicine or device) defects. The technical complaint may be associated with an AE, but does not concern the AE itself. A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a medical device itself as well as any inadequacy in the labelling or the directions for use. A medical device incident is therefore a complaint about a medical device and therefore considered as a subset of technical complaints.

Examples of technical complaints:

- Problems with the physical or chemical appearance of fast-acting insulin aspart (PumpCart®) (e.g. discoloration, particles or contamination)
- Problems with packaging material including labelling of fast-acting insulin aspart (PumpCart®)
- Problems related to iLet™ (e.g. pump failure)

Furthermore, problems related to the combined system (iLet™ and fast-acting insulin aspart (PumpCart®)) are considered as a technical complaint where it is not possible to determine if the problem is related to the iLet™ or the PumpCart®.

Time period for detecting technical complaints
All technical complaints, which occur from the time of receipt of the product at trial site until the time of the last usage of the product, must be collected for the following products. • Fast-acting insulin aspart (PumpCart®) • iLet™ • Combined system (iLet™ and fast-acting insulin aspart (PumpCart®))

Reporting of technical complaints on fast-acting insulin aspart (PumpCart®) to Novo Nordisk
Complaints must be registered on technical complaint form specific for the trial. Contact details (fax, e-mail and address) for Customer Complaint Center, Novo Nordisk – refer to Attachment I One technical complaint form must be completed for each affected DUN

Reporting of technical complaints on iLet™ and the combined system (iLet™ and fast-acting insulin aspart (PumpCart®)) to Beta Bionics and Novo Nordisk
Complaints must be reported both to Beta Bionics and to Novo Nordisk using trial specific form. Contact details (fax, e-mail and address) for Customer Complaint Center, Novo Nordisk, and Beta Bionics – refer to Attachment I For the combined system, one technical complaint form must be completed for each affected DUN of fast-acting insulin

aspart (PumpCart®)

For iLet™, it must be evaluated on the technical complaint form if the technical complaint (medical device incident) could have led to an SAE.

If the technical complaint (medical device incident) could have led to an SAE (serious medical device incident), AE form and safety information form must be completed as described in Appendix 4.

Timelines for reporting of technical complaints to Novo Nordisk and Beta Bionics

The investigator must complete and forward the technical complaint form by fax, e-mail or courier to Customer Complaint Center, Novo Nordisk, within the timelines specified in Figure 9–3.

Follow-up of technical complaints

The investigator is responsible for ensuring that new or updated information will be recorded on the originally completed form. This includes re-evaluation if the technical complaint (medical device incident) could have led to an SAE.

Collection, storage and shipment of technical complaint samples

The investigator must collect the technical complaint sample and all associated parts and notify the monitor within 5 calendar days of obtaining the sample at trial site. The sample and all associated parts must be sent as soon as possible to Beta Bionics:

- iLet™
- Combine system (iLet™ and fast-acting insulin aspart (PumpCart®))

Or Customer Complaint Center, Novo Nordisk:

- fast-acting insulin aspart (PumpCart®)

A copy of the completed technical complaint form(s) must be included in the delivery of the sample(s).

The technical complaint sample for fast-acting insulin aspart (PumpCart®) should contain the batch, number and, the DUN. The technical compliant sample for iLet™ should contain the device serial number. If the technical complaint sample is unobtainable, the reason must be stated on the technical complaint form. If several samples are shipped in one shipment, the sample and the corresponding technical complaint form should be kept together.
Storage of the technical complaint sample must be done in accordance with the conditions prescribed for the product.

Reporting of technical complaints for Novo Nordisk products not included in technical complaint form

Technical complaints on Novo Nordisk products not included in the technical complaint form should be reported to local Novo Nordisk affiliate with a reference to trial ID.

Appendix 7 Hypoglycaemic episodes

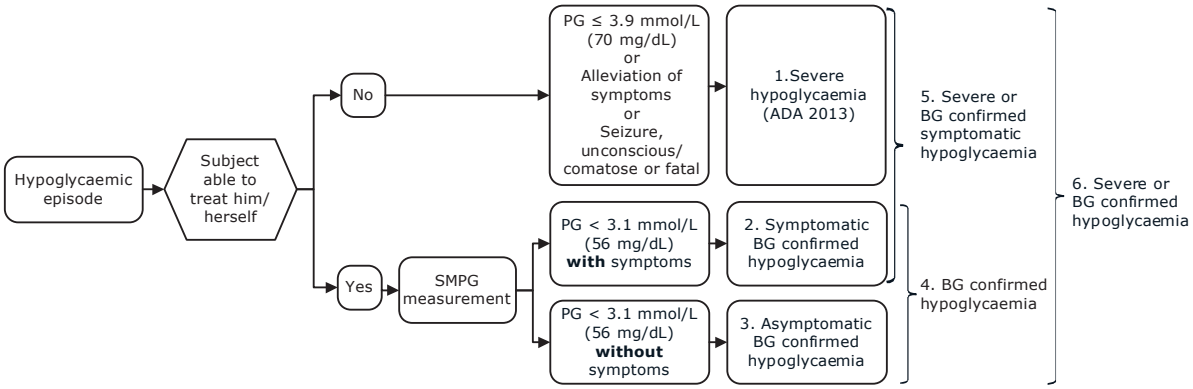
Novo Nordisk classification of hypoglycaemia

In normal physiology, symptoms of hypoglycaemia occur below a PG level of 3.1 mmol/L (56 mg/dL)[19]. Therefore, Novo Nordisk has included hypoglycaemia with PG levels below this cut-off point in the definition of BG confirmed hypoglycaemia.

Novo Nordisk uses the following classification (Figure 12–1) in addition to the American Diabetes Association (ADA) classification[20]:

1. Severe hypoglycaemia according to the ADA classification[20].
2. Symptomatic BG confirmed hypoglycaemia: An episode that is BG confirmed by PG value <3.1 mmol/L (56 mg/dL) **with** symptoms consistent with hypoglycaemia.
3. Asymptomatic BG confirmed hypoglycaemia: An episode that is BG confirmed by PG value <3.1 mmol/L (56 mg/dL) **without** symptoms consistent with hypoglycaemia.
4. BG confirmed hypoglycaemia: The union of 2. and 3.
5. Severe or BG confirmed symptomatic hypoglycaemia: The union of 1. and 2.
6. Severe or BG confirmed hypoglycaemia: The union of 1., 2. and 3.

For hypoglycaemic episodes reported with missing information related to the classification, the following applies when classifying the episode according to the Novo Nordisk classification:
A hypoglycaemic episode with missing information on symptoms will be classified as without symptoms.
A hypoglycaemic episode with missing information on being able to self-treat will be regarded as an episode where the subject was able to self-treat and classified in accordance with the able to self-treat classifications.
Episodes that cannot be classified according to the above, are included in one of the following categories:
'Novo Nordisk unclassifiable' includes episodes where subjects were able to self-treat and with PG≥3.1 mmol/L (56 mg/dL) and hypoglycaemic episodes for a subject able to self-treat with missing PG as it is to be treated as an episode with PG>3.9 mmol/L (70 mg/dL).
'Not able to self-treat – unclassifiable' includes episodes where the subjects were not able to self-treat but neither of the following conditions were reported: PG≤3.9 mmol/L (70 mg/dL), alleviation of symptoms, seizure, unconscious/comatose or fatal.



Note: Glucose measurements are performed with capillary blood calibrated to plasma equivalent glucose values

BG: blood glucose PG: plasma glucose SMPG: Self-measured plasma glucose

Figure 12–1 Novo Nordisk classification of hypoglycaemia

ADA classification[20] of hypoglycaemia

- Severe hypoglycaemia: An episode requiring assistance of another person to actively administer carbohydrate, glucagon or take other corrective actions. PG concentrations may not be available during an event, but neurological recovery following the return of PG to normal is considered sufficient evidence that the event was induced by a low PG concentration.
- Asymptomatic hypoglycaemia: An episode not accompanied by typical symptoms of hypoglycaemia, but with a measured PG concentration ≤3.9 mmol/L (70 mg/dL).
- Documented symptomatic hypoglycaemia: An episode during which typical symptoms of hypoglycaemia are accompanied by a measured PG concentration ≤ 3.9 mmol/L (70 mg/dL).
- Pseudo-hypoglycaemia: An episode during which the person with diabetes reports any of the typical symptoms of hypoglycaemia with a measured PG concentration > 3.9 mmol/L (70 mg/dL) but approaching that level.
- Probable symptomatic hypoglycaemia: An episode during which symptoms of hypoglycaemia are not accompanied by a PG determination but that was presumably caused by a PG concentration ≤ 3.9 mmol/L (70 mg/dL).

For hypoglycaemic episodes reported with missing information related to the classification, the following applies when classifying the episode according to the ADA classification:

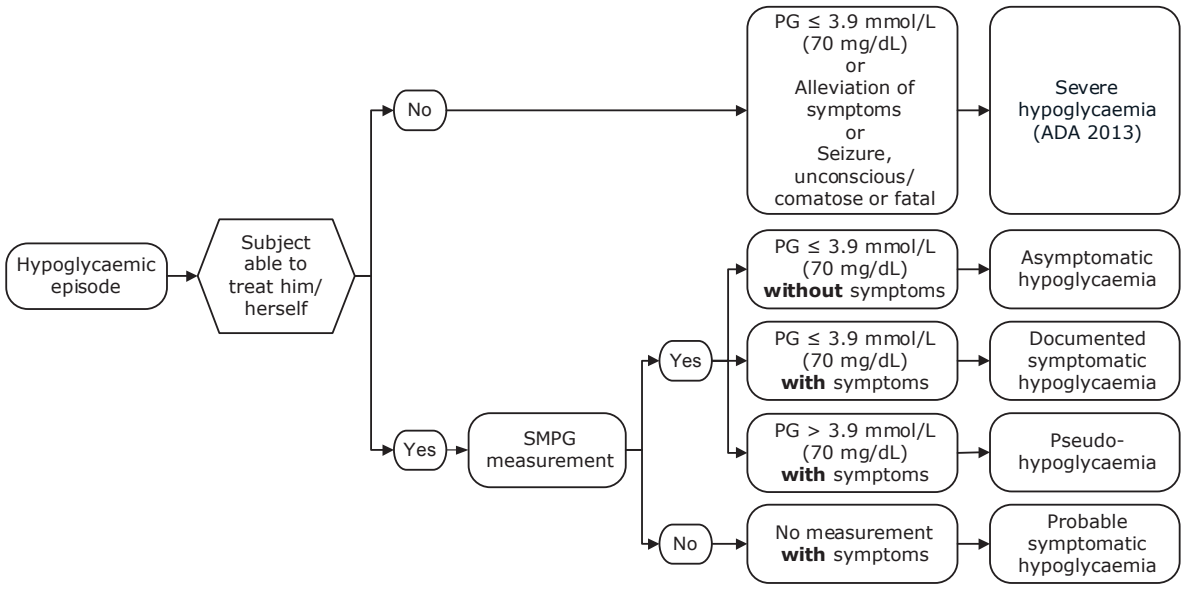
- A hypoglycaemic episode with missing information on symptoms will be classified as without symptoms.

- A hypoglycaemic episode with missing information on being able to self-treat will be regarded as an episode where the subject was able to self-treat and classified in accordance with the able to self-treat classifications

Episodes that cannot be classified according to the above, are included in one of the following categories

- 'ADA unclassifiable' includes episodes where subjects were able to self-treat and with PG>3.9 mmol/L (70 mg/dL) or missing PG, and with no information on symptoms.

'Not able to self-treat – unclassifiable' includes episodes where the subjects were not able to self-treat but neither of the following conditions were reported: PG≤3.9 mmol/L (70 mg/dL), alleviation of symptoms, seizure, unconscious/comatose or fatal.



Note: Glucose measurements are performed with capillary blood calibrated to plasma equivalent glucose values

PG: plasma glucose SMPG: Self-measured plasma glucose

Figure 12–2 ADA classification of hypoglycaemia

Treatment-emergent: hypoglycaemic episodes will be defined as treatment-emergent, if the onset of the episode occurs in the on-treatment period (see definition in Section 10.2).

Nocturnal hypoglycaemic episodes: episodes occurring between 00:01 and 05:59 both inclusive.

Hypoglycaemic episodes are classified according to the Novo Nordisk classification of hypoglycaemia and the ADA classification of hypoglycaemia[20].

Reporting of hypoglycaemic episodes:

PG should always be measured and recorded when a hypoglycaemic episode is suspected or when a hypo alarm is triggered on the iLet™.
All PG values:
≤3.9 mmol/L (70 mg/dL) or
>3.9 mmol/L (70 mg/dL) occurring in conjunction with hypoglycaemic symptoms should be reported as a hypoglycaemic episode according to the flowchart and instructions below. When a subject experiences a hypoglycaemic episode, subject should record the general information in relation to the hypoglycaemia (timing, PG measurements, symptoms etc. as described in the diary). In case a subject is not able to fill in the diary (e.g. in case of hospitalisation or at the 'follow-up phone contact'), then investigator should report the hypoglycaemic episode in the CRF.

Upon onset of a hypoglycaemic episode the subject is recommended to measure PG every 15 minutes until the SMPG value is >3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved in accordance with current guidelines[20].

Repeated SMPG measurements and/or symptoms, occurring within a period of 60 minutes after onset of a hypoglycaemic episode, will by default be considered as one hypoglycaemic episode until a succeeding SMPG value is >3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved and should be reported on one hypoglycaemic episode form. SMPG measurements ≤3.9 mmol/L (70 mg/dL) or hypoglycaemic symptoms after the 60 minutes period shall trigger the reporting of a new hypoglycaemia episode.

In case of several low SMPG values within the 60 minutes interval, the lowest value is the one that will be reported as the SMPG value for the hypoglycaemic episode but the start time of the episode will remain as the time for the first low SMPG value and/or symptom.

The lowest value measured during the hypoglycaemic episode will be reported as the PG value for the episode. The remaining values will be kept as source data in the diary.

A hypoglycaemic episode starting without symptoms should be updated to symptomatic if the subject experiences symptoms later during the episode.
If the severity of a hypoglycaemic episode worsens, only one hypoglycaemic episode should be reported, reflecting the most severe degree of hypoglycaemia.

Investigator must instruct subjects that the answer to the question: "Was the subject able to treat him/herself?" must be answered "No" for an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. PG concentrations may not be available during an event, but neurological recovery following the return of PG to normal is considered sufficient evidence that the event was induced by a low PG concentration[20].

Additional information (e.g. description of symptoms, alleviation of symptoms, seizure, coma, fatal) in relation to these severe hypoglycaemic episodes must be recorded.

Oral carbohydrates must not be given if the subject is unconscious.

The investigator must review the diary for low SMPG values not reported as hypoglycaemic episodes. The subject must be questioned whether any of the low values were severe, i.e. whether the subject was able to self-treat or not. If the subject was not able to self-treat, it has to be reported as a severe hypoglycaemic episode.

For low SMPG values for hypoglycaemic episodes where the subject was able to self-treat: If a hypoglycaemic episode form is not completed within 7 calendar days of the SMPG measurement, the episode should be reported on a hypoglycaemic episode form with as much information as possible. Novo Nordisk will not query for additional data except for the start date, SMPG value and whether the subject was able to self-treat due to decreased validity of such data[21, 22].

The subject must be re-trained in how to report hypoglycaemic episodes if the investigator identifies low SMPG values not reported as hypoglycaemic episodes.

Appendix 8 Country-specific requirements

There is no country specific requirement applicable for US in this trial.

Global and country key Novo Nordisk staff

Attachments I and II (if applicable) to the protocol are located in the Trial Master File.

Content: Global key staff and Country key staff

Protocol Amendment

no 1

to Protocol, version *2* dated 07 June 2018

Trial ID:NN1218-4360

An Exploratory Trial investigating the Safety and Efficacy of Fast-acting Insulin Aspart in a Closed-loop Insulin Delivery System (bionic pancreas) in Adults with Type 1 Diabetes

Trial phase: 2
Applicable to all countries

Table of Contents

1 Introduction including rationale for the protocol amendment

This protocol amendment will serve to address the comments raised by the health authorities, specifically the US Food and Drug Administration (FDA) comments received during the Investigational Device Exemption (IDE) review.

The changes are mainly related to safety of the subject.

In this protocol amendment:

- Any new text is written *in italics*.
- Any text deleted from the protocol is written using ~~strike through.~~

Protocol has been amended to include the following major changes:

- Addition of exclusion criteria related to the use of acetaminophen
- Extension of "in-patient" period to 2 days
- Addition of individual subject's discontinuation criteria
- Addition of trial stopping criteria
- Addition of further instructions for subjects in case of a hyperglycaemia or hypoglycaemia

A number of inconsistencies has been found and corrected and minor clarifications have been added. The subject informed consent has been updated accordingly to the changes implemented.

2 Changes to protocol

Section 1.2.2: Key exclusion criteria

- *Unwilling or unable to avoid acetaminophen throughout the trial*

Section 2: Flowchart

Footnote
h) Subject will spend ~~the 1~~st *-2* night*s* at a hotel for close observation during each treatment period and each cross-over visit

Section 5.1: Overall Design

For each subject, an 'in-patient' period is implemented for the first ~~1~~ *2* day*s* (*48*~~24~~ hours ± ~~3~~ *6* hours) following treatment initiation, i.e. at visit 2 and at cross-over visit (visit 3). This entails that subjects will stay at a designated place (such as a hotel) for the specified duration and will be discharged *following* ~~as per~~ PI's *evaluation* ~~discretion~~, see section 9.15. This period is included in the 7 days treatment period. The 'out-patient' period is defined as the period after the discharge

from the designated place where the subject stays during the 'in-patient' period and until the end of treatment. *During the 'in-patient' period, subjects will be allowed to the leave the designated place during the day but they will be restricted to the area immediately surrounding the designated place (e.g. within 15mins walk).*

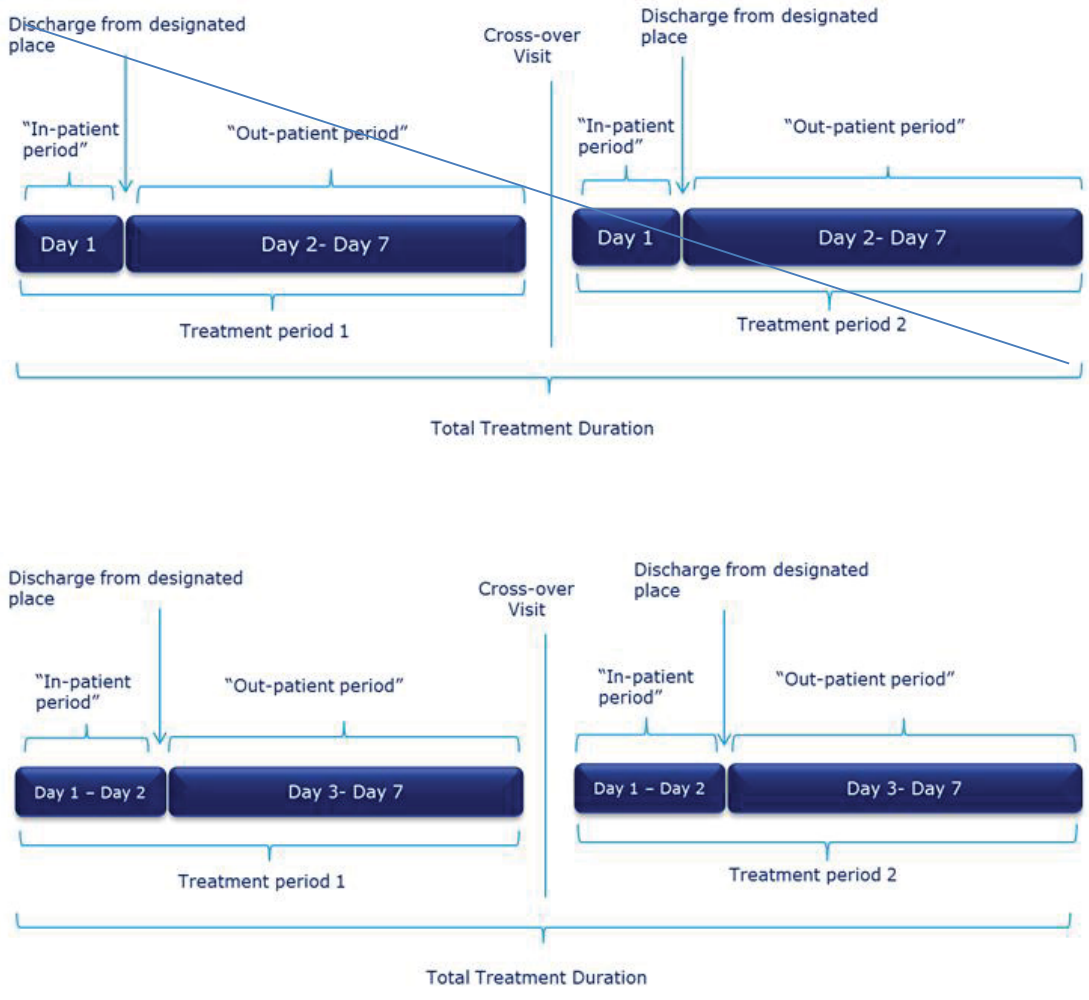


Figure 5-2 In-patient and Out-patient period

Each treatment period will have *2~~1~~* days of "in-patient" period and *5~~6~~* days of "out-patient" period, see Figure 5–2.

Section 6.2: Exclusion criteria

16. Unwilling or unable to avoid acetaminophen throughout the trial

Section 7.1.1: Investigational ~~and non-investigational~~ medicinal products

Table 7–1 Trial products provided by Novo Nordisk A/S

Trial product name:	Fast-acting insulin aspart , 100 U/ml (Investigational medicinal product (IMP), test product)	~~Fiasp® , 100 U/ml(Non-Investigational medicinal product (NIMP))~~
Dosage form:	Solution for injection	~~(Non-Investigational medicinal product (NIMP))~~
Route of administration:	Subcutaneous	~~Solution for injection~~
Dosing instructions:	Dosing is handled by iLet™ autonomously	~~Subcutaneous~~
Packaging	1.6 mL cartridge (PumpCart®)	~~Dosing as per PI's discretion~~

Section 7.1.2: Medical devices

Investigational medical device(s):

Beta Bionics will provide the iLet™ and the StudyPhone with CGM application (app). For complaints related to the iLet™, the investigator should report it to both Novo Nordisk and Beta Bionics, see Appendix 6. And for complaints related to the Study phone *and the apps*, the investigator must contact Beta Bionics directly.

Non-investigational medical device(s):

- CGM device (Dexcom G5®) and its auxiliaries
- StudyPhone with CGM app *(Dexcom G5® and CGMRelay app)***
- *Remote Monitoring app (iLet-RM)*
- BG meter (Contour® Next One) and its auxiliaries
- Infusion set with 60 cm tube (Contact™ detach)
- *Blood ketone meter (Precision Xtra®) and its auxiliaries*

Novo Nordisk will provide the aforementioned non-investigational medical devices (except StudyPhone with CGM app and *Remote Monitoring app*) to the subjects along with the paper diary.

For complaints related to the BG meter, *ketone meter*, infusion set or CGM device, the investigator must contact the device manufacturer's technical support according to Operator's Manuals provided with the BG meter*, ketone meter,* infusion set and the CGM device.

Training in the medical devices

iLet™

- How to replace the PumpCart®
- How and when to replace the batteries
- Troubleshooting in case of iLet™ failure or any technical problems
- *How to react in case of an alarm*

CGM – Dexcom G5®

- How and when to change the sensor
- How and when to calibrate the sensor
- How to use the CGM app on StudyPhone
- *How to react in case of an alarm*

BG Measurement - Contour® Next One

- When to perform self-measured plasma glucose (SMPG) measurements
- How and where to report the SMPG measurements
- ~~How and when to perform ketone measurement~~

Ketone measurement - Precision Xtra®

- *How and when to perform ketone measurement*

Section 7.8: Treatment after the end of the trial

When discontinuing trial product, the subject should be transferred *back* to *the insulin* ~~a suitable marketed~~ product *that was used for CSII therapy prior to the initiation of the trial* ~~at the discretion of the investigator~~.

Section 8.1: Discontinuation of trial treatment

The subject must be discontinued from trial treatment, if the following applies:

5. ≥2 episodes of severe hypoglycaemia (see Appendix 7 for definition), possibly/probably related to investigational medicinal product and/or investigational medical device

6. *Diabetic ketoacidosis possibly/probably related to investigational medicinal product and/or investigational medical device*

8.1.4: Trial stopping criteria

If any of below listed criterion are met, then the PI must suspend the further treatment of all subjects via the iLet™ and communicate the same to Novo Nordisk within 24 hours. Novo Nordisk safety committee will then evaluate the need for further investigation and makes the final decision on stopping the trial. All subjects must be transitioned to their usual CSII treatment until the final decision on stopping the trial has been made.

- *≥3 subjects experience any serious adverse events possibly/probably related to investigational medical device*
- *≥3 subjects experience any severe hypoglycaemic episodes (see Appendix 7 for definition) possibly/probably related to investigational medical device*
- *≥3 subjects experience any diabetic ketoacidosis possibly/probably related to investigational medical device*

Section 9.2.1: Time period and frequency for collecting AE and SAE information

Table 9-1 AEs requiring additional data collection (via specific event form)

Event type	AE requiring additional event form
Hypoglycaemic episode[a]	X
Infusion site reaction[b]	X
Medication error[c]	X

[a] Non-serious hypoglycaemic episode should only be reported on the hypoglycaemic episode form. *All severe* ~~H~~hypoglycaemic episode*s are* qualified~~ying~~ as ~~a~~ SAE*s and* should be reported on the AE form, SIF and Hypoglycaemic episode form. Refer to Section 9.2.6 and Appendix 4 for reporting details

Section 9.2.6: Disease-related events and/or disease-related outcomes not qualifying as an AE or SAE

Hypoglycaemia

Hypoglycaemic episodes should follow the below reporting:

- Non-serious hypoglycaemia must be reported on a hypoglycaemic episode form.
- *All severe hypoglycaemic episodes are qualified as SAEs and should be reported on a hypoglycaemic episode form, an AE form and a safety information form.* One AE form and

safety information form can cover several hypoglycaemic episode forms, if the subject has not recovered between the episodes. *Severe hypoglycaemic episodes should follow the same reporting timelines as SAEs.'*

~~If the hypoglycaemic episode fulfils the criteria for an SAE then in addition to the above, an AE form and a safety information form must also be filled in.~~

Section 9.5.1: Change of infusion set

Infusion sets must be replaced if any change in the insulin solution or occlusion is perceived by the subject, e.g. because of an iLet™ alarm indicating an occlusion or other observations pointing towards obstruction of the insulin flow. *Infusion sets should also be changed in case of prolonged hyperglycaemia and if the ketone measurement is positive*. Infusion set changes can be considered as a 'non-routine change' or 'routine change'.

Section 9.10: Continuous glucose measurement

Subjects should be instructed to avoid medications with acetaminophen/paracetamol while wearing the CGM sensor. These medications may affect the performance and readings of the CGM sensor (e.g. false high CGM readings) [7-9]. *If a subject inadvertently takes acetaminophen during the trial, they will be instructed to contact study staff. Site staff will closely monitor their CGM readings and instruct the subject to measure BG using the BG meter to verify CGM readings as frequently as needed. If the BG is closely correlated with the subject's CGM glucose, study staff will continue to monitor closely. If CGM glucose is consistently higher than BG by >20 mg/dL(1.1 mmol/L) for BG ≤100 mg/dL (5.55 mmol/L) or >20% for BG >100 mg/dL(5.55 mmol/L), then the study staff may temporarily discontinue the iLet™ for the duration of action of the acetaminophen.*

Also, subject should be instructed to remove the Dexcom G5 sensor, transmitter, and receiver before x-ray, Magnetic Resonance Imaging (MRI), Computed Tomography (CT) scan, or high-frequency electrical heat (diathermy).

Section 9.13: Back-up Kits

- Fiasp® *FlexTouch®* ~~pen injector~~ *(supplied by Novo Nordisk)*
- Needles (to be used with Fiasp® ~~pen injector~~ *FlexTouch®*)
- ~~Urine sticks for ketone monitoring~~

Subjects will also be encouraged to always carry the BG - meter, *Ketone meter* and test strips.

Section 9.15: Discharge criteria

The discharge of subjects from the "in-patient" period (during which subjects will be at a designated place such as a hotel) is at the discretion of the PI. In order to make the evaluation whether it is safe for the subjects to continue to the "out-patient" period of the trial, the PI may rely on data that include but are not limited to: hypoglycaemic episodes, the number of times carbohydrates are taken by subjects to prevent or treat hypoglycaemic episodes and time in low interstitial glucose (defined as < 54 mg/dL; 3 mmol/L). *Subjects will not be discharged if they have any severe hypoglycaemic episode possibly/probably related to investigational medicinal product and/or investigational medical device in the last 24 hours.*

In the event of diabetic ketoacidosis or ≥2 episodes of severe hypoglycaemia, possibly/probably related to investigational medicinal product and/or investigational medical device, the subject will discontinue the trial treatment as per section 8.1.

Section 9.16: Remote Monitoring

An alert will be generated *after 15 minutes* if remote monitoring for a subject goes offline. *Site staff will contact the subject to troubleshoot the issue and will ask subject to replace the sensor if it is not possible to recover the sensor and/or connectivity within 20-30 minutes.* Site staff will call the subject every 2 hours to check on safety and device function until remote monitoring is restored. If there are no indications of device malfunction as the cause for lost connectivity, the glucose level is in safe range, and a subject chooses to remain in an area with poor network coverage, site staff will instruct the subject to check the iLet™ display or the CGM app *(Dexcom G5®)* on the study phone at least every 20 minutes for alert icons and to be aware that we are unable to monitor for severe lows or highs at this time. *If the subject is unable to establish the CGM connectivity after 6 hours, they should transition to their usual CSII treatment until the Site staff can assess the functionality of the device and the subject's ability to use it in person.*

Section 9.16.1: Remote Monitoring for Hypoglycaemia

Site staff will verify that the subjects, or their designated contacts, are aware of the hypoglycaemia and are taking action to treat it. Subjects will be reminded of the procedures to follow in case of hypoglycaemia and the site staff will ensure they understand and will follow the procedures. *Subjects will be instructed to measure BG in response to an alarm to verify the CGM reading. If the BG measurement confirms hypoglycaemia, the subjects will be instructed to treat with 15 grams of rapid acting carbohydrates and check the BG again in 15 mins. Subjects will be instructed to treat with another 15 grams of rapid acting carbohydrates if they are still hypoglycaemic. Subjects will be instructed to continue to monitor BG until it returns to≥ 70 mg/dL (3.9 mmol/L).* Subjects will be encouraged to follow up with any questions or concerns. All contact with the subjects in response to hypoglycaemia alarms will be documented in the subjects' medical records.

Section 9.16.2: Remote Monitoring for Hyperglycaemia

Subjects will be reminded to contact the site immediately in case they have been hyperglycaemic for ≥ 2 hours. Site staff will recommend the subjects to measure BG and ketones every hour until the BG is < 180 mg/dl (10 mmol/L) and the ketones measurement is negative. *If ketone measurement is positive (≥ 0.6 mmol/L), they will be instructed to change their infusion set immediately. If ketones measurement is negative (< 0.6 mmol/L), they will be instructed to inspect their infusion set and the iLet™ for proper functioning, and consider replacing the infusion set if they are suspicious it has failed.* Subjects will be encouraged to follow up with any questions or concerns. All contact with the subjects in response to a hyperglycaemia alarms will be documented in the subjects' medical records.

Appendix 3: Trial governance considerations

1) Regulatory and ethical considerations

- This trial will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki[11] and applicable ICH Good Clinical Practice (GCP) Guideline[12] and ISO 14155[13] *and 21CFR[14].*

Appendix 4: Adverse events: definitions and procedures for recording, evaluation, follow-up, and reporting

Important medical event:

The following adverse events must always be reported as SAEs using the important medical event criterion, if no other seriousness criteria are applicable:

- suspicion of transmission of infectious agents via the trial product.
- risk of liver injury defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 x UNL and total bilirubin >2 x UNL, where no alternative aetiology exists (Hy's law).
- *Severe hypoglycaemic episodes (see Appendix 7 for definition)*

Reporting of AEs for Non-investigational medical devices provided by Novo Nordisk for use in the trial
Reporting of AEs on Contour® Next One BG meter, *Precision Xtra® ketone meter*, Contact™ detach infusion set and Dexcom G5® CGM device: All complaints (including AEs) should be reported directly to the manufacturer.

3 Changes to subject informed consent

Figure 1 - Overview of study visits and phone contacts.

Visit Schedule

Trial period	Screening	Study Treatment Period 1 (7 days)		Study Treatment Period 2 (7 days)			Not on study treatment	Follow up
Location Clinic, At home, phone								
Day number	-35 to -14	1	2-7	8	9-14	15	16-21	22
Visit Number	Visit 1	Visit 2		Visit 3		Visit 4		Phone Contact
Reminders: Bring all study drugs and equipment								
Reminders: Bring diary back to clinic								
Reminders: Change infusion set and reservoir every 2 days								
Assessments: Medical history								
Assessments: Body measurements								
Assessments: Physical exam including vital signs								
Assessments: Blood sample								
Assessments: Overnight stay at a hotel								
Assessments: Change of CGM sensor								
Assessments: First day on new insulin delivery setting via iLet™								

Visit Schedule

Trial period	Screening	Study Treatment Period 1 (7 days)		Study Treatment Period 2 (7 days)			Not on study treatment	Follow up
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Assessments: Body measurements								
Assessments: Physical exam including vital signs								
Assessments: Blood sample								
Assessments: Overnight stay at a hotel								
Assessments: Change of CGM sensor								
Assessments: First day on new insulin delivery setting via iLet™								

Section: Across the entire document

~~24 hours~~ *2 days including 2 overnight stays*

Section: 6: What might the benefits be to you?

- Ketone *meter and* strips

Protocol Amendment

no 2

to Protocol, version *2*
dated 07 June 2018 & Protocol Amendment 1 dated 11 July 2018

Trial ID:NN1218-4360

An Exploratory Trial investigating the Safety and Efficacy of Fast-acting Insulin Aspart in a Closed-loop Insulin Delivery System (bionic pancreas) in Adults with Type 1 Diabetes

Trial phase: 2
Applicable to all countries

Table of Contents

1 Introduction including rationale for the protocol amendment

This protocol amendment will serve to address the comments raised by the health authorities, specifically the US Food and Drug Administration (FDA) comments received during the Investigational Device Exemption (IDE) review.

The change is mainly related to safety of the subject.

In this protocol amendment:

- Any new text is written *in italics*.
- Any text deleted from the protocol is written using ~~strike through.~~

2 Changes to protocol

Section 5.1 Overall design

For each subject, an 'in-patient' period is implemented for the first 2 days (48 hours ± 6 hours) following treatment initiation, i.e. at visit 2 and at cross-over visit (visit 3). This entails that subjects will stay at a designated place (such as a hotel) for the specified duration and will be discharged following PI's evaluation see section 9.15. This period is included in the 7 days treatment period. The 'out-patient' period is defined as the period after the discharge from the designated place where the subject stays during the 'in-patient' period and until the end of treatment. During the 'in-patient' period, *subjects will be under close supervision, for at least 4 hours following their first meal, as well as during the initial period following initialization of the iLet™.* Subjects will be allowed to the leave the designated place during the day but they will be restricted to the area immediately surrounding the designated place (e.g. within 15mins walk).

Protocol Amendment

no 3

to Protocol, version *3* dated *23 Jul 2018*

Trial ID: NN1218-4360

An Exploratory Trial investigating the Safety and Efficacy of Fast-acting Insulin Aspart in a Closed-loop Insulin Delivery System (bionic pancreas) in Adults with Type 1 Diabetes

Trial phase: 2
Applicable to *all countries*

Table of Contents "Double click to update Table of Content"

1 Introduction including rationale for the protocol amendment

For this exploratory trial with a specific purpose of establishing the safety of the iLet™ with modified settings when using faster aspart, it is deemed appropriate to limit the patient population in terms of how low the HbA_{1c} can be to enter the trial. Patients with a relatively low HbA_{1c} (lower than 6.5%) are in good control and may not be the ones who will benefit the most from the iLet™ system.

While reducing the lover level of HbA_{1c}, the upper level is being increased to allow subjects with a slightly higher HbA_{1c} (9%) to enter the trial. Those subjects are deemed to have similar safety risks/benefit compared to subjects with a lower HbA_{1c}.

To accommodate for the recruitment of the subjects with the now restricted HbA_{1c} criteria, the number of screened patients is increased from 32 to 56 subjects.

In this protocol amendment:

- Any new text is written *in italics.*
- Any text deleted from the protocol is written using ~~strike through.~~

2 Changes

Section 1.2.3 Number of subjects

Approximately ~~32~~ *56* subjects will be screened to achieve 24 randomised subjects.

Section 5.2 Subject and trial completion

Approximately ~~32~~ *56* subjects will be screened to achieve 24 subjects randomly assigned to two treatment sequences i.e. the default t_{max} setting followed by the non-default t_{max} setting or the non-default t_{max} setting followed by the default t_{max} setting all in combination with fast-acting insulin aspart.

Section 6.1 Inclusion criteria

9. HbA_{1c} *is ≥ 6.5% (47 mmol/mol) and* ~~equal to or below~~ ~~≤ 8.5% (69 mmol/mol)~~ *9% (75 mmol/mol)* at screening

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Meaning		*Date and Time of Signature (Server Time)*

[redacted]

Protocol Amendment

no 4

to Protocol, version *4* dated *19 Dec 2018*

Trial ID: NN1218-4360

An Exploratory Trial investigating the Safety and Efficacy of Fast-acting Insulin Aspart in a Closed-loop Insulin Delivery System (bionic pancreas) in Adults with Type 1 Diabetes

Trial phase: 2
Applicable to *all countries*

Table of Contents "Double click to update Table of Content"

1 Introduction including rationale for the protocol amendment

In this trial the subjects will be using a blood glucose (BG) meter that has the capacity to store the date, time and values of all BG measurements taken in course of the trial. This data can be downloaded to the site computer at the site.

Following discussions at the investigator meeting, the sponsor and the investigator are in agreement that the data downloaded from the BG meter is a more accurate representation of the glucose values measured during the trial, than a collection of the data entered by the subjects in the subject diary, as the latter is a source to potential human error.

Hence, this amendment aims to modify the way of recording BG values used for CGM calibration in the subject's diary. The subject diaries will be modified to include only the date and time of the twice daily CGM calibrations performed by the subjects. This subject-entered time will be considered the approximate time, and will be used by the site staff to identify the corresponding actual time and glucose values in the downloaded BG meter data. Only the accurate dates, times, and values for CGM calibrations from the BG meter download will be entered into the CRF by the site staff. As a consequence, the subject will not be asked to correct the diary entries in case of a discrepancy with the BG meter download.

In this protocol amendment:

- Any new text is written *in italics*.
- Any text deleted from the protocol is written using ~~strike through.~~

2 Changes

Section 9.11 Self-measured plasma glucose

Subjects will be provided with a BG meter including auxiliaries as well as instructions for use. The subjects will be instructed in how to use the device and the instruction should be repeated, if needed

The BG meters use test strips calibrated to plasma values. Therefore, all measurements performed with capillary blood are automatically calibrated to plasma equivalent glucose values, which will be shown on the display.

The BG meter provided by Novo Nordisk should be used for the measurements required in the protocol. SMPGs must be performed to calibrate the CGM sensor (section 9.10) and in the event of hypoglycaemic episode (Appendix 7) and should *for the latter* be reported in the diary, see section 9.14.

~~All SMPGs values must be recorded in the paper diary. In addition to paper diary, SMPGs performed for the calibration of the CGM sensor must also be recorded on the StudyPhone with~~

~~CGM app. The record of each SMPG value on paper diary should include date, time and value. All data from the diary must be transcribed into the CRF during or following the contact.~~

The subjects should use the SMPG values for the calibration of the CGM sensor by entering the measured values into the StudyPhone with CGM app. The record of these calibrations on paper diary should include date and time. The subjects must be instructed to bring the BG meters to the site at every site visit. The site will download the BG meter data at every site visit. Further the site will use the date and time reported by the subjects in the diary to identify the correct date, time and value in the data downloaded from the BG meter and report these in the CRF.

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