

Cover Page for Protocol

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Sponsor trial ID:	NN1218-3854
Official title of study:	Efficacy and Safety of Continuous Subcutaneous Insulin Infusion of Faster-acting Insulin Aspart compared to NovoRapid® in Adults with Type 1 Diabetes
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16.1.1 Protocol and protocol amendments

List of contents

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Novo Nordisk

Protocol

Trial ID: NN1218-3854

Efficacy and Safety of Continuous Subcutaneous Insulin Infusion of Faster-acting Insulin Aspart compared to NovoRapid[®] in Adults with Type 1 Diabetes

onset[®] 5

*Redacted protocol
Includes redaction of personal identifiable information only.*

Trial phase: 3b

Protocol originator



ClinOps, Insulin, GH & Devices

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List of abbreviations

ADA	American Diabetes Association
AE	adverse event
ALT	alanine aminotransferase
ANOVA	Analysis of variance
AP	alkaline phosphatase
AST	aspartate aminotransferase
AUC	area under the curve
BG	blood glucose
BMI	body mass index
CCDS	Company Core Data Sheet
CE	European Union European Conformity
CGM	Continuous Glucose Monitoring
CI	Confidence Interval
CLAE	clinical laboratory adverse event
CRF	case report form
CRO	contract research organisation
CV	Coefficient of Variation
CSII	continuous subcutaneous insulin infusion
CT	computerised tomography
CTR	clinical trial report
DCCT	Diabetes Control and Complication Trial
DCF	Data Clarification Form
DMC	Data monitoring committee
DUN	dispensing unit number
ECG	Electrocardiogram
eCRF	electronic case report form
eGFR	Estimated glomerular filtration rate
EDC	electronic data capture

EMA	European Medicines Agency
EoT	End of trial
FAS	full analysis set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendment Act
FSFV	first Subject first visit
FPG	fasting plasma glucose
GCP	Good Clinical Practice
HbA _{1c}	glycosylated haemoglobin
hCG	human chorion gonadotropin
HDL	high density lipoprotein
IB	Investigator's Brochure
ICH	international conference on harmonisation
ICMJE	international committee of medical journal editors
ID	identification
IEC	independent ethics committee
IND	investigational new drug
IG	interstitial glucose
IMP	investigational medicinal product
IRB	institutional review board
IV/WRS	interactive voice/web response system
LDL	low density lipoprotein
LSFV	last Subject first visit
MAR	missing at random
MCMC	Markov Chain Monte Carlo
MedDRA	medical dictionary for regulatory activities
MIDF	monitor-Initiated Discrepancy Form
MRI	magnetic resonance imaging
NA	not applicable

ND	not done
NYHA	New York heart association
PG	plasma glucose
PP	per protocol
PPG	postprandial (plasma) glucose
PRO	patient reported outcome
SAE	serious adverse event
SAP	statistical analysis plan
s.c.	subcutaneous
SD	standard deviation
SDV	source data verification
SIF	Safety Information Form
SI/IC	Subject Information / Informed Consent Form
SmPC	Summary of Product Characteristics
SMPG	self-measured plasma glucose
SUSAR	suspected unexpected serious adverse reaction
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TEAE	Treatment Emergent Adverse Event
TMM	Trial Materials Manual
UKPDS	UK Prospective Diabetes Study
UTN	Universal Trial Number

1 Summary

Primary objective

To confirm the effect of continuous subcutaneous insulin infusion (CSII) treatment with faster-acting insulin aspart in terms of glycaemic control by comparing it to CSII treatment with NovoRapid[®], in adults with Type 1 Diabetes Mellitus (T1DM), using a non-inferiority approach.

Secondary objectives

To confirm superiority of CSII treatment with faster-acting insulin aspart compared to CSII treatment with NovoRapid[®] in adults with T1DM, in terms of:

- Postprandial glucose (PPG) regulation (meal test)
- Overall glycaemic control (HbA_{1c})
- Postprandial glucose excursions (1,5-anhydroglucitol)
- Time spent in low interstitial glucose (IG) (Continuous Glucose Monitoring (CGM))

To compare the effect and safety of CSII treatment with faster-acting insulin aspart vs CSII treatment with NovoRapid[®] in adults with T1DM.

Primary endpoint

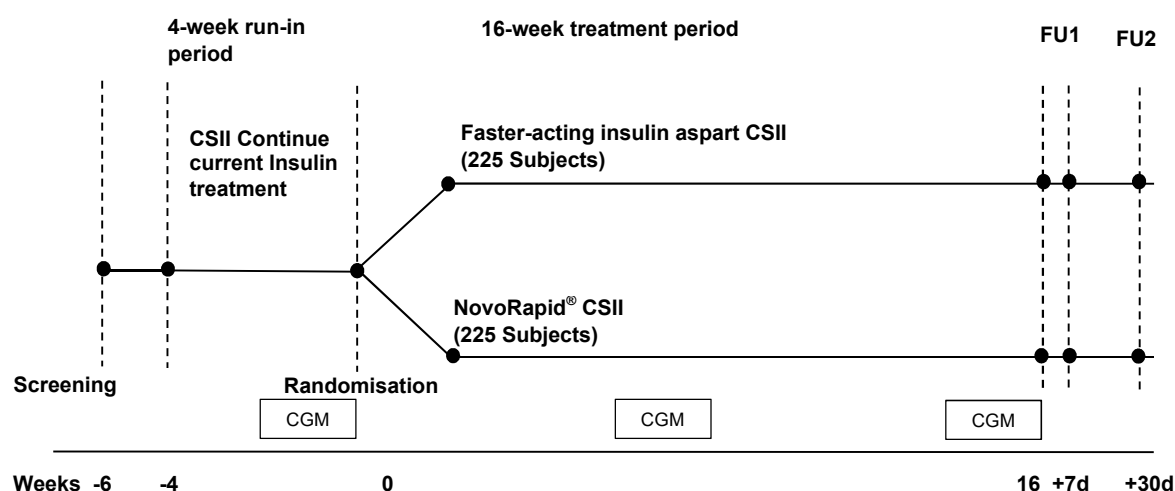
Change from baseline in glycosylated haemoglobin (HbA_{1c}) 16 weeks after randomisation.

Confirmatory secondary endpoints

- Change from baseline in 1-hour PPG increment 16 weeks after randomisation (meal test).
- Change from baseline in 1,5-anhydroglucitol 16 weeks after randomisation
- Change from baseline of time spent in low IG (≤ 3.9 mmol/L [70 mg/dL]) during CGM 16 weeks after randomisation

Trial design

This is a double-blind, randomised, multicentre, multinational, active controlled, treat-to-target, parallel group trial with a 4-week run-in and a 16-week treatment period comparing the effect and safety of CSII of faster-acting insulin aspart vs. NovoRapid[®] in adult Subjects with T1DM . Subjects entering the trial will stay on their own insulin pump, see [Figure 17-1](#).



Note: Prior to randomisation and after end of treatment Subjects are on marketed product.

Baseline is defined as randomisation.

Figure 1–1 Trial design

The trial includes a screening visit to assess Subjects' eligibility and additional weekly visits/phone contacts during the trial. All Subjects eligible for the trial will enter the 4-week run-in period; they will continue on their current insulin treatment and adhere to the protocol requirements as instructed by the Investigator. After the 4-week run-in period Subjects who, based on the Investigator's discretion, have shown ability and willingness to adhere to the protocol and satisfactory handling of the pump will be randomised (1:1) to blinded NovoRapid® or faster-acting insulin aspart. After the 16-week treatment period, the Subject will have a 7-day follow up (FU1) and 30-day (FU2) safety follow-up.

Up to 50% of the enrolled Subjects will be allowed to wear their own real-time CGM device during the entire course of the trial. The remaining enrolled Subjects will not be allowed to wear a CGM device except for three pre-specified periods. On specific days (11 to 13 days) a blinded CGM device will be handed out to all Subjects by the Investigator (provided by Novo Nordisk), including Subjects wearing their own real-time CGM. Randomisation will be stratified for the use of own real-time CGM.

Trial population

A total of approximately 666 Subjects with T1DM are planned to be screened, approximately 506 Subjects to enter the run-in period, of which 450 are expected to enter randomised treatment.

Key inclusion criteria

- Male or female, age ≥ 18 years at the time of signing the informed consent
- Diagnosed with T1DM ≥ 1 year prior to the day of screening
- Using the same Medtronic pump (Minimed 530G (551/751), Paradigm Veo (554/754), Paradigm Revel (523/723), Paradigm (522/722)) for CSII in a basal-bolus regimen with a rapid acting insulin analogue for at least six months prior to screening and willing to stay on the same pump model throughout the trial (if the model is changed the change should not exceed 7 consecutive days.)
- HbA_{1c} 7.0-9.0% (53-75 mmol/mol) as assessed by central laboratory at screening
- Body mass index (BMI) ≤ 35.0 kg/m² at screening
- Ability and willingness to take at least 3 daily meal-time insulin bolus infusions every day throughout the trial

Key exclusion criteria

- Any of the following: myocardial infarction, stroke, hospitalization for unstable angina or transient ischaemic attack within the past 180 days prior to the day of screening
- Planned coronary, carotid or peripheral artery revascularisation known on the day of screening
- History of hospitalization for ketoacidosis ≤ 180 days prior to the day of screening
- Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria in a period of 90 days before screening
- Any condition which, in the opinion of the Investigator, might jeopardise a Subject's safety or compliance with the protocol

Key efficacy assessments

- HbA_{1c}
- PPG increments (meal test)
- 1,5-anhydroglucitol
- IG measurements (CGM)

Key safety assessments

- Number of treatment emergent hypoglycaemic episodes
- Number of adverse events

Trial products

- Faster-acting insulin aspart, 100 U/mL solution for subcutaneous (s.c.) infusion provided in 10 mL vial (Investigation Medicinal Product (IMP)– blinded)

Protocol
Trial ID: NN1218-3854
UTN: U1111-1118-2480
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- Insulin aspart (NovoRapid[®]), 100 U/mL solution for s.c. infusion provided in 10 mL vial (Investigational Medicinal Product (IMP), comparator – blinded)

[illegible]

NN1218-3854	Protocol section	Screening	4-week Run-in					Randomisation	0-16 weeks treatment period															End of treatment	Follow-up 1	Follow-up 2	Premature discontinuation of trial product	
		V 1	V 2	P 3	V 4	P 5	V 6	P 7	V 8	P 9	V 10	P 11	V 12	P 13	V 14	P 15	V 16	P 17	V 18	P 19	V 20	P 21	V 22	V 23	P 24	V 22A	V 22B ⁸	
Visit (V) Phone contact (P)	8.1.5 8.1.6																											
Time of visit (weeks)		-6	-4	-3	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	20			
Visit window (days) ¹		+10	±3	±3	±3	±3	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+5	+5	+3	+3	
Infusion site reactions	8.3.3.3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X ⁴	X	X	
Technical complaints	12.1.5 12.4		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
Height	8.3.4	X																										
Body weight	8.3.4	X					X								X								X			X		
Vital signs	8.3.9	X					X								X								X			X		
Physical examination	8.3.8	X					X								X								X			X		
ECG	8.3.5	X																					X			X		
Eye examination	8.3.6	X																					X			X		
Meal test	8.3.7						X																X			X		
LABORATORY ASSESSMENTS																												
Fasting Plasma Glucose	8.4.3						X								X								X			X		
HbA _{1c}	8.4.5	X					X				X				X				X				X			X		
1,5-anhydroglucitol	8.4.1						X				X				X				X				X			X		
Biochemistry	8.4.2	X					X								X								X			X		
Haematology	8.4.4	X					X								X								X			X		
Lipids	8.4.6	X					X								X								X			X		
Pregnancy testing	8.4.7	X ⁷					X ⁷																X ⁷			X ⁷		
Urinalysis	8.4.8	X					X								X								X			X		
OTHER ASSESSMENTS																												
CGM fitting	8.5.1.3 , 8.5.1.4				X	X							X	X							X	X				X ⁸		
CGM removal	8.5.1.3					X	X							X	X							X	X				X	

NN1218-3854	Protocol section	Screening	4-week Run-in					Randomisation	0-16 weeks treatment period															End of treatment	Follow-up 1	Follow-up 2	Premature discontinuation of trial product	
		V 1	V 2	P 3	V 4	P 5	V 6	P 7	V 8	P 9	V 10	P 11	V 12	P 13	V 14	P 15	V 16	P 17	V 18	P 19	V 20	P 21	V 22	V 23	P 24	V 22A	V 22B ⁸	
Visit (V) Phone contact (P)	8.1.5 8.1.6																											
Time of visit (weeks)		-6	-4	-3	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	20			
Visit window (days) ¹		+10	±3	±3	±3	±3	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+5	+5	+3	+3	
CGM data transfer	8.5.1.5						X								X								X			X ⁵	X	
Change of infusion set and reservoir	8.3.2.3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	
PRO questionnaire	8.5.3		X																									
TRIAL MATERIAL																												
IV/WRS	10	X					X		X		X		X		X		X		X		X		X			X	X	
Dispensing visit (drug)	9						X		X		X		X		X		X		X		X					X		
Dosing ²							X																X			X ⁸	X	
Drug accountability	9.4								X		X		X		X		X		X		X		X			X	X	
REMINDERS																												
Hand-out Subject participation card	8.1.2	X																										
Pairing of Subjects Pump and Subject Number in CareLink	8.1.3		X																									
Hand out and instruct in use of BG meter	8.3.2.2		X																									
Hand out and instruct in use of back-up kit	8.3.2.6		X		X		X		X		X		X		X		X		X		X					X		
Hand out and instruct in use of diary	8.5.2		X		X		X		X		X		X		X		X		X		X		X			X		
Hand out of infusion set and reservoir			X				X								X											X ⁸		
Attend visit fasting	8.1.7						X								X								X			X		
Training in diabetes and carbohydrate counting	8.3.2.5		X				X																					
Training in pump use (and trial procedures)	8.3.2.4		X		X		X		X		X		X		X		X		X		X							
Remind Subjects to bring BG meter to site visit	8.3.1			X		X		X		X		X		X		X		X		X		X				X		
Upload pump and BG meter data	8.3.2				X		X		X		X		X		X		X		X		X		X			X	X	
Instruct in use of trial product	9.2, 9.3						X		X		X		X		X		X		X		X							
End of treatment	8.1.9																						X			X	X	

NN1218-3854	Protocol section	Screening	4-week Run-in					Randomisation	0-16 weeks treatment period Blinded trial product													End of treatment	Follow-up 1	Follow-up 2	Premature discontinuation of trial product		
Visit (V) Phone contact (P)	8.1.5 8.1.6	V 1	V 2	P 3	V 4	P 5	V 6	P 7	V 8	P 9	V 10	P 11	V 12	P 13	V 14	P 15	V 16	P 17	V 18	P 19	V 20	P 21	V 22	V 23	P 24	V 22A	V 22B
Time of visit (weeks)		-6	-4	-3	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	20		
Visit window (days) ¹		+10	±3	±3	±3	±3	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+5	+5	+3	+3
End of trial	8.1.10.2 8.1.9																								X		
Casebook sign off ³																									X		

Key visits are highlighted in light blue.

¹ Visit windows are relative to randomisation (Visit 6), except the two follow-up visits which are relative to Visit 22/22A. Visit 2 can take place as soon as the Subject has been found eligible and must take place no later than 17 days after screening (Visit 1)

² Start/stop date of trial product (depending on when the Subject discontinues treatment)

³ The casebook should be signed of at the Subjects very last visit

⁴ Infusion site reactions must be captured on the Adverse Event Form (no additional infusion site reaction information needs to be completed)

⁵ Assessment not applicable if Subject prematurely discontinues treatment after Visit 12

⁶ Only unexplained Hyperglycaemic episodes

⁷ Blood pregnancy test

⁸ For Subjects prematurely discontinuing treatment before Visit 12

3 Background information and rationale for the trial

The trial will be conducted in compliance with this protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP)¹ and applicable regulatory requirements, and in accordance with the Declaration of Helsinki².

In this document, the term Investigator refers to the individual responsible for the overall conduct of the clinical trial at a trial site.

3.1 Background information

Data from the Diabetes Control and Complication Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS) shows that improvement in long term glucose control, as obtained with intensified insulin therapy, can reduce the incidence of complications and delay the progression of existing complications in Type 1 Diabetes Mellitus (T1DM) and Type 2 Diabetes Mellitus (T2DM)^{3,4}. Control of postprandial hyperglycaemia significantly contributes to the glycosylated haemoglobin (HbA_{1c}) level, and its treatment is essential for achieving the HbA_{1c} target level⁵.

Basal-bolus insulin therapy aims at approaching the physiological insulin secretion profile in the healthy state to the largest possible extent. For that purpose, faster-acting insulin analogues have been developed to more effectively control the postprandial glucose (PPG) excursions as compared to subcutaneously (s.c.) injected regular human insulin, primarily through offering a faster onset of action and shorter duration of action⁶. However, unmet needs exist within faster-acting insulin therapy. The current insulin analogues are not able to match the speed of the physiological post-meal insulin secretion, and a faster onset of action is preferred for tighter PPG control. In addition, a more rapid delivery of the exogenous insulin to meet postprandial needs is likely to offer increased convenience and dosing flexibility for the patient⁷.

For an assessment of benefits and risks of the trial, see section [18.2](#).

3.1.1 Therapeutic area

The purpose of continuous subcutaneous insulin infusion (CSII) therapy in patients with diabetes is administration of insulin in a pattern which mimics physiological insulin secretion in people without diabetes. Basal insulin requirements are delivered by the pump in a continuous, slow infusion mode that is augmented by timed, meal-related bolus infusions. CSII offers advantages over multiple injection therapy, such as better flexibility and control over the basal insulin requirements and more predictable amounts of bolus insulin absorbed⁶. Results from clinical trials indicate that CSII for some patients is a more optimal therapy than multiple daily injections; resulting in improved glycaemic control without an increased risk of hypoglycaemia^{8,9}.

3.1.2 Faster-acting insulin aspart

Faster-acting insulin aspart (also called faster aspart) is insulin aspart in a new formulation. Insulin aspart is marketed worldwide as NovoRapid[®] (in US it is NovoLog[®]). In the remainder of this document, the name NovoRapid[®] will be used. Faster-acting insulin aspart is being developed with the objective of achieving an increased early absorption of insulin aspart compared to NovoRapid[®] thereby providing a faster insulin action. Faster-acting insulin aspart aims at mimicking the physiological prandial insulin secretion pattern better than currently available treatment and thereby more effectively controlling the PPG excursion and achieving a better PPG control, and increased flexibility in the time of dosing around meals compared with NovoRapid[®]. Results from clinical pharmacology trials in adults comparing pharmacokinetic and pharmacodynamic properties of faster-acting insulin aspart and NovoRapid[®] have shown that faster-acting insulin aspart elicited an earlier onset of appearance and a greater early exposure to insulin aspart than NovoRapid[®] in Subjects with T1DM, with the largest difference found within the first 15 minutes after injection. Faster-acting insulin aspart also elicited a greater early glucose-lowering effect than NovoRapid[®], but no statistically significant difference between faster-acting insulin aspart and NovoRapid[®] in total glucose-lowering effect⁷. Similar results were found in a clinical pharmacology trial in a CSII pump setting, where the difference in onset of exposure and early insulin exposure were even greater for faster-acting insulin aspart compared with NovoRapid[®] than observed for single dose s.c. injection⁷.

In a therapeutic confirmatory basal-bolus trial in adult Subjects with T1DM, faster-acting insulin aspart taken with the meal effectively improved glycaemic control and the reduction in HbA_{1c} was statistically significantly larger than with NovoRapid[®]. Mealtime faster-acting insulin aspart provided superior PPG control compared to NovoRapid[®]. No statistically significant difference was seen in overall rate of severe or blood glucose (BG) confirmed hypoglycaemic episodes between mealtime faster-acting insulin aspart and NovoRapid[®]. The rate during the first 1 hour after start of a meal, constituting a small fraction of all severe or BG confirmed hypoglycaemic episodes was statistically significantly higher for faster-acting insulin aspart compared to NovoRapid[®]. The overall safety profile for faster aspart and NovoRapid[®] was similar and as expected for insulin aspart.

In a 6-week confirmatory pump compatibility trial, no microscopically confirmed episodes of infusion set occlusions (primary endpoint) were observed with either faster-acting insulin aspart or NovoRapid[®] in adult Subjects with type 1 diabetes⁷.

In this trial, the safety profile of faster-acting insulin aspart is expected to be similar to that of NovoRapid[®]. The insulin aspart molecule has a well-known safety profile based on more than 15 years of clinical experience. Compared to NovoRapid[®], faster-acting insulin aspart contains excipients which results in a faster initial absorption of insulin aspart following s.c. injection. The added excipients are included in the Food and Drug Administration's (FDA) list for approved drug

products for injections and no toxicological concerns have been predicted for s.c. use in humans at the proposed concentrations.

For further details, please refer to the current version of the faster-acting insulin aspart Investigator's Brochure (IB)⁷ and any updates hereto.

3.1.3 NovoRapid[®] (insulin aspart)

Insulin aspart is homologous to human insulin, with the exception of the substitution of proline with aspartic acid at position B28. The rapid action of insulin aspart is related to a weakened tendency of the insulin molecules to self-associate due to this modification, and is thereby related to faster absorption as compared to regular human insulin. Compared with human insulin, insulin aspart has a faster onset and a shorter duration of action, resulting in superior postprandial glycaemic control by means of lowering total glucose excursion following a meal, both in Subjects with T1DM¹⁰ and in Subjects with T2DM¹¹⁻¹³. This also allows insulin aspart to be injected immediately before a meal, in contrast to regular human insulin. NovoRapid[®] is approved for use in CSII.

For further details, please refer to the current version of the NovoRapid[®] EU Summary of Product Characteristics (SmPC)¹⁴, the U.S. NovoLog[®] Label Information¹⁵.

For an assessment of benefits and risks of the trial, see section [18](#).

3.2 Rationale for the trial

This trial aims to confirm the effect and to evaluate the safety of faster-acting insulin aspart with the use of CSII in adults with T1DM. In the European Medicines Agency (EMA) and FDA note for guidance on clinical investigation of medicinal products for the treatment of diabetes, HbA_{1c} is considered the most widely accepted measure of overall, long-term glucose control. Consequently, change from baseline in HbA_{1c} 16 weeks after randomisation will be included as the primary endpoint^{16,17}.

The trial is intended to confirm that faster-acting insulin aspart, with a faster onset of action, is capable of demonstrating superior control of excessive postprandial glycaemic excursion during a standardised meal test and of demonstrating superiority of faster aspart in 1, 5-anhydroglucitol as another measure of PPG control, compared to NovoRapid[®].

The trial also aims to confirm superiority and investigate the differences in interstitial glucose (IG) of faster-acting insulin as compared to NovoRapid[®] based on data from continuous glucose monitoring (CGM) in adults with T1DM treated with CSII.

Further the trial is designed to confirm superiority of faster aspart in terms of overall glycaemic control measured as HbA_{1c} when compared to NovoRapid[®].

Protocol
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UTN: U1111-1118-2480
EudraCT no.: 2010-024054-11

~~CONFIDENTIAL~~

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Novo Nordisk

The trial is a part of phase 3 clinical development program designed to meet the regulatory requirements for obtaining a CSII indication for faster-acting insulin aspart worldwide.

4 Objectives and endpoints

4.1 Objectives

4.1.1 Primary objective

To confirm the effect of continuous subcutaneous insulin infusion (CSII) treatment with faster-acting insulin aspart in terms of glycaemic control by comparing it to CSII treatment with NovoRapid[®], in adults with Type 1 Diabetes Mellitus (T1DM), using a non-inferiority approach.

4.1.2 Secondary objectives

To confirm superiority of CSII treatment with faster-acting insulin aspart compared to CSII treatment with NovoRapid[®] in adults with T1DM, in terms of:

- Postprandial glucose regulation (meal test)
- Overall glycaemic control (HbA_{1c})
- Postprandial glucose excursions (1,5-anhydroglucitol)
- Time spent in low interstitial glucose (CGM)

To compare the effect and safety of CSII treatment with faster-acting insulin aspart vs. CSII treatment with NovoRapid[®] in adults with T1DM.

4.2 Endpoints

Baseline is defined as randomisation (Visit 6).

4.2.1 Primary endpoint

Change from baseline in glycosylated haemoglobin (HbA_{1c}) 16 weeks after randomisation.

4.2.2 Confirmatory secondary endpoints

- Change from baseline in 1-hour PPG increment 16 weeks after randomisation (meal test)
- Change from baseline in 1,5-anhydroglucitol 16 weeks after randomisation
- Change from baseline of time spent in low IG (≤ 3.9 mmol/L [70 mg/dL]) during CGM 16 weeks after randomisation

4.2.3 Supportive secondary endpoints

Supportive secondary endpoints are detailed in section [17.4.2](#) and are therefore only listed below without a detailed explanation.

4.2.3.1 Supportive secondary efficacy endpoints

16 weeks after randomisation:

- Change from baseline in fasting plasma glucose (FPG)
- Percentage of Subjects reaching HbA_{1c} targets
 - HbA_{1c} <7.0% (53 mmol/mol)
 - HbA_{1c} <7.0 % (53 mmol/mol) without severe hypoglycaemic episodes
- Change from baseline in 30- min, 1- hour, 2- hour, 3- hour and 4- hour PPG and in 30- min, 2- hour, 3- hour and 4- hour PPG increment 16 weeks after randomisation (meal test)
- Change from baseline in 7-7-9 point self-measured plasma glucose (SMPG) profile assessed by:
 - Mean of the 7-7-9 point SMPG profile
 - PPG and PPG increment (mean, breakfast, lunch and main evening meal)
 - Pre-prandial plasma glucose (PG) (mean, pre-breakfast, pre-lunch, pre-main evening meal)
 - Fluctuation in 7-7-9 point profile
 - Change in nocturnal SMPG measurements
- Percentage of Subjects reaching PPG target (overall mean of daily post prandial glucose measurements in 7-7-9-point self-measured plasma glucose):
 - Overall PPG (1 hour) ≤7.8 mmol/L [140 mg/dL]
 - Overall PPG (1 hour) ≤7.8 mmol/L [140 mg/dL] without severe hypoglycaemia
- Change from baseline in lipids-lipoproteins profile (total cholesterol, high density lipoproteins, low density lipoproteins)
- Insulin dose (Units/day and Units/kg/day; total basal, total bolus, total daily insulin dose and individual meal insulin dose):
- Insulin delivery pump parameters including insulin carbohydrate ratio, glucose sensitivity factor and active insulin time

4.2.3.2 Supportive secondary CGM and meal characteristics related endpoints excluding meal test

16 weeks after randomisation:

- Change from baseline in mean IG increment (0-30 min, 0-1 hour and 2 hours after start of meal)
- Change from baseline in mean time to the IG peak after start of meal

- Change from baseline in mean IG peak after start of meal

4.2.3.3 Supportive secondary endpoints CGM related endpoints excluding meal test

16 weeks after randomisation:

- Percentage of time spent with IG ≤ 2.5 , 3.0, 3.5 mmol/L [45, 54, 63 mg/dL]) and IG > 10.0 , 12.0 mmol/L [180, 216 mg/dL])
- Incidence of episodes with IG ≤ 2.5 , 3.0, 3.5, 3.9 mmol/L [45, 54, 63, 70 mg/dL]) and IG > 10.0 , 12.0 mmol/L [180, 216 mg/dL])
- Change from baseline in mean of the IG profile
- Percentage of time spent within target range 4.0-7.8 mmol/L (71-140 mg/dL)
- Variation in the IG profile
- Area under the curve ($AUC_{3.9-IG}$) for IG ≤ 3.9 mmol/L [70 mg/dL]

4.2.3.4 Supportive secondary endpoints related to CGM and meal test

16 weeks after randomisation:

- Change from baseline in $AUC_{IG,0-15min}$
- Change from baseline in $AUC_{IG,0-30min}$
- Change from baseline in $AUC_{IG,0-1h}$
- Change from baseline in $AUC_{IG,0-2h}$
- Change from baseline in $AUC_{IG,0-4h}$
- Change from baseline in time to the IG peak after start of meal
- Change from baseline in IG peak after start of meal

4.2.3.5 Supportive secondary safety endpoints

- Number of treatment emergent adverse events (AEs) during 16 weeks after randomisation
- Number of treatment emergent infusion site reactions during 16 weeks after randomisation
- Number of treatment emergent hypoglycaemic episodes classified both according to the American Diabetes Association definition and Novo Nordisk definition during 16 weeks after randomisation:
 - Overall
 - Daytime and nocturnal hypoglycaemic episodes (00:01-05:59 – inclusive)
 - Hypoglycaemic episodes from start of meal until 1, 2, 4 hours and from 2 hours (exclusive) to 4 hours (inclusive) after start of meal
- Number of unexplained episodes of hyperglycaemia (confirmed by SMPG) during 16 weeks after randomisation
- Change from baseline 16 weeks after randomisation in clinical evaluations:
 - Physical examination
 - Electrocardiogram (ECG)
 - Vital signs (blood pressure, pulse)
 - Fundus photography/fundoscopy
- Change from baseline 16 weeks after randomisation in central laboratory assessments:
 - Haematology (haemoglobin, haematocrit, erythrocytes, thrombocytes, and leucocytes)
 - Biochemistry (total protein, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP), sodium, potassium, albumin, and total bilirubin)
 - Urinalysis (for blood, protein, and ketones)
- Change from baseline 16 weeks after randomisation in body weight and body mass index (BMI)
- Number of change-of-infusion-sets per week during 16 weeks after randomisation
- Number of Subjects with at least one non-routine change-of-infusion-sets categorised by reasons for change-of-infusion-sets during 16 weeks after randomisation

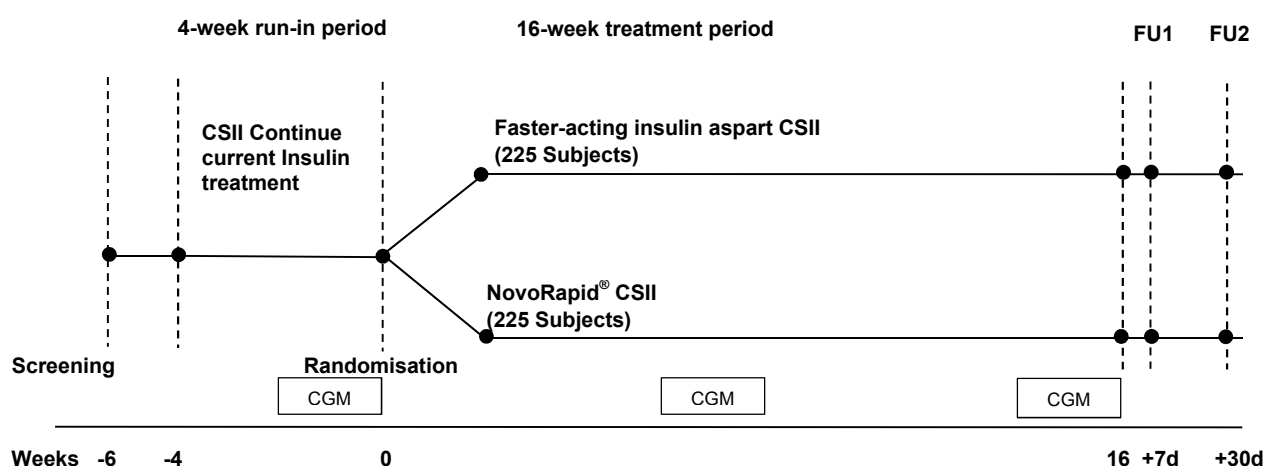
5 Trial design

5.1 Type of trial

This is a double-blind, randomised, multicentre, multinational, active controlled, treat-to-target, parallel group trial with a 4-week run-in and a 16-week treatment period comparing the effect and safety of CSII of faster-acting insulin aspart vs. NovoRapid[®] in adult Subjects with T1DM. Subjects entering the trial will stay on their own insulin pump.

The total duration of the trial is approximately 26 weeks split into the following periods (see [Figure 5-1](#)):

- ≤ 2-week for screening period
- A 4-week run-in period primarily for reinforcement of Subject training in trial procedures, diabetes education and collecting baseline assessments
- A 16-week double-blinded treatment period
- A 7-day and 30-day follow-up period



Note: Prior to randomisation and after end of treatment Subjects are on marketed product.

Baseline is defined as randomisation.

Figure 5-1 Trial design

The trial includes a screening visit (Visit 1) to assess Subjects' eligibility and additional weekly visits/phone contacts during the trial. All Subjects eligible for the trial will at Visit 2 enter the 4-week run-in period, and they will continue on their currently prescribed insulin treatment. During the run-in period the Investigator will focus on reinforcement of training in pump use and diabetes as well as in trial procedures including the 4-point SMPG profiles, infusion set changes and completion of the diaries. Based on the Investigator's discretion after the run-in period, Subjects who have shown ability and willingness to adhere to the trial procedures and satisfactory handling of the pump will be randomised (Visit 6) in a 1:1 manner to NovoRapid® or faster-acting insulin aspart as described in section 11. After the 16-week treatment period, the Subject will have a 7-day follow-up (FU1, V 23) and 30-day (FU2, P 24) safety follow-up visit.

Up to 50% of the eligible Subjects will be allowed to wear their own real-time CGM device during the entire course of the trial. The remaining enrolled Subjects will not be allowed to wear a CGM device except for three pre-specified periods. During these periods a blinded CGM device will be

handed out to all Subjects by the Investigator (provided by Novo Nordisk), including Subjects wearing their own CGM.

5.2 Rationale for trial design

A 4-week run-in period has been included to ensure that the Subjects are being trained in the trial procedures and to collect 11 to 13 days baseline CGM measurements prior to randomisation.

A 16-week double-blinded, randomised treatment period is needed to obtain valid and adequate data regarding the effect and the safety. Treatment duration of 16 weeks is considered sufficient to reach a stable HbA_{1c} level in a CSII setting.

By including at least 50% of the Subjects without their own real-time CGM it will allow for assessing safety data in a population that does not have the possibility to look and react on real-time CGM data. The Subjects who enter the trial without their own real-time CGM device must not start wearing one when enrolled in the trial. The other 50% wearing an own GGM device are included to comply with the still-growing insulin pump population wearing a real-time CGM without changing their current normal practice when entering the trial. Subjects wearing their own CGM are not allowed to use the low glucose suspend mode in the relevant pumps during the trial in order to assess the safety profile of faster-acting insulin aspart. Randomisation will be stratified according to the use of own real-time CGM to ensure a comparable number of Subjects in each treatment group.

The rationale of the blinded CGM assessment is to obtain a thorough knowledge of the glycaemic control achieved with the different treatments in this trial.

The rationale for the meal test is to evaluate PPG excursions after a standardised meal when infusing faster-acting insulin aspart compared to NovoRapid[®].

A 7-day and 30-day follow-up visit is included in order to collect information on AEs occurring in the 30 days after discontinuation of trial drug.

The treat-to-target approach, and thereby the very high frequency of contacts, has been chosen in order to ensure optimal titration of faster-acting insulin aspart and NovoRapid[®].

This trial will be conducted at multiple centres to ensure that the required Subject population can be included.

5.2.1 Rational for choice of non-inferiority margin

Placebo controlled trials will usually be considered unethical to conduct in a T1DM diabetic population and it can therefore be difficult to assess the true insulin aspart effect. In a recently finalised faster-acting insulin aspart trial (NN1218-4049) in a bolus insulin naïve T2DM adult population comparing a basal insulin treatment in addition to metformin to a full basal bolus insulin

treatment in addition to metformin the estimated treatment difference in change from baseline HbA_{1c} was - 0.94%-point [-1.17; -0.72] (data on file). In that trial the addition of 3-times daily faster-acting insulin aspart lead to a reduction in HbA_{1c} of 1.16%-point after 18 weeks of treatment. In a similar phase 4 trial¹⁹ investigating the stepwise addition of NovoRapid[®] to a full basal bolus regimen in bolus naïve T2DM adults the observed reduction in HbA_{1c} after 21 weeks of treatment was 1.15%-point (data on file) with 3-times daily NovoRapid[®] added to basal insulin. This gives some indication that the effect of NovoRapid[®] versus placebo would be close to the 0.94%-point observed in trial NN1218-4049. Using a non-inferiority margin of 0.4, one of the suggested margins in the FDA guidance¹⁸, an improvement of approximately 0.54% would have been preserved using the 0.4% non-inferiority margin. It is also worthwhile to state that the T1DM population would not have any or limited endogenous insulin production and the true effect of NovoRapid[®] might be comparable to what is seen in a T2DM population.

5.3 Treatment of Subjects

At the start of the run-in period (Visit 2), Subjects will remain on their pre-trial insulin treatment. At randomisation (Visit 6), Subjects will be switched from their current insulin treatment to either faster-acting insulin aspart or NovoRapid[®] in a 1U:1U manner, keeping the current insulin delivery parameters in the pump. After the transfer to trial insulin treatment the insulin pump delivery parameters should be reviewed with regards to the need for adjustments. During the run-in period (Visit 2 to Visit 6), the basal rates and Bolus Wizard[®] should not be adjusted unless indicated for safety reasons.

In the treatment period starting at randomisation (Visit 6), the Investigators must strive to achieve a glycaemic target of fasting and pre-prandial BG between 4.0-6.0 mmol/L [71-108 mg/dL] in a treat-to-target fashion based on frequent SMPG profiles and safety. No maximum dose of insulin is specified. All Subjects will perform at least 4-point SMPG profiles on a daily basis, in accordance with section [8.3.2.2](#), throughout the trial. Guideline documents for the management of Insulin Pump Therapy will be provided both to the Investigators and the Subjects^{20,21}.

The dose adjustments must be done based on SMPG values only. No other anti-diabetic medication except the current insulin treatment is allowed during the trial after start of run-in period (Visit 2) until randomisation (Visit 6). No other insulin products except the trial medication are allowed from start of the randomisation (Visit 6) until end of treatment (Visit 22).

5.3.1 Basal rate insulin adjustment

The purpose of adjusting the basal rates is to ensure that BG is kept in a stable range within 2 mmol/L [35 mg/dL] in a fasting state and during the night. After randomisation (Visit 6), the Subjects should perform basal rate checks based on frequent measurements of SMPG values and the skipped meal principle, or similar, following instructions from the Investigator according to insulin adjustment guidelines for insulin pump users^{20,21}.

During the treatment period, starting at randomisation (Visit 6), the Investigator must review and adjust if necessary the individual basal rates at each site and phone visit and inform the Subject accordingly. The Novo Nordisk insulin titration group will review the progress of treatment (please see section [5.4](#)).

5.3.2 Bolus insulin titration

The Subjects should use meal-time boluses based on carbohydrate-counting using the Bolus Wizard[®] according to their usual practice and according to instructions from the Investigator. Meal-time dosing is defined as bolus infusion initiated 0-2 minutes before a meal. At randomisation (Visit 6), the individual BG target should be set in the pump to a mean of the upper and lower value in the target range and the Bolus Wizard[®] settings should be evaluated by the Investigator after basal rates checks or adjustments.

During the treatment period starting at randomisation (Visit 6), the Investigator must review and adjust if necessary the insulin to carbohydrate ratios and correction factors at each site and phone visit according to insulin adjustment guidelines for pump users^{[20,21](#)}, and advise the Subject accordingly. The Investigator should also review correction boluses and adjust the active insulin setting in case of any signs of incorrect settings. The Subject must be informed not to change the active insulin setting without discussing this with the Investigator. The Novo Nordisk insulin titration group will review the progress of treatment.

5.4 Titration review procedure

Surveillance of titration data will be performed centrally by Novo Nordisk in a blinded manner. During the trial HbA_{1c} will be monitored by Novo Nordisk for additional surveillance of the glycaemic control. Novo Nordisk will be in contact with sites (visit or phone contact) to discuss progress in glycaemic control and titration of individual Subjects based on SMPGs and HbA_{1c}. This will be done in a blinded manner. When the Investigator receives an inquiry, a response should be received at Novo Nordisk within 24 hours (on weekdays).

5.5 Treatment after end of trial product

When discontinuing trial products, either at end of treatment (Visit 22) or earlier, the Subject should be switched to a suitable marketed product at the discretion of the Investigator. Please see section [8.1.9](#).

5.6 Rationale for treatment

CSII treatment of adult patients with T1DM was introduced more than 30 years ago and found to generate improvements with respect to glucose control. Data from the DCCT show that intensive treatment is beneficial in terms of reducing the risk for long term complications^{[3](#)}.

The currently available clinical pharmacology data demonstrates that injection with faster-acting insulin aspart formulations results in an increased early absorption of insulin aspart compared to NovoRapid[®] and thereby provides a faster onset of insulin action.

A delay between the glucose measurements and the insulin absorption (so called lag-time) due to the s.c. route of insulin delivery can limit the possibility of reducing the excessive PPG excursions. The rapid action of faster-acting insulin aspart could prove more effective in achieving PPG control in a CSII regimen because of the shortened absorption time of faster-acting insulin aspart from the s.c. depot at the infusion site.

NovoRapid[®] will be applied as a comparator to faster-acting insulin aspart in order to compare and confirm clinical effect and safety of faster-acting insulin aspart to the currently marketed insulin aspart formulation NovoRapid[®]. As the trial is double-blinded, faster-acting insulin aspart and NovoRapid[®] will be titrated following the same recommendations.

6 Trial population

6.1 Number of Subjects

Number of Subjects planned to be screened: 666

Number of Subjects planned to be included in the run-in period: 506

Number of Subjects planned to be randomised: 450

Approximately a 24% screening failure rate and 11% run-in failure rate are expected for this trial.

6.2 Inclusion criteria

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

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial
2. Male or female, age ≥ 18 years at the time of signing informed consent
3. Diagnosed with T1DM ≥ 1 year prior to the day of screening
4. Using the same Medtronic pump (Minimed 530G (551/751), Paradigm Veo (554/754), Paradigm Revel (523/723), Paradigm (522/722)) for CSII in a basal-bolus regimen with a rapid acting insulin analogue for at least six months prior to screening and willing to stay on the same pump model throughout the trial (if the model is changed the change should not exceed 7 consecutive days.)
5. Ability and willingness to refrain from using low glucose suspend mode in the pump throughout the trial
6. Willingness to use one of the following types of infusion sets: Medtronic Quick-Set[®], Medtronic Mio[®], Medtronic Silhouette[®] or Medtronic Sure-T[®] (Easy-set[®]) throughout the trial
7. Willing to use CSII as the insulin treatment during the entire trial
8. Using the same insulin for at least 90 days prior to screening
9. HbA_{1c} 7.0-9.0% (53-75 mmol/mol) inclusive as assessed by central laboratory at screening
10. BMI ≤ 35.0 kg/m² at screening

11. Ability and willingness to take at least 3 daily meal-time insulin bolus infusions every day throughout the trial
12. Ability and willingness to adhere to the protocol including performing SMPG profiles, CGM and meal test

6.3 Exclusion criteria

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

1. Known or suspected hypersensitivity to trial products or related products
2. 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 adequate contraceptive methods (adequate contraceptive measures as required by local regulation or practice)

For UK: Females of child-bearing potential who are pregnant, breast-feeding or intend to become pregnant and are sexually active and not using adequate contraceptive methods (Adequate contraceptive measures are defined as established use of oral, intravaginal, transdermal combined estrogen and progestogen hormonal methods of contraception; oral, injected or implanted progestogen only hormonal methods of contraception; placement of an intrauterine device or intrauterine hormone releasing system, bilateral tubal occlusion, barrier methods of contraception (condom or occlusive cap with spermicidal foam/gel/film/cream/suppository), female sterilisation, vasectomised partner (where partner is sole partner of Subject), or true abstinence (when in line with preferred and usual lifestyle))

For Belgium: Highly effective methods of birth control are defined as those, alone or in combination, that result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly; such as implants, injectables, combined oral contraceptives, some IUDs, true sexual abstinence (i.e. refraining from heterosexual intercourse during the entire period of risk associated with the study treatments) or vasectomised partner.

For Germany: Adequate contraceptive measures are defined as implants, injectables, combined oral contraceptives, hormonal intrauterine device and sexual abstinence or vasectomised partner.

4. Participation in another clinical trial within 28 days before the screening visit. Participation is defined as having signed SI/IC. Note: clinical trials do not include non-interventional studies

5. Anticipated significant change in lifestyle (e.g. eating, exercise or sleeping pattern) throughout the trial
6. Any of the following: myocardial infarction, stroke, hospitalization for unstable angina or transient ischaemic attack within the past 180 days prior to the day of screening
7. Subjects classified as being in New York Heart Association²² (NYHA) Class IV at screening
8. Planned coronary, carotid or peripheral artery revascularisation known on the day of screening.
9. Inadequately treated blood pressure defined as Grade 3 hypertension or higher (Systolic ≥ 180 mmHg or diastolic ≥ 110 mmHg) at screening
10. Impaired liver function, defined as ALT ≥ 2.5 times upper normal limit at screening
11. Renal impairment measured as estimated Glomerular Filtration Rate (eGFR) value of eGFR < 60 ml/min/1.73 m² as defined by KDIGO 2012 classification using isotope dilution mass spectrometry (IDMS) for serum creatinine measured at screening. (KDIGO 2012²³)
12. Anticipated initiation or change in concomitant medications (for more than 14 consecutive days) known to affect weight or glucose metabolism (e.g. treatment with orlistat, thyroid hormones, or corticosteroids)
13. Proliferative retinopathy or maculopathy requiring acute treatment as verified by fundus photography or dilated fundoscopy performed within 90 days prior to the screening visit or as part of the screening assessments. Results must be present at Visit 2.
14. History of hospitalization for ketoacidosis ≤ 180 days prior to the day of screening
15. Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria within 90 days before screening
16. Presence or history of malignant neoplasms within the past 5 years prior to the day of screening. Basal and squamous cell skin cancer and any carcinoma in-situ is allowed.
17. Any condition which, in the opinion of the Investigator might jeopardise Subject's safety or compliance with the protocol
18. Intention to start using a flash glucose monitoring or real-time CGM system device for personal use at any time after screening until the end of trial

6.4 Run-in failure criteria

Subjects fulfilling any of the below listed criteria or withdrawing consent prior to randomisation are considered run-in failures and should follow the procedures described in section [8.1.3.1](#).

1. Included in the trial in violation of the inclusion and/or exclusion criteria
2. Pregnancy
3. Intention of becoming pregnant
4. Participation in other clinical trials throughout the trial. Participation is defined as signed informed consent (note; clinical trials do not include non-interventional studies)

6.5 Randomisation criterion

To be randomised, the below randomisation criterion must be answered "Yes".

1. Subjects ability and willingness to adhere to the protocol and satisfactory handling of the pump, including regular changes of the infusion sets and adequate bolus dosing based on the Investigator's judgment

6.6 Criteria for premature discontinuation of trial product or withdrawal from trial

Efforts should be made to ensure Subjects attend and complete all scheduled visits and procedures. There will be a clear distinction between trial product discontinuation and withdrawal from trial by Subject.

6.6.1 Premature discontinuation of trial product

The Subject may be discontinued from trial product at the discretion of the Investigator due to a safety concern.

The Subject must be discontinued from trial product if any of the following applies:

1. Included in the trial in violation of the inclusion and/or exclusion criteria and/or randomised in violation of the randomisation criterion
2. Pregnancy
3. Intention of becoming pregnant
4. Participation in other clinical trials throughout the trial. Participation is defined as signed informed consent (note: clinical trials do not include non-interventional studies)

Discontinuations from trial product criteria are applicable from start of the randomisation (Visit 6) throughout the trial until end of treatment (Visit 22).

Subject discontinued from trial product will be followed up as described in Section [8.1.8.1](#).

6.6.2 Withdrawal from trial

The Subject may withdraw at will at any time. The Subject's request to discontinue from the trial must always be respected.

If the Subject considers withdrawing the Informed Consent the Investigator must underline to the Subject the importance of continuing in the trial despite trial product discontinuation. If the Subject agrees to discontinue trial product but stay in the trial, procedures described in Section [8.1.8.2](#) should be followed.

If a Subject decides to withdraw consent, the Subject should be encouraged to undergo procedures described in Section [8.1.8.2](#).

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

- The site must attempt to contact the Subject and to reschedule the missed visit as soon as possible
- The site must re-train the Subject in the importance of maintaining the scheduled visits
- In cases where a Subject is deemed lost to follow up the Investigator must make every effort to regain contact to the Subject (by e.g. telephone calls, e-mails, certified letters or calls to family members or friends as applicable). These contact attempts should be documented in the Subject's medical records. Only if the Subject continues to be unreachable after all contact attempts, the Subject should be considered to have withdrawn from the study with the primary reason being "lost to follow up".

6.7 Subject replacement

Subjects who are withdrawn after randomisation (Visit 6) will not be replaced.

6.8 Rationale for trial population

The purpose of this trial is to assess the effect and safety of CSII of faster-acting insulin aspart in the treatment of adult Subjects with T1DM.

The trial population consists of adult Subjects with T1DM who have been treated with CSII for at least six months with the same pump and the same insulin for at least 90 days. This is to reduce pump user-related variability and to increase the likelihood that the Subjects will be able to adhere to the protocol requirements. To avoid potential influence on effect and safety data, at least 50% of the Subjects should consent to not use their own real-time CGM during the trial. Subjects entering the trial using own real-time CGM must switch off the low glucose suspend mode in order to avoid

potential impact of the safety results. This is only applicable for Subjects entering the trial using own real-time CGM integrated with their pump.

In diabetes, a likely cause of elevated HbA_{1c} is poor compliance with treatment regimens or atypical course of the disease. Consequently individuals with an HbA_{1c} greater than 9.0% (75 mmol/mol) are not included in the trial. Subjects in good glycaemic control defined as HbA_{1c} < 7.0% may not benefit from further optimisation of glucose control and therefor the lower cut-off value has been chosen. A BMI limit of ≤ 35.0 kg/m² is chosen to include as broad a population as possible, while excluding exceedingly obese individuals. The trial protocol requires strict adherence and good Subject compliance.

7 Milestones

Planned duration of recruitment period, first Subject first visit (FSFV) – last Subject first Visit (LSFV): 26 weeks

End of trial (EoT) is defined as last Subject last visit (LSLV) after 16 weeks of randomised treatment and a 30-day follow-up.

The recruitment period will depend on the screening rate and the screening/run-in failure rate. Recruitment will be closed as soon as the total number of randomised Subjects is possible to reach, taking into account the number of Subjects currently in screening/in the run-in period and the previous screening/run-in failure rate. All Subjects who are in screening/run-in when recruitment closes will be randomised if eligible. All Investigators will be notified immediately when the recruitment period ends and when the limit of 50% of the Subjects wearing their own CGM is met. When the recruitment period ends, no further Subjects may be screened and the interactive voice/web response system (IV/WRS) will be closed for further screening.

Trial registration:

Information of the trial will be disclosed at clinicaltrials.gov and novonordisk-trials.com. According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure, it will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE)²⁴, the Food and Drug Administration Amendment Act (FDAAA)²⁵, European Commission Requirements²⁶⁻²⁸ 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

8 Methods and assessments

8.1 Visit procedures

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

Throughout this section the term Investigator refers to Investigator or delegated personnel, unless otherwise stated.

8.1.1 Informed Consent

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

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

The process for providing trial information and obtaining informed consent is described further in section [18.3](#).

8.1.2 Screening visit

At screening (Visit 1), each Subjects will be assigned a unique 6-digit Subject number which will remain the same throughout the trial. A screening session must be performed in the IV/WRS.

Subjects will continue on their current diabetes treatment until start of randomisation (Visit 6) and they will not be supplied with any trial products until then.

Any abnormal and clinically significant findings at Visit 1 must be recorded on the medical history/concomitant illness form in the electronic case report form (eCRF).

At screening, Subjects will be provided with a card (Subject Participation Card) stating that they are participating in a trial and given contact address(es) and telephone number(s) of relevant trial site staff. Subjects should be instructed to return the card to the Investigator at last trial visit or to destroy the card after the last visit.

The Investigator must keep a Subject Screening Log, a Subject Identification Code List and a Subject Enrolment Log. The Subject Screening Log and Subject Enrolment Log may be combined in one list.

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

8.1.2.1 Screening failures

If a Subject is not eligible to participate in the trial, the Subject will be considered a screening failure. Consequently, a Screening/Run-in Failure Session must be made in the IV/WRS.

For screening failures, the Screening Failure Form must be completed in the eCRF with the reason for not continuing in the trial. Serious adverse events (SAEs) from screening failures must be transcribed by the Investigator into the eCRF. Follow-up of SAEs must be carried out according to section [12.3](#).

When data has been monitored and queries have been resolved the case book must be signed in the eCRF.

8.1.2.2 Re-screening

Re-screening is NOT allowed if the subject has failed one of the inclusion or exclusion criteria related to laboratory parameters.

8.1.3 Run-in

If the Subject is found eligible to continue in the trial the Subject will enter a 4-week run-in period (Visit 2 to Visit 6). Visit 2 can take place as soon as the Subject has been found eligible and must take place no later than 17 days after screening (Visit 1). The results of all the screening assessments must be available (including central laboratory results) and must have been reviewed by the Investigator before the Subject can enter the run-in period.

A BG meter will be handed out to the Subjects, which needs to be coupled by site personnel with the Subjects pump by entering the BG meter serial number into the pump.

At the run-in visit (Visit 2) a pump data upload should be performed in order to pair the Subject's pump with the Subject number created in CareLink Clinical.

The Subjects must be instructed to bring their BG meter to the site at every visit for data upload.

For procedures to be performed in the run-in period, please see flowchart in section [2](#).

8.1.3.1 Run-in failures

If the Subject discontinues from the trial during the run-in period or is not eligible to be randomised (i.e. withdrawn their SI/IC, or not met the randomisation criterion, fulfils any of the run-in failure criteria, please see section [6.4](#)), then the Subject will be considered a run-in failure. Consequently, a Screening / Run-in Failure session must be made in the IV/WRS. A Run-in Failure Form must be recorded in the eCRF with the reason for not continuing in the trial. No end of treatment visit (Visit 22) and follow-up visits (Visit 23 and Visit 24) should take place. SAEs and non-serious AEs from run-in failures must be recorded in the eCRF. Follow-up of AEs should be carried out according to section [12.3](#).

When data has been monitored and queries have been resolved the case book must be signed in the eCRF.

8.1.4 Randomisation

Randomisation (Visit 6) should occur after the four-week run-in period has been completed.

The Subject must attend randomisation (Visit 6) fasting. For definition of fasting, please see section [8.1.7](#).

If the Subject meets the randomisation criterion at Visit 6, the Subject will be randomised into one of the two treatment arms by using IV/WRS; please see section [10](#). The Subject will undergo a meal test (please see section [8.3.7](#)). When the meal test is completed the Subject will be instructed to discontinue their current insulin and start treatment with the trial product according to randomisation. A new infusion set and reservoir containing trial product must be inserted while the Subject is still at site. Stop date of the current insulin treatment and start date of the randomised trial product must be recorded in the eCRF.

Subjects will keep the same Subject number as allocated at screening.

For randomisation (Visit 6) procedures, please see flowchart in section [2](#).

8.1.5 Site visits

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

Scheduled dispensing of trial product should be performed at the visits indicated in the flowchart in section [2](#). A dispensing session must be performed in the IV/WRS when dispensing trial drug. Drug accountability should be performed at each dispensing visit from start of randomisation (Visit 6) until end of treatment (Visit 22)

For assessments performed at the site visits, please see flowchart in section [2](#).

8.1.6 Phone contacts

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

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

The run-in failure/ discontinuation from trial product criteria must be reviewed during the phone contact to ensure the Subject is eligible to continue in the trial.

For assessments performed at the phone contacts please refer to the flowchart in section [2](#).

8.1.7 Fasting visits

Fasting is defined as no intake of drink or food for at least 8 hours prior to blood sampling (only water is allowed). The Subjects must attend the visits specified in section [2](#) in a fasting condition. Correction boluses are allowed until four hours before the measurement of the FPG. Subjects should not make any changes in the current basal rate setting 4 hours prior to the meal test.

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

If the Subject attends the fasting visits in a non-fasting condition, all blood samples, meal test and body weight measurements must be rescheduled within the visit window. The date of the meal test and body weight measurement in the eCRF should reflect the actual date of the meal test/body weight measurement (i.e. the actual visit date will differ from the assessment date under the same visit).

8.1.8 Withdrawal procedures

8.1.8.1 Premature discontinuation of trial product

If a Subject is discontinued from trial product, as described in Section [6.6.1](#) after randomisation (Visit 6), the Investigator must ensure that every possible effort is made to undertake the following procedures:

Subjects discontinuing before or at Visit 12 (Week 6)

- The Subject needs to be called in for a 22A including CGM fitting as soon as possible after awareness of the trial product discontinuation intention. The meal test at Visit 22A should be performed while the Subject still is on trial product according to randomisation unless this is not feasible for safety reasons as judged by the Investigator. (Confirmation that the meal test was performed on trial product will be recorded in the eCRF).
- The Subject will be asked to remain on trial product until completion of Visit 22B (Confirmation that the Subject was on trial product will be recorded in the eCRF)
- The Visit 22B needs to be scheduled 7 days after Visit 22A and serves mainly for transfer of CGM data as specified in Section [2](#). No additional CGM fitting is needed for these Subjects at this visit.
- The CGM assessment on visit 14 can be omitted for these Subjects

At Visit 22B a treatment discontinuation session must be made in IV/WRS and reason for discontinuation of trial product must be specified in the End of Treatment/Trial form in the eCRF. Final drug accountability must be performed even if the Subject is not able to come to the trial site.

At Visit 22B the Subject should be switched to a suitable marketed product at the discretion of the Investigator. The medication should be recorded on the diabetes treatment history form (please see [8.2.5](#)) in the eCRF.

If the Subject does not wish to continue on trial product until visit 22B (or if continuation on trial product is not possible due to a safety concern as judged by the investigator) then all assessments related to trial product discontinuation must be completed at visit 22A.

Subjects discontinuing after Visit 12 (Week 6)

- The Subject needs to be called in for a 22A as soon as possible after awareness of the trial product discontinuation intention. The meal test at Visit 22A should be performed while the Subject still is on trial product according to randomisation unless this is not feasible for safety reasons as judged by the Investigator. (Confirmation that the meal test was performed on trial product will be recorded in the eCRF).
- For Subjects discontinuing between Visit 12 and 14 the CGM and 7-7-9 profile assessment on Visit 14 should be performed as planned, since the CGM has been fitted at Visit 12 for these Subjects

- For Subjects discontinuing between visit 14 and 20 the CGM assessment at visit 22A is not required and will be performed at the key Visit 22.
- For Subjects discontinuing between Visit 20 and 22 the CGM and 7-7-9 profile assessment on Visit 22 should be performed as planned, since the CGM has been fitted at Visit 20 for these Subjects

At Visit 22A a treatment discontinuation session must be made in IV/WRS and reason for discontinuation of trial product must be specified in the End of Treatment/Trial form in the eCRF.

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

At Visit 22A the Subject should be switched to a suitable marketed product at the discretion of the Investigator. The medication should be recorded on the diabetes treatment history form (please see [8.2.5](#)) in the eCRF.

All Subjects prematurely discontinuing the trial product

In addition, all Subjects prematurely discontinued from trial product should after Visit 22A (22B respectively) attend the FU1 and FU2 and continue in parallel with the per-protocol planned key visits: Visit 10, Visit 14, Visit 18 and Visit 22, after randomisation depending on when the Subject discontinues trial product. The following assessments are not applicable for prematurely discontinued Subjects at V22: 4-point SMPG profile, technical complaints, IWRS call.

Contact after premature discontinuation of trial product:

Subjects that prematurely discontinue trial product will be asked to attend an End of Treatment visit (Visit 22A) and follow-up visit 1 (FU1) 7-12 days after visit 22A and follow-up visit 2 (FU2) 30-35 days after V22A. In parallel they will continue with the per-protocol planned key visits: Visit 10, Visit 14, Visit 18 and Visit 22.

In the following situations, only one visit should take place:

- If V22A is more than 12 weeks after randomisation and before the planned V22, only V22A should be performed instead of V22
- If V14 /V18, and FU2 visit windows overlap according to visit schedule, only V14/V18 should be performed
- If V22 and FU1 visit windows overlap according to visit schedule, only V22 should be performed

- If V22 and FU2 visit windows overlap according to visit schedule, only V22 should be performed

Diary records after premature discontinuation of trial product:

The Subject will be handed out premature discontinuation diaries at Visit 22A to record the following:

- Hypoglycaemic episodes. The following information should be recorded:
 - Start date and time of hypoglycaemic episode
 - Time and value of plasma glucose level before treating the episode (if available) and any follow up measurements
 - Whether the episode was symptomatic (Yes/No)
 - Whether the Subject was able to treat him/herself
- Unexplained hyperglycaemic episodes (see section [8.3.3.2](#))
- Change of Infusion sets and reservoirs (see section [8.3.2.3](#))
- Meal dates and times (breakfast, lunch, main evening meal, other) in relation to performance of 7-7-9-point profiles and during the CGM period.(see section [8.5.1.4](#))

Hypoglycaemic and/or unexplained hyperglycaemic episode must be reported in the diary until Visit 22 has been completed.

8.1.8.2 Withdrawal from trial

If a Subject withdraws consent from the trial after randomisation (Visit 6), the Investigator must ensure every possible effort is made to undertake procedures same as those for end of treatment (Visit 22A) including the meal test, as soon as possible after decision of ending trial. The meal test should be performed with trial product according to randomisation unless this is not feasible due to safety reasons as judged by the Investigator.

The Subject should also complete the follow-up visits (Visit 23 and Visit 24). The End of Treatment/Trial form must be completed in the eCRF. A treatment discontinuation session must be made in IV/WRS and reason for withdrawing consent must be specified in the End of Treatment/Trial form in the eCRF. Final drug accountability must be performed even if the Subject is not able to come to the trial site.

Although a Subject is not obliged to give his/her reason(s) for withdrawing from a trial, the Investigator must make a reasonable effort to ascertain the reason(s), while fully respecting the

Subject's rights. Where the reasons are obtained, the primary reason for not completing the trial must be specified on the End of Treatment/Trial form in the eCRF.

8.1.9 End of treatment

At end of treatment (Visit 22), the trial product should be discontinued via a Completion session in IV/WRS and stop date of trial product must be recorded in the eCRF.

The Subject should be switched to a suitable marketed product at the discretion of the Investigator and this product should be recorded on the Concomitant Diabetes Medication form in the eCRF, as described in section [8.2.5](#). For procedures to be performed at end of treatment (Visit 22), please see flowchart in section [2](#).

At the End of Treatment Visit (Visit 22), the Investigator must fill out the End of Treatment/Trial Form in the eCRF.

8.1.10 Follow-up

The follow-up period is covered by two visits, a 7-day follow-up (Visit 23, FU1) and a 30-day follow-up (Visit 24, FU2) both relative to the end of treatment visit (Visit 22).

8.1.10.1 Follow-up 1 (FU1, Visit 23)

During the 7-day follow-up period (Visit 23) the following information will be collected and recorded in the eCRF:

- AEs
- Concomitant medication
- Concomitant diabetes medication
- Hypoglycaemic events (collected in the Subjects' diary and recorded in the eCRF)
- Infusion site reaction (recorded in the eCRF)
- Unexplained hyperglycaemic events (collected in the Subjects' diary and recorded in the eCRF)

8.1.10.2 Follow-up 2 (FU2, Visit 24)

During the last follow-up period (from day 8 to day 30 after end of treatment) the following will be collected and recorded in the eCRF:

- AEs (including infusion site reactions)
- Concomitant medication
- End of Treatment/ Trial Form

For procedures performed in the follow-up period (Visit 23 and Visit 24), please see flowchart in section [2](#).

8.2 Subject related information

8.2.1 Demography and smoking status

The following demographic data will be obtained by the Investigator and recorded in the eCRF:

- Date of birth (if not permitted according to local laws the year of birth will be collected)
- Age at screening
- Ethnicity (if permitted according to local laws)
- Race (if permitted according to local laws)
- Sex
- Smoking habits
- Use of own CGM

Details of smoking status must be recorded at screening (Visit 1). Smoking is defined as smoking at least one cigarette, cigar or pipe daily. The collected information should include whether or not the Subject smokes or has smoked. For previous smokers, stop dates must be recorded. If the Subject smokes or has smoked, the approximate duration of smoking and the average number of cigarettes per day should be recorded in the Subjects medical records and the eCRF.

8.2.2 Diagnosis of Type 1 Diabetes Mellitus and diabetes complications

At screening (Visit 1) the date of diagnosis of T1DM and information regarding diabetes complications (i.e. diabetic retinopathy/neuropathy/nephropathy and macroangiopathy including peripheral vascular disease) will be obtained and recorded in the Diabetes History/Diabetes Complications Form in the eCRF. Information on diabetes complications, hypoglycaemia unawareness (according to Clarke questionnaire, question 8) and recurrent hypoglycaemia must also be recorded, if present.

8.2.3 Concomitant illness and medical history

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

Any change to a concomitant illness should be recorded on the Concomitant Illness form in the eCRF during the trial. A clinically significant worsening of a concomitant illness must be reported as an AE as described in section [12](#).

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

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

Concomitant illness and medical history must be recorded on the corresponding pages of the eCRF.

8.2.4 Childbearing potential

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

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

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

Pregnancy testing must be performed on females with childbearing potential, as described in Section [8.4.7](#).

The Subjects must be instructed to use contraceptive methods, as described in Exclusion Criterion number 3, throughout the trial and until 1 week after end of treatment.

8.2.5 Diabetes treatment history

Any diabetes medication taken from run-in (Visit 2) to randomisation (Visit 6) must be recorded as diabetes medication in the eCRF including the trade name or generic name, and start date. Any initiation of diabetes treatment during the trial (e.g. in relation to hospitalisation) must be documented in the medical records and entered in the eCRF.

At randomisation (Visit 6) all diabetes medication should be discontinued and a stop date recorded in the eCRF. At end of treatment the marketed insulin product which the Subject is being switched to must be recorded as concomitant diabetes medication in the eCRF including the trade name or generic name, total daily dose and start date.

8.3 Clinical assessments

8.3.1 Concomitant medication

A concomitant medication is any medication, other than trial products and diabetes medication (which should be reported in accordance with section [8.2.5](#)) which is taken during the trial, including in the screening, run-in, and follow-up periods.

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

If a change is due to an AE, then this must be recorded and reported according to section [12](#). If the change influences the Subject's eligibility to continue in the trial, then the monitor must be informed.

8.3.2 Use of Pumps and BG meters

During the trial, from start of the run-in period (Visit 2) until end of treatment (Visit 22), each time the Subjects attends a site visit the following data will be uploaded to CareLink Clinical (a web based database):

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

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

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

Insulin pump data (including supporting metadata, i.e. pump type) to be used to address objectives and endpoints of the trial will be transferred from CareLink Clinical and stored in the trial database. Other pump data used for titration or medical surveillance and will be stored in a Novo Nordisk data repository.

8.3.2.1 Insulin dose

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

During the trial, from start of the run-in period (Visit 2) until end of treatment (Visit 22), the below listed information will be transferred to the trial database. The remaining data will be transferred to a data repository at Novo Nordisk.

Insulin dose data from one day prior to each visit:

- Total daily insulin dose (units of insulin) and date for the day
- Bolus doses
 - Date and time
 - Bolus delivered
 - Bolus programmed
 - Bolus type
 - Bolus duration
- Bolus Wizard[®] events
 - Insulin : carbohydrate ratio(s)
 - Sensitivity factor(s)
 - Active insulin
 - Total bolus estimate
 - Total food estimate
 - Correction estimate
 - Carbohydrate input
 - BG input
 - BG target ranges
 - Low target
 - High target

Insulin dose data from the day of each site visit:

- Basal rate settings
 - Basal delivery rates
 - Date and start times of basal rates

Insulin dose data from all days:

- Temporary basal rate durations and types
- Insulin doses (bolus dose and basal rate) prior to each reported hypoglycaemic and unexplained hyperglycaemic episode (as described in section [8.3.3.1](#) and [8.3.3.2](#))

During the trial, from start of randomisation (Visit 6) until end of treatment (Visit 22), the Investigator must review and adjust the pump settings according to insulin dose adjustment guidelines for insulin pump users^{20,21} to achieve the Subjects' set glycaemic target.

8.3.2.2 Self-measured plasma glucose

At the start of the run-in visit (Visit 2), the Subject will be provided with a BG meter, including lancets, plasma calibrated test stripes for BG meters. The Subject will be instructed verbally on how to use the device according to the manufacturer's instructions. The Subject will also be provided with written instructions. Sites will, as necessary, go through the instructions of use with the Subject during visits to the site.

Throughout the trial, only the BG meter provided by Novo Nordisk must be used to measure the plasma glucose values and to calibrate the blinded CGM when in use, please see section [8.5.1.4](#).

The BG meter uses test strips calibrated to plasma values. Therefore, all measurements performed with capillary blood are automatically calibrated to plasma equivalent glucose values (SMPG), which will be shown on the display. These are the values to be used for dose adjustments.

The BG meter and the pump should be linked by the site personnel at start of the run-in period (Visit 2) by entering the BG meters Identifications number into the pump to ensure SMPGs are automatically transferred to the pump. The BG meter must be set to transfer all SMPG values automatically.

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

The Investigator will be able to review the SMPG profiles in a number of CareLink Clinical reports and use them to evaluate the Subject's glycaemic control and make adjustments to the pump settings in order to optimise insulin titration.

Site personnel will review the diary data, compare it to the CareLink Clinical report, and enter the reconciled SMPG values related to hypoglycaemic episodes and unexplained hyperglycaemic episodes into the eCRF during the site visit.

If clarification of entries is needed or discrepancies between diary and report are found, the Subject must be questioned and a conclusion made in the Subject's medical record or in the CareLink Clinical Report.

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

- If a SMPG value is ≤ 3.9 mmol/L [70 mg/dL], the Subject should record the hypoglycaemic episode, as detailed in section [8.3.3.1](#)
- If a SMPG value is > 3.9 mmol/L [70 mg/dL], but the Subject feels typical symptoms of hypoglycaemia and interprets those as indicative of hypoglycaemia but with a SMPG value > 3.9 mmol/L [70 mg/dL], as detailed in section [8.3.3.1](#)

- If an SMPG value is ≥ 16.7 mmol/L [300 mg/dL], the Subject should record the unexplained hyperglycaemic episode, if applicable according to section [8.3.3.2](#)

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

4-point self-measured plasma glucose profile

Subjects will be instructed to perform 4-point profiles every day during the conduct of the trial (from Visit 2 to Visit 22). While wearing the CGM the Subject will continue to perform 4-point profiles and must be instructed to use at least two of these measurements for calibration of the CGM. The SMPGs should be measured at the following time points:

- Before breakfast
- Before lunch
- Before main evening meal
- At bedtime

SMPG measurements before breakfast should be performed in a fasting condition. SMPG measurements before lunch, main evening meal, and at bedtime should be performed before any bolus insulin infusion. The 4-point profile is part of the 7-7-9-point profiles.

The 4-point profiles will be recorded mainly for insulin titration purposes.

7-7-9-point self-measured plasma glucose profile

The Subject will be instructed to perform a 7-7-9-point profile before selected visits; please see the flowchart in section [2](#).

Measurement of the 7-7-9-point profile should be performed on the three consecutive days just before the visit as detailed in [Table 8-1](#).

Table 8–1 7-point profiles with the additional 9-point profile

Time point	Day -3 7-point profile	Day -2 7-point profile	Day -1 9-point profile	Day of visit
Before breakfast	X	X	✓	✓
60 mins after the start of breakfast	X	X	✓	
Before lunch	X	X	✓	
60 mins after the start of lunch	X	X	✓	
Before main evening meal	X	X	✓	
60 mins after the start of main evening meal	X	X	✓	
At bedtime	X	X	✓	
At 4 AM			✓	

(7-point profiles indicated as X and the 9-point profile indicated as ✓)

The 7-7-9-point profiles will be used for effect analysis of the trial. The 7-7-9 profile will be identified based on Subject's meal and bed time. An algorithm will be developed in order to select the appropriate SMPG measurements from the data transferred from CareLink Clinical using meal and bed times from the Subject's diary.

The Investigator must review the CareLink Clinical report and ensure that SMPG values, that correspond to the mealtimes and bedtimes entered in the Subject's diary, are present. If it is evident from the review that the Subject has only taken the daily required 4-point SMPG profile, then the Subject should be asked to perform the 7-7-9-point SMPG profile at the next possible opportunity along with recording the dates and times of the corresponding days' meals and bedtimes. The review will be documented by signing and dating the CareLink Clinical reports.

8.3.2.3 Change of infusion set and reservoir

Infusion sets (Medtronic Quick-Set[®], Medtronic Mio[®], Medtronic Silhouette[®] or Medtronic SureT[®] (Easy-set[®])) and reservoirs (1.8/3.0 mL) will be provided by Novo Nordisk. Infusion sets and reservoirs will be dispensed at site visits indicated in the flowchart in section 2. The type of infusion set and size of reservoir should be recorded in the eCRF at each dispensing visit.

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

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

The Subject should change infusion set and reservoir at the site under supervision by the Investigator at randomisation (Visit 6) and at end of treatment (Visit 22) due to the change from pre-trial insulin to trial product. The Investigator should evaluate the skin for any local skin irritation or skin infection at every visit at the clinic. Any abnormal clinically significant findings should be recorded as an infusion site reaction, as detailed in section [8.3.3.3](#).

The Subject should be instructed to record all infusion set change in their diary. Investigator should ensure that instructions for change are being followed by reviewing the CareLink Report. The review must be documented by signing the CareLink Report. Infusion set changes can be considered as a 'routine change' or 'non-routine change'.

Routine change

A routine change of the infusion set and reservoir is defined as a regular change performed in no more than 3-days intervals (2 days for SureT[®] (Easy-set[®])). Infusion set change at site in the morning the day before randomisation (Visit 6) and end of treatment (Visit 22) are considered a routine change. All infusion set changes due to Subject's decision and not due to any problem with the pump, the infusion set or glucose values (e.g. inconvenient location of infusion set) must be considered a routine change.

Non-routine change

A non-routine change is defined as any change of infusion set and reservoir not fulfilling the criteria for a routine change.

Infusion sets and reservoirs must be replaced if any change in the insulin solution or occlusion is perceived by the Subject, e.g. because of a pump alarm indicating an occlusion or other observations pointing towards obstruction of the insulin flow. For every perceived occlusion the Subject must:

- Check the perceived occlusion with an air shot of at least 10 units of insulin performed using the pump's manual bolus option

Collection of infusion set change information

All infusion set changes from Visit 2 to Visit 22 will be collected in the Subjects' diary. For all infusion set and reservoir changes the Subject must record the following in the diary:

- The date and time of change
- Was the infusion set and reservoir change considered a routine change (Yes/No)?

In case the above question is answered "Yes" and the infusion set is changed prior to the 3 days (2 days for SureT[®] (Easy-set[®]), the Subject should confirm that the change was not due to any of the reasons listed below.

In case the above question is answered "No" the Subject must choose one main reason from the below ("a" to "f") and record the following in the diary.

Was the change due to any of the following:

- a) A **perceived occlusion** by the Subject
 - Was an air shot performed? (Yes/No)
 - Was there any insulin flow when an air-shot was performed (Yes/No)?
 - Did a 'No delivery' alarm sound (Yes/No)?
 - Was there a visible plug obstructing the flow (Yes/No)?
- b) Changes in the **insulin solution in the infusion set or reservoir** (e.g. any visual change in colour or presence of particles) ?
- c) Any problems related to the **infusion set** (e.g. leakages, dislodging of infusion set, large air bubbles etc.)?
- d) Any **infusion site reactions** (The Subject should be instructed to contact the site in case of any infusion site reactions; please see section [8.3.3.3](#))
- e) Any **technical issues** with the pump (Yes/No)
 - Did an alarm sound (Yes/No)?
 - If "Yes", specify the alarm
- f) Persistent **high BG** with no other explanation and not covered by any of the reasons above, which made the Subject change the infusion set (Yes/No)? A persistent high BG is defined as a high SMPG level not decreasing by at least 2.8 mmol/L (50 mg/dL) an hour after a

correction bolus. If the episode fulfils the criteria for unexplained hyperglycaemia an Unexplained Hyperglycaemia Form should be completed by the Subjects, as detailed in section [8.3.3.2](#).

The Investigator or delegated site personnel must review all changes and verify that the time and date registered in the diary corresponds to the pump data.

The Investigator should check the CareLink Clinical reports for “no delivery alarms” and ensure infusion set changes performed due to “no delivery alarms” have been reported in the diary.

8.3.2.4 Training in pump use

At start of the run-in period (Visit 2), the Investigator should ensure that the Subject knows how to use the insulin pump and perform appropriate training. The Investigator will, as necessary, repeat the training at all visits (Visit 2 to Visit 22) to the site. The Investigator should ensure that the Subjects know about the following:

- How to set the time and date on their pump
 - Importance of maintaining the correct time and date (e.g. when traveling or entering time changes due to daylight savings)
- How to ensure the SMPG values are recorded in the pump
- Pump settings including settings for basal rates and bolus doses
- Dose adjustment of insulin and use of Bolus Wizard[®]
- When to perform a routine and non-routine change of infusion set and reservoir
 - How to perform an air-shot
- How to report infusion set change information
- Filling reservoir from vials including priming of infusion set and checking for air in the infusion set before insertion of reservoir
- Carbohydrate counting
- Troubleshooting in case of hypoglycaemia and hyperglycaemia
- When and how to measure ketones (see section [8.3.3.2](#))
- Troubleshooting in case of pump failure or any technical problems with the pump

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

8.3.2.5 Training in diabetes and carbohydrate counting

During the run-in period, all Subjects should have reinforced diabetes training including carbohydrate counting e.g. sessions with a diabetes educator, dietician or qualified site staff (i.e. diabetes specialised nurse) according to local practice.

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

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

8.3.2.6 Back-up kit

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 Subject 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
- Extra infusion set (including inserter) and reservoir
- Syringes for injection of insulin (for use with vial)
- Fast acting glucose preparation (e.g. tablets or powder)
- Glucagon for injection (reimbursed by Novo Nordisk affiliate, or supplied by the central lab in Russia)
- Extra vial with the Investigational Medical Product (IMP) the Subject is randomised to
- Extra battery for the insulin pump
- Urine sticks for ketone monitoring

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

8.3.3 Adverse events requiring special forms in the electronic case report form

For some AEs the Investigator must fill in special forms in the eCRF. The AEs that require special forms in the eCRF are:

- Hypoglycaemic episodes; (section [8.3.3.1](#))
- Unexplained hyperglycaemic episodes; (section [8.3.3.2](#))
- Infusion site reactions; (section [8.3.3.3](#))
- Medication errors (MESIs); (section [12.1.4](#))

8.3.3.1 Hypoglycaemic episodes

Plasma glucose should always be measured and recorded by the Subject in the diary, when a hypoglycaemic episode is suspected.

All plasma glucose 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 in the diary according to the instructions below throughout the trial from Visit 2 to Visit 23.

Upon onset of a hypoglycaemic episode the Subject is recommended to measure plasma glucose every 15 minutes until the SMPG value is > 3.9 mmol/L (70 mg/dL) or symptoms have been resolved in accordance to current guidelines²⁹.

A SMPG value ≤ 3.9 mmol/L (70 mg/dL) or hypoglycaemic symptoms must trigger a Hypoglycaemic Episode form to be completed by the Subjects in the diary. Repeated SMPG measurements and/or symptoms will per 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. One Hypoglycaemic Episode form is to cover these measurements and/or symptoms. However, each Hypoglycaemic Episode form will cover a period of maximum 60 minutes after onset of a hypoglycaemic 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 SMPG value and/or symptom.

If a new low SMPG value is measured or the Subject still has symptoms more than 60 minutes after the first reported low SMPG value and/or symptom it is considered as a new hypoglycaemic episode and a new hypoglycaemic episode form is to be filled in.

Information on the hypoglycaemic episode will be collected partly in Subject's diary (please refer to ^A in below bulleted text) and partly recorded by the pump automatically (please refer to ^B in below text) The Investigator or designated site personnel must complete the Hypoglycaemic Episode form in the eCRF for each hypoglycaemic episode by collecting relevant data from the Subject's diary and from the CareLink Clinical Reports. If for any reason the required data is not present in CareLink Clinical the Subject's diary data can be considered as the source data.

At each contact the Investigator must review the CareLink Clinical Report showing low SMPG values to ensure consistency with the hypoglycaemic episodes reported in the Subject's diary (reconcile). For each hypoglycaemic episode identified in the CareLink Clinical report the Investigator must record a Hypoglycaemic Episode form in the eCRF.

If clarification of entries is needed or discrepancies between diary and report are found, the Subject must be questioned during the site visit and a conclusion recorded in the Subject's medical record or in the CareLink Clinical Report.

The Subject must be questioned whether any of the low SMPG values listed in the CareLink Clinical report and not reported in the diary were severe i.e. whether the Subject was able to treat him/herself or not. If the Subject was not able to self-treat it has to be reported as a severe hypoglycaemic episode on a Hypoglycaemic Episode form in the eCRF.

Low SMPG values found in the CareLink Clinical report, for non-severe hypoglycaemic episodes not having a Hypoglycaemic Episode form completed within 7 days since the SMPG measurement 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 date, SMPG value and whether the Subject was able to self-treat or not, due to decreased validity of such data^{30,31}.

The Subject must be re-trained in how to report hypoglycaemic episodes if the Investigator identifies low SMPG values not reported as hypoglycaemic episodes. The CareLink Clinical report must be signed and dated by the Investigator to document that the cross-checking with the diary has been performed.

The eCRF Hypoglycaemic Episode form should include the following information:

- Start date and time of hypoglycaemic episode^A
- The SMPG value before treating the episode (if available) and any follow up measurements^B
The lowest value measured during the hypoglycaemic episode will be reported as the plasma glucose value for the episode.
- Whether the episode was symptomatic (Yes/No)^A
A hypoglycaemic episode starting without symptoms should be updated to symptomatic if the Subject experience symptoms later during the episode.
- Whether the Subject was able to treat him/herself^A
If the severity of a hypoglycaemic episode aggravates, only one hypoglycaemic episode should be reported reflecting the most severe degree of hypoglycaemia.
- Date and time of last main meal prior to episode^A
- Whether the episode occurred in relation to physical activity^A
- Any sign of fever or intercurrent disease?^A
- Whether the Subject was asleep when the episode occurred?^A
 - If “Yes”, whether the symptoms of the episode woke up the Subject

^A collected on the Subjects diary and entered in the eCRF

^B to be retrieved from the CareLink Clinical report and entered in the eCRF

The following information related to each hypoglycaemic event will be retrieved directly from the insulin dose data transferred from the pump into the trial database:

- Date and time and dose of last basal rate change prior to episode
- Date, time, type (meal bolus, correction or combination) and dose of last bolus insulin administration prior to episode

The answer to the question: "Was 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. SMPG concentrations may not be available during an event, but neurological recovery following the return of SMPG to normal is considered sufficient evidence that the event was induced by a low SMPG concentration.

Oral carbohydrates should **not** be given if the Subject is unconscious.

If the question "Was Subject able to treat him-/herself?" is answered "No", the following information should be recorded (recorded in the Subjects' diary, to be entered in the eCRF):

- Who assisted in the treatment of the hypoglycaemic episode (i.e. medical person or non-medical person)? ^A
- Where the treatment was administered (i.e. in clinic/emergency room/hospital or other if the Subject was treated in a clinic/emergency room/hospital, whether they were transported in an ambulance or not)? ^A
- Type of treatment provided by other person (i.e. oral carbohydrates, glucagon, intravenous glucose or other)? ^A
- Were symptoms alleviated after administration of treatment? ^A
- Factors contributing to the episode (i.e. physical activity, missed meal, diet changed, medication error (i.e. overdose, mix-up between products), miscalculation of insulin dose, other factors not listed, or unknown)? ^A
- Did the Subject experience seizure? ^A
- Was the Subject unconscious/comatose? ^A
- Did the Subject experience any of the following symptoms (layman term used in the diary is specified in brackets if different from the protocol term)³²? ^A
 - Autonomic: sweating, trembling, hunger or palpitations (rapid or irregular heart beat)
 - Neuroglycopenic: confusion, drowsiness, speech difficulty, visual disturbances, odd behaviour, impaired balance or incoordination (reduced ability to coordinate movement)
 - General malaise: headache or malaise (feeling discomfort/unease)
 - Other symptoms? ^A

In the Subjects diary the above questions will be formulated in layman language which is indicated in brackets.

If the Subject experiences a severe hypoglycaemic episode the Subject should be instructed to contact the site staff as soon as possible after recovery for further guidance on titration.

If the hypoglycaemic episode fulfils the criteria for an SAE and/or a medical event of special interest (MESI) then an AE form and a safety information form (SIF) must also be filled in, see section 12. On the SIF, the following information must be reported by the investigator:

- Date and time and dose of last basal rate change prior to episode
- Date, time, type (meal bolus, correction or combination) and dose of last bolus insulin administration prior to episode

8.3.3.2 Unexplained hyperglycaemic episodes

Any unexplained hyperglycaemic episode with SMPG values ≥ 16.7 mmol/L [300 mg/dL] and no apparent explanation (i.e. no apparent medical, dietary, insulin dosage, or pump failure reason) must be recorded in the Subjects' diary. Symptoms should be treated in accordance with instructions from Investigator. If the Subject is referred to any clinic/hospital, elevated urine ketone levels should be confirmed by blood ketone measurements and the result should be recorded in the eCRF.

Information on the hyperglycaemic episode will be collected partly in Subject's diary (please refer to ^A in below text), partly recorded by the pump automatically and entered by the Investigator into the eCRF (please refer to ^B in below text) from Visit 2 to Visit 23. If for any reason the required data is not present in CareLink Clinical the Subject's diary data can be considered as the source data.

The Investigator must review the CareLink Clinical Reports in conjunction with the Subjects diary (reconcile) and ensure that the unexplained hyperglycaemic episodes reported in the diary are present in the report. For each unexplained hyperglycaemic episode (present in the diary and the report) the Investigator must complete the Unexplained Hyperglycaemic Episode form in the eCRF. To document this reconciliation the Investigator must date and sign the CareLink Clinical Report. If clarification of entries is needed or discrepancies between diary and report are found, the Subject must be questioned and a conclusion made in the Subject's medical record or in the CareLink Clinical Report.

The Unexplained Hyperglycaemic Episode Form should include:

- Date and time of unexplained hyperglycaemic episode ^A
- The SMPG level before treating the episode (if available) ^B
The highest value measured during the hyperglycaemic episode will be reported as the plasma glucose value for the episode.
- Result from urine ketone test, if available (trace, small, moderate, and large) or negative ^A
- Date and time of last main meal prior to episode ^A

^A collected on the Subjects diary, to be entered in the eCRF

^B to be retrieved from the CareLink Clinical report and entered in the eCRF

The following information related to each unexplained hyperglycaemic event will be retrieved directly from the insulin dose data transferred from the pump into the trial database:

- Date and time and dose of last basal rate change prior to episode
- Date, time, type (meal bolus, correction or combination) and dose of last bolus insulin administration prior to episode

If the unexplained hyperglycaemic episode fulfils the criteria for an SAE, then a SIF must also be filled in accordance to section [12](#). On the SIF, the following information must be reported by the investigator:

- Date and time and dose of last basal rate change prior to episode
- Date, time, type (meal bolus, correction or combination) and dose of last bolus insulin administration prior to episode

Multiple (>1) unexplained hyperglycaemic values of SMPG ≥ 16.7 mmol/L (300 mg/dL) are considered as one unexplained hyperglycaemic episode until the SMPG is <16.7 mmol/L (300 mg/dL). One episode is set to a maximum of 24 h for the first SMPG ≥ 16.7 mmol/L (300 mg/dL).

All hyperglycaemic episodes that are not unexplained should be reported as AEs in accordance to section [12](#) if the Investigator judges that the hyperglycaemic episode is clinically significant.

8.3.3.3 Infusion site reactions

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

Infusion site reactions at the site of trial product(s) administration must be recorded as an AE and on an Infusion Site Reaction form in the eCRF throughout the trial from start of run-in period (visit 2) to 7-day follow-up (visit 23) and as AEs at follow-up phone contact (visit 24). By questioning the Subject the Investigator should obtain the following information and record it in the eCRF:

- Previous allergy. If “Yes”, specify
- History of current reaction(s):
 - Was the skin normal before the event? (Yes/No) If “No”, specify
 - Time of appearance of the reaction after infusion set change
 - Associated local symptoms (burning, pain, numbness, itching etc.)
 - Duration of reaction
 - Have the symptoms been relieved? (Yes / No)
 - The time and date of the last infusion set change prior to the episode
- Clinical evaluation and detailed description including:
 - The time between appearance of infusion site reaction and Investigator inspection of the reaction
 - 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)
 - Was the product stored according to recommendations
 - Was the infusion site reaction related to the tape/adhesive
- Dermatological description of the reaction (redness, swelling, macula, haematoma, bleeding etc.)
- 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)

The Investigator has to evaluate whether further actions are needed (e.g. extra visits, discontinuation from trial product, dermatologist consultation).

8.3.4 Body measurements

All values of the body measurements will be recorded in the eCRF.

Height (without shoes) will be measured by the Investigator at screening (Visit 1) only and recorded rounded to the nearest centimetre (cm) or inch (in).

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

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

BMI will automatically be calculated by the eCRF.

8.3.5 12 lead-Electrocardiogram

An ECG-12 lead must be performed locally. The ECG must be interpreted by the Investigator, and documented by Investigator signature and date on the ECG print-out. The Investigator must write the interpretation of the ECG in the eCRF.

The evaluation must follow the categories:

- Normal
- Abnormal
 - Clinically significant? (Yes/No)

Any abnormal and/or clinically significant findings at screening (Visit 1) must be recorded on the Concomitant Illness/Medical History form in the eCRF.

Any clinically significant deterioration as well as any new clinically significant signs or symptoms should be reported as an AE in accordance with section [12](#).

If an ECG-12 lead has already been performed within three weeks before screening (Visit 1), and if the results are available at the screening visit, the procedure does not need to be repeated. However, if clinically warranted as judged by the Investigator, the ECG-12 lead should be repeated. If performed before the Subject consents to participate in the trial it must also be stated in the Subject's medical records that this procedure was not performed in relation to the trial.

ECGs performed three weeks in advance of the remaining visits as specified in the flowchart in section [2](#) are acceptable if the results are available at the scheduled visit.

8.3.6 Eye examination

Fundus photography or dilated fundoscopy must be performed by the Investigator, a local ophthalmologist, or an optometrist according to local practice. The result of the fundus photography or dilated fundoscopy will be interpreted locally by the Investigator and must be available prior to run-in (Visit 2). To document this, the Investigator must sign and date the result page and write the interpretation in the eCRF.

The evaluation must follow the categories:

- Normal
- Abnormal
 - Clinically significant? (Yes/No)

Any abnormal and/or clinically significant findings at screening must be recorded on the Medical History/Concomitant Illness Form in the eCRF.

Any clinically significant deterioration as well as any new clinically significant signs or symptoms should be reported as an AE in accordance with section [12](#).

If fundus photography or dilated fundoscopy has been performed within 90 days before screening (Visit 1) and if the results are available at the screening visit, the procedure does not need to be repeated. However, if clinically warranted the fundus photography or dilated fundoscopy should be repeated at screening (Visit 1). If performed before the Subject consents to participate in the trial, it must also be stated in the Subject's medical records that this procedure was not performed in relation to the trial.

Fundus photography or dilated fundoscopy performed within three weeks in advance of Visit 22 is acceptable if the results are available at the scheduled visit.

8.3.7 Meal test

The Subject will undergo a standardised liquid meal test at certain visits (see section [2](#)) and will have their 30 minute and 1 to 4 hour PPG measured. During that time 6 blood samples will be drawn, as specified in the [Table 8-2](#). The samples will be analysed by the central laboratory and the values transferred directly into the trial database.

The Subject must attend the meal test visits in a fasting condition, as detailed in section [8.1.7](#). Bolus infusion and other medication which should be taken before, in a relation to or after a meal should be withheld until the meal test has been performed.

The Subject should before the meal test be instructed to:

- Follow normal routine regarding eating and exercise habits on the day prior to the meal test
- Refrain from intake of alcohol and use of medications that affect motility (i.e. prokinetics, anticholinergics, tricyclic antidepressants) on the day prior to the meal test, unless the Subject was on this medication at trial entry and does not change the product or product dose
- Not to make any changes in the current basal rate setting 4 hours prior to the meal test
- Measure a SMPG value at 4 AM the night before and in the morning before the meal test. The 4 AM SMPG value and before-meal-test SMPG value is part of the 9-point profile
- Change infusion set and reservoir in the morning the day before the meal test
- Continue to wear the CGM device until end of meal test
- Take a correction bolus according to guidance from Bolus Wizard[®] if the PG value above the target level

There should be a minimum of four hours between any correction bolus dose and the start of the meal test.

Any hypoglycaemic episodes from midnight before the meal test should be treated and the hypoglycaemic episode should be recorded in the diary, please see section [8.3.3.1](#). In this case, the meal test should be re-scheduled within the visit window and at Visit 6 before randomisation to trial product.

The Subject should have SMPG values within a range of 4.0-8.8 mmol/L [71-160 mg/dL] before beginning the meal test and bolus insulin dosing. The SMPG values should be verified and recorded at the site before starting the meal test. If the Subject is not fasting or the SMPG value is outside the range, the meal test should be rescheduled within the visit window.

At randomisation (Visit 6) the Investigator must evaluate the Subjects' eligibility to continue in the trial before the meal test is performed. Only Subjects eligible for randomisation should have the Visit 6 meal test performed. Thus, this assessment should not be performed for run-in failure Subjects. Randomisation (Visit 6) should not take place until the meal test has ended.

The Subject's body weight must be measured and a blood sample must be drawn two minutes before intake of the standardised liquid meal. The bolus insulin dose should be calculated by the Investigator based on the dose level of 0.1 unit/Kg body weight. The calculated dose should be rounded to the nearest whole unit. The 0.1 unit/kg dose is chosen as an approximation of a clinically relevant bolus dose needed for the given size of a standardised meal for T1DM. Only a normal bolus type is allowed. The Investigator must review the pump settings before the start of the meal in accordance to section [8.3.2.1](#). The start of bolus infusion will be defined as time point 0. The Subject will have a carbohydrate-rich standardised meal served immediately after bolus infusion and must consume this as quickly as possible (within 12 minutes). The Investigator should confirm that the Subject consumed the required volume of the standardised liquid meal in the eCRF and actual clock time of start of infusion and meal consumption should be noted.

The standardised meal will be provided by Novo Nordisk. The volume of the standardised meal to be consumed should be measured out by the Investigator to be the equivalent to 78 grams of carbohydrate.

Table 8–2 Meal test for Visit 6 and Visit 22

Time point – minutes	Bolus insulin infusion / Standardised meal	Blood sample (PG)*	SMPG values
Before start of meal test			X (within target range 4.0-8.8 mmol/L [71-160 mg/dL])
-2		X	X (as appropriate to ensure Subject's safety)
0	X		
30		X	
60		X	
120		X	
180		X	
240		X	
End of meal test			X (Subject's safety)

*All blood samples must be sent to the central laboratory for analysis

Laboratory results from meal test data will be loaded directly into the trial database by the central laboratory. The meal test results will not be provided to the Investigator until after EoT (Visit 24).

The Subject should wait in the clinic to have the blood samples drawn after 30 minutes, 1, 2, 3 and 4 hours from the start of the standardised meal, as detailed in [Table 8–2](#). During the meal test the Subject should be resting in a chair. No smoking or intake of meals and liquids will be allowed during the meal test, except for water, which is allowed two hours after intake of the standardised meal.

If SMPG values ≤ 3.9 mmol/L [70 mg/dL] are measured then the hypoglycaemia should be treated according to local practice and the meal test should continue according to the Investigator's discretion. The hypoglycaemic episode must be reported. Please see section [8.3.3.1](#).

The following must be recorded in the eCRF in relation to the meal test:

- Fasting status
- Time and value of SMPG measurement confirming that the Subject's glucose is within the target of 4.0-8.8 mmol/L (71-160 mg/dL)
- Body weight
- Start and end-time of standardised meal
- Volume and carbohydrate content of standardised meal consumed
- Confirmation that the Subject consumed the required volume of the standardised meal
- Batch number of standardised meal consumed
- Time of blood samples
- Hypoglycaemic episode number, if relevant
 - Time of intervention and amount of glucose rescue treatment

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

When the meal test is finished, the Novo Nordisk provided CGM device should be removed and data uploaded to the computer by the Investigator, please see section [8.5.1.5](#).

When the meal test at randomisation (Visit 6) is completed, the Subject will be instructed to discontinue their current insulin and start treatment with randomised trial product. When the meal test at the end of treatment (Visit 22) is completed, the Subject will be switched to a marketed insulin product according to Investigator's discretion as detailed in section [5.5](#).

The treatment should be initiated after the meal test and the Subjects must change infusion set and reservoir before the Subject leaves the site.

8.3.8 Physical examination

The physical examination will be performed as outlined in the flow chart (section [2](#)). Physical examination will include examination of:

- The respiratory system
- The cardiovascular system
- The central and peripheral nervous system
- The gastrointestinal system, including the mouth
- The musculoskeletal system
- The skin
- The head, ears, eyes, nose, throat and neck

Any abnormal and/or clinically significant findings at screening (Visit 1) must be recorded on the Concomitant Illness Form/Medical History in the eCRF, please see section [8.2.3](#), and the Investigator must add a comment in the Subject's medical record.

Any clinically significant worsening from screening, as well as any new abnormal and clinically significant findings, must be reported as an AE in accordance with section [12](#).

8.3.9 Vital signs

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

Vital signs will be assessed according to the flow chart, please see section [2](#). At screening (Visit 1) blood pressure needs to be measured three times and all values should be recorded in the eCRF. The

mean value will be calculated by the eCRF, and must be evaluated against the relevant exclusion criterion; please see section [6.3](#).

Any abnormal and/or clinically significant findings at screening (Visit 1) must be recorded on the Concomitant Illness/Medical History form in the eCRF.

Any clinically significant deterioration of a pre-existing condition, as well as any new clinically significant signs or symptoms, should be reported as an AE in accordance with section [12](#).

8.4 Laboratory assessments

Except for urine pregnancy testing, ketone measurements (blood/urine, in case of a hyperglycaemic episode) which will be performed locally, all laboratory analyses will be performed by a central laboratory contracted by Novo Nordisk. The central laboratory will provide all laboratory supplies for the sampling and transportation of all blood and urine samples taken during the trial. The central laboratory may utilise subcontractors.

A detailed description of the assay methods, reference ranges and procedures for obtaining the samples, handling, storage and shipment of the samples are specified in a trial-specific laboratory manual provided to the sites by the central laboratory. Information regarding laboratory materials such as tubes and labels are also described in there.

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

If laboratory samples need to be retaken due to missing result(s) (e.g. haemolysed, sample leaked during transit, sample not being conclusive, lost in transit, etc.), the Subject should be called in for resampling. Please see the laboratory manual for further guidance. The repeated blood sampling must be marked with the related visit number and missing lab measurements. The laboratory sample date must be recorded in the eCRF should reflect the actual date of sampling (i.e. the actual visit date will differ from the assessment date under the same visit.)

Only laboratory samples specified in the protocol should be sent to the central laboratory for analysis. If additional laboratory sampling is needed, e.g. to follow up on AEs, this should be done at the local laboratory. Samples for the central laboratory will be coded in order to keep Subject's identity anonymous.

Laboratory results will be made available by the central laboratory. The laboratory provides results to the trial sites in the units preferred by the trial sites while the results that are transferred to the trial database will always be in SI units.

Final laboratory reports must be reviewed, dated and signed by the Investigator on the day of evaluation. It must be specified by the Investigator whether out of range results are clinically significant.

If any clinically significant abnormalities occur at screening (Visit 1) and for lipids at randomisation (Visit 6), then these must be recorded on the Concomitant Illness/Medical History form in the eCRF. Any clinically significant deterioration of a pre-existing condition as well as any new clinically significant signs or symptoms should be reported as an AE in accordance with section [12](#).

Laboratory equipment in the central laboratories may provide standard 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 available laboratory results for concomitant illnesses and AEs and report these according to this protocol. The review of laboratory reports must be documented either on the front page of the documents and/or in the Subject's medical record.

Laboratory samples will be destroyed after analysis on an ongoing basis.

8.4.1 1,5-anhydroglucitol

Blood samples will be drawn to determine the level of 1,5-anhydroglucitol in order to evaluate postprandial glycaemic fluctuations. The analysis will be performed by the central laboratory. Sampling timings are indicated in the flow chart, please see section [2](#).

8.4.2 Biochemistry

Blood samples for biochemistry will be analysed to determine:

- ALT
- AST
- Albumin
- AP
- Creatinine
- Estimated glomerular filtration rate (eGFR)
- Potassium
- Sodium
- Total bilirubin
- Total protein

8.4.3 Fasting plasma glucose

FPG is measured in order to evaluate glycaemic control. The Subject must attend visits fasting. Please see section [2](#). For definition of fasting, please see section [8.1.7](#).

A FPG result ≤ 3.9 mmol/L (70 mg/dL) should not be reported as a hypoglycaemic episode but as a clinical laboratory adverse event (CLAE) at the discretion of the investigator (see Section [12.1.1](#)).

8.4.4 Haematology

Blood samples for haematology will be collected as indicated in the flow chart (section [2](#)) and analysed to determine:

- Erythrocytes
- Haematocrit
- Haemoglobin
- Leucocytes
- Thrombocytes

8.4.5 HbA_{1c}

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

8.4.6 Lipids

Blood samples for lipids will be as specified in the flow chart (section [2](#)) analysed to determine:

- Total cholesterol
- High density lipoprotein (HDL)
- Low density lipoprotein (LDL)

8.4.7 Pregnancy testing

For females of childbearing potential (for definition please see section [8.2.4](#)), a blood human Chorionic Gonadotropin (hCG) pregnancy test will be performed at the visits, as detailed in the flowchart in section [2](#). In addition, urine pregnancy tests will be performed locally during the trial if a menstrual period is missed or if deemed necessary by the Investigator or required by local law. A positive urine pregnancy test should be followed by a confirmatory serum-hCG (central laboratory).

The central laboratory will provide the pregnancy kits for urine testing performed locally at the site.

8.4.8 Urine samples

A urine dipstick microscopic analysis of the following parameters will be performed:

- Albumin/creatinine ratio
- Erythrocytes
- Protein
- Ketones

In case of a clinically significant positive outcome of the dipstick analysis, a microscopic urine analysis will be performed.

8.5 Other assessments and procedures

8.5.1 Continuous glucose monitoring

As indicated in the flow chart in section [2](#), all Subjects will have CGM profiles generated for 11 to 13 consecutive days in three periods during the trial. The profiles will be generated by a FDA approved and European Union European Conformity (CE) labelled CGM device, developed for continuous monitoring of glucose levels in persons with diabetes mellitus.

The CGM device will be blinded to the Subject during the CGM period. Upon upload of CGM data at site, the Investigator or delegated staff should review the CGM data and document this according to section [8.5.1.5](#). The CGM data must remain blinded to the Subject prior to End of Treatment visit (V22). The CGM values generated must not be used for insulin dose titration or for hypoglycaemic event reporting, unless otherwise supported by SMPG values.

8.5.1.1 CGM Receiver setting and test upload

The CGM Receiver must be set up before use. The set up includes: date and time setting, entry of CGM Transmitter ID and blinding of the CGM Receiver. Upon set up of the CGM Receiver a test

upload must be performed by the site personnel to verify correct installation of CGM software and correct set up of the CGM Receiver.

Upon set-up of the test upload a CGM device status report will be available in the CGM Software system. The CGM device status report shows the CGM Receiver serial number, the CGM Transmitter Id, the blinded status, the clock accuracy and verification that no data exists on the CGM Receiver prior to use.

The CGM device status report should be printed out, dated and signed by the Investigator and filed as a source document in the Investigator's trial master file.

8.5.1.2 Eligibility for baseline continuous glucose monitoring

The first fitting visit in the first CGM period (during run-in period Visit 2 - 6) has to be planned from 11 to 13 days prior to the randomisation visit in order to register baseline CGM data while the meal test is performed at Visit 6.

If the Subject is not eligible to continue the meal test should not be performed at randomisation (Visit 6).

At the first fitting visit, the Investigator must ensure that the Subject is eligible to continue in the trial, before the CGM device is fitted.

8.5.1.3 Fitting and removal of the continuous glucose monitoring device

The first fitting visit in the second CGM period (during treatment Visit 6 - 14) has to be planned from 11 to 13 days prior to Visit 14 in order to register treatment CGM data while the meal test is performed at Visit 14. The CGM device should be fitted to the Subject at the site. The Subject should perform CGM calibration with SMPG values beginning two hours after the device is fitted.

The first fitting visit in the third CGM period (during treatment Visit 14- 22) has to be planned from 11 to 13 days prior to Visit 22 in order to register treatment CGM data while the meal test is performed at Visit 22. The CGM device should be fitted to the Subject at the site. The Subject should perform CGM calibration with SMPG values beginning two hours after the device is fitted.

If a Subject withdraws consent, a site visit must be scheduled in order to stop the CGM sensor measurement and have the CGM device removed from the Subject.

The CGM sensor has an in-use period of seven days. The CGM device will automatically stop recording data exactly 7 days after sensor insertion. Therefore a second sensor will have to be fitted to the Subjects after the first seven days period in order to obtain 11 to 13 days data. This should be taken into account when scheduling the Subject visits. The CGM device should be worn for at least 11 days by each Subject and should be planned so the Subject wear the CGM during the meal test.

Additional fitting of sensors can be planned if the meal test assessment has to be rescheduled more than seven days after the second fitting visit, which means the Subject can be on CGM for more than 13 days. If the sensor is dislodged and needs to be replaced or if a visit window must be accommodated, additional fitting of sensors can be planned as well. In case of sensor is dislodged, the Subject must contact site in order to schedule a new fitting at site or at home according to the Investigator's judgement.

The meal test must not be scheduled on the first or seventh day after having fitted the second sensor. Hence the fitting of the sensors must be scheduled accordingly and as a minimum one day before the meal test visit; please see [Table 8–3](#). The rationale for this is: firstly, the sensor will not start measuring IG until after the 2-hour start-up calibration on the first day, and the Subject will have to wait two hours after the sensor insertion before the meal test can start. Secondly, the risk of the CGM device stopping before or during the meal test is possible as the CGM device will automatically stop recording data exactly seven days after sensor insertion.

Table 8–3 Overview of scheduled CGM sensor fitting and removal days relative to meal test based on two sensor periods

Visit	V4/V12/V20 (±3 days)							P5/P13/P21 (±3 days)									V 6/ V22(A [*])	
Days	-17	-16	-15	-14	-13	-12	-11	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	0
Procedure					Schedule Fitting 1							Schedule Removal 1 and Fitting 2						Meal test and Removal 2

*Fitting and removal need to be scheduled as soon as the Investigator becomes aware of premature discontinuation of trial product of a Subject.

During the fitting visit, the Investigator will insert a glucose sensor under the Subject's skin, measuring the concentration of glucose in the interstitial fluid every five minutes. The sensor is attached to a transmitter and both are worn by the Subject. The transmitter will transfer the IG data automatically to the receiver where data is stored.

Removal of the first sensor and fitting of the second sensor can be performed at home by the Subject if the Subject has been trained and is able to perform it correctly; according to the Investigator judgment.

In order to ensure that the CGM device is measuring correctly the abdominal insulin infusions site must be in a distance of minimum 7.6 cm (three inches) from where the CGM sensor has been inserted. This will also ensure that local skin reactions, if any, may be related to the correct trial product and/or device.

The Subject should be instructed to remove the CGM device prior to any x-ray, computerised tomography (CT) scan or magnetic resonance imaging (MRI).

After wearing the device for 11 to 13 days, and having performed the meal test assessment, the Subject should have the device removed during the scheduled visit; please see flowchart in section [2](#).

Inserting the sensor and wearing the adhesive patch might cause infection, bleeding, pain or skin irritations (redness, swelling, bruising, itching, scarring or skin discoloration). On rare occasions the sensor may fracture on rare occasion and a sensor fragment may remain under the skin. Adequate medical care must then be provided to the Subject.

For further information on preparing, fitting, and removal of the CGM device, please refer to the CGM manufacturer's user guide and quick user guide.

It is not considered an unscheduled visit when Subjects visit the site for a CGM fitting between visits. This needs to be documented in the Subject's medical record.

8.5.1.4 Wearing and calibration of the continuous glucose monitoring device

The CGM assessment should be performed on days representing the Subject's daily life. Subjects should be instructed to avoid:

- Changing their diet during the CGM period of 11 to 13 consecutive days unless absolutely required
- Unusual strenuous exercise during the CGM period
- Medications with acetaminophen/paracetamol while wearing the CGM device (these medications may affect the performance and readings of the CGM (e.g. false high CGM readings))

The accuracy of the CGM system is dependent on calibration values from the Subject. It is therefore essential that Subject and site personnel are fully trained in the use of the CGM device according to the CGM manufacturer's user guide or quick user guide. Start-up calibration should be performed two hours after fitting the device; two SMPG values are needed for start-up calibration. While wearing the device, the Subjects will continue to perform the 4-point and in some cases 7-7-9-point profiles, (according to section [8.3.2.2](#)) and to use at least two of these SMPG values for calibration as required according to the CGM manufacturer's user guide. The SMPG value for calibration should be entered directly into the CGM receiver within five minutes of performing the SMPG value measurement. The device will give an alert if calibration values are missing after 12 hours.

Some additional measurement may be required for calibration if the SMPG value entered in the device is very different from the sensor glucose reading.

The SMPG values used for calibration must be in the range of 2.2 - 22.2 mmol/L [40 - 400 mg/dL].

The Subjects must be instructed to enter the following into the CGM receiver when wearing the CGM device:

- 2-hour start-up: Two SMPG values used for calibration and for starting the CGM measuring (two hours after the sensor has been inserted)
- 12 hour update: Two SMPG values used for calibration per day (every 12 hours after the 2-hour start-up calibration)

The following data should be recorded in the diary when wearing the CGM device:

- Date and time of meals (breakfast, lunch, main evening meal and other meals)

The meal times recorded during the CGM periods should match the timings in the 4-point profile.

The receiver battery will need to be charged by the Subject during the 11 to 13 day periods, this should be done taking into account the transmission range from the transmitter to the receiver (i.e. six meters (20 feet)).

For further information on wearing and calibrating the CGM device, please refer to the CGM manufacturer's user guide.

8.5.1.5 Uploading of continuous glucose monitoring data

Each CGM period is made up of two sensor periods. Uploading data after the first sensor period is optional, but data from both sensor periods must be uploaded within three days after randomisation (Visit 6), Visit 14, and end of treatment (Visit 22 / 22A), respectively. The upload will be documented by the system directly.

A CGM software program will be provided to allow upload of the CGM data. The following information must be entered in the CGM software program when uploading CGM data:

- Trial identification (ID)
- Subject ID
- Visit ID

The following information must be recorded and transferred into the trial database for every CGM assessment:

- Serial number of the CGM device

8.5.1.6 CGM Reports

CGM data capture report

Upon each data upload a CGM data capture report will be available in the CGM Software system. The CGM data capture report shows the CGM data capture in percentage and the daily SMPG calibration values entered into the CGM receiver for each CGM period.

The CGM data capture in percentage shows whether the Subject has kept the CGM Receiver within the required transmission range of six meters (20 feet) from the CGM transmitter and that the wireless communication between the transmitter and receiver has worked well. Deviation from this requirement should lead to re-training of the Subject or technical troubleshooting.

The daily SMPG calibration values shows whether the Subject has entered their SMPG value twice per day (every 12 hour) into the CGM Receiver. Deviation from this requirement should lead to re-training of the Subject.

The CGM data capture report should be printed out, dated and signed by the Investigator and filed as a source document.

CGM trend pattern report

Upon each data upload a CGM trend pattern report will be available in the CGM Software system. The CGM trend pattern report shows the CGM data values measured by the CGM sensor during each CGM period.

- The CGM data value shows any trends or patterns which could lead to consideration whether additional plasma glucose measurements may be needed.

The CGM trend pattern report should be printed out, dated and signed by the Investigator and filed as a source document.

8.5.1.7 The continuous glucose monitoring data

During the data recording period the CGM device, in which the data is “born”, is regarded as an intermediate media, as the data cannot be accessed until uploaded to an electronic system. Data will be transferred from the CGM device to an electronic system, and then to the trial database. During each CGM period the Subject will be blinded to the CGM data. The Investigator will be able to review the CGM data upon data upload at site but the CGM data must remain blinded to the Subject prior to End of Treatment visit (V22). After the end of the trial, all CGM data for all Subjects at the site will be provided to the Investigator and then stored and archived on site.

8.5.1.8 Pump Data collected during CGM

During all 3 CGM periods the following data will be collected by the pump and electronically transferred to the trial database:

Bolus per meal:

- Date and time
- Carbohydrate counts
- Bolus dose

8.5.2 Diary

Diaries will be used in this trial and handed out to the Subjects as specified in section [2](#). At Visit 23 the Subjects have to return their last diaries.

The Investigator must carefully instruct the Subject in how to fill out the diary. The Subject should bring the diary at each visit to the site and there the Investigator or delegated site personnel must review the diary together with the Subject to ensure consistency/compliance. The information in the diary must be transferred into the eCRF by the trial personnel. 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 made in the Subject's medical record or in the CareLink Clinical Report. Care must be taken not to bias the Subject.

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

- Hypoglycaemic episodes
- Unexplained hyperglycaemic episodes (including any urine/blood ketone values measured, if available)
- Change of infusion set and reservoir
- Meal dates and times (breakfast, lunch, main evening meal, other) in relation to performance of 7-7-9-point profiles and during the CGM period.

It is the Investigator responsibility to ensure that relevant information from the diary and the medical record is transcribed into the eCRF. Furthermore the site personnel must ensure to cross-check the diary content with the information in the CareLink Clinical Reports.

Any incomplete diary data older than 7 days should not be queried for completeness by the Investigator due to decreased validity of such data^{[30,31](#)}. Exceptions being safety questions as specified in section [8.3.3.1](#).

8.5.3 Patient reported outcomes (PRO) questionnaire

Baseline information regarding eating habits, level of exercise, diabetes management and glucose levels will be collected at visit 2 (Diet and Activity Information for Type 1 Diabetes).

It is the responsibility of the Investigator to review the questionnaires for completeness and possible AEs (refer to section [12](#) for AE reporting) immediately following completion. The review must be documented either on the documents and/or the Subjects' medical record. The Investigator should solely review the questionnaire for possible AEs and blank fields. If clarification of entries or discrepancies in PRO questionnaire is needed, the Subject must be questioned and a conclusion made in the Subject's medical record. Care must be taken not to bias the Subject.

Data from the questionnaire will be transferred into the eCRF by the Investigator, and the questionnaire should be kept as source documentation at the site

8.6 Subject compliance

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

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

9 Trial supplies

Trial supplies comprise trial products and auxiliary supplies. Additional details regarding trial supplies can be found in the Trial Materials Manual (TMM).

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

Trial product must not be used if it does not appear clear and colourless.

9.1 Trial products

Table 9–1 The following will be provided by Novo Nordisk A/S, Denmark

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

* Faster aspart is the short name for faster-acting insulin aspart and only the short name will be used as text on the labels. Trial products are visually identical.

9.2 Labelling

Labelling of the trial products will be in accordance with Annex 13³³, local regulations, and trial requirements.

Labelling will include the product related requirements and precautions.

Each trial site will be supplied with sufficient trial products for the trial on an on-going basis controlled by the IV/WRS. Dispensing unit numbers (DUNs) will be distributed to the sites according to enrolment and randomisation.

9.3 Storage

Table 9–2 Storage of trial products

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

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

When the IMP is in the pump reservoir the in-use condition is to keep it below 37°C for a maximum of 6 days. Therefore the IMPs in the pump reservoir should be discarded after no more than 6 days of use or after exposure to temperatures that exceeds 37°C¹⁵.

The Investigator must ensure the availability of proper storage conditions, and also record and evaluate the temperature. The Investigator must inform Novo Nordisk **immediately** if any trial product has been stored outside specified conditions (e.g. outside temperature range).

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 must take appropriate action to ensure correct storage.

Sensors for the CGM system should not be exposed to excessive heat or direct sunlight. Sensors not in use must be stored in accordance with the manufacturer instructions and must be temperature monitored according to the temperature range on the labelling. If the sensors are stored in a cool environment, allow the sensors to warm to room temperature for about 15 minutes to prevent condensation before insertion. Discard sensors past the expiration date on label, if the package is damaged, or the seal is broken.

9.4 Drug accountability and destruction

Drug accountability is the responsibility of the Investigator. The Investigator will perform the drug accountability using the IV/WRS Drug Accountability Module.

Subjects are instructed to return all used, partly used and unused trial product at each dispensing visit, and then finally at end of treatment (Visit 22/22A). Please see flowchart in section [2](#) for timing of the dispensing visits.

Returned trial product (used, partly used or unused including empty packaging material) can be stored at room temperature and must be stored separately from non-allocated trial product.

The monitor will reconcile the drug accountability using the IWRS Drug Accountability Module.

The monitor is responsible for ensuring that there is a process for the destruction of used and unused trial product. The destruction of trial product will be recorded on a Destruction Form, which will be signed by the person responsible for destruction. Destruction of product must be documented.

Destruction will be done according to local procedures after accountability is finalised and verified by the monitor. Destruction of products must be documented.

9.5 Auxiliary supplies

The Subject will use their own insulin pump during the trial.

9.5.1 Auxiliaries supplied by Novo Nordisk

- Bayer Contour[®] Next Link meters (CE approved), and strips, lancets and control solution for BG meters
- Insulin reservoirs (1.8/3.0 mL)
- Infusion sets (Medtronic Mio[®], Medtronic Silhouette[®], Medtronic Quick-set[®] or Medtronic Sure-T[®] (Easy-set[®]) will be reimbursed or supplied by Novo Nordisk according to local regulations
- Standardised liquid meal (for the meal test)
- CGM supplies (please see section [9.5.3](#))
- Urine sticks for ketone measurement
- Syringes for injection of insulin (for use with vial)
- Extra vial with the IMP the Subject is randomised to
- Extra battery for the insulin pump
- A fast-acting glucose preparation (e.g. tablets or powder)

9.5.2 Auxiliaries supplied by site

- Glucagon for injection (reimbursed by Novo Nordisk affiliate, supplied by the central lab in Russia)

9.5.3 Continuous glucose monitoring equipment supplies

Novo Nordisk will provide the following:

- CGM device (receiver and transmitter)
- CGM user guide and quick user guide (for site use)
- Instructions for Subjects

CGM equipment should be returned to Novo Nordisk at end of treatment (Visit 22).

The CGM manufacturer will provide the following:

- CGM installation link to CGM software
- CGM sensors (customs clearance must be expected)
- CGM training (webinar or on-site)

A PC with internet connection must be available at site (same PC as used for the eCRF system can be utilised). For further instruction and requirements, please see CGM manufacturer's user guide.

10 Interactive voice/web response system

A trial-specific IV/WRS will be set up which can be accessed at any time via the internet or telephone. Access to the IV/WRS must be restricted to and controlled by authorised persons.

IV/WRS is used for:

- Screening
- Screening / Run-in failure
- Randomisation
- Medication arrival
- Dispensing
- Discontinuation from trial product
- Completion
- Code break
- Drug accountability
- Data change

IV/WRS user manuals will be provided to each trial site.

11 Randomisation procedure and breaking of blinded codes

At randomisation (Visit 6) the Subject will be randomised to either faster-acting insulin aspart or NovoRapid® in a 1:1 manner to the two different treatment arms described below using the IV/WRS:

- Faster-acting insulin aspart
- NovoRapid®

The randomisation will be stratified based on the following factor:

- Use of own CGM (Yes/No)

11.1 Breaking of blinded codes

The code for a particular Subject may be broken in a medical emergency if knowing the actual treatment would influence the treatment of the Subject. Whenever a code is broken the person breaking the code must print the Code Break Confirmation Notification generated by the IV/WRS, record the reason, and sign and date the document.

The IV/WRS will notify Novo Nordisk (monitor and the Global Safety department) immediately after the code is broken.

When the code is broken, the treatment allocation will be accessible to the Investigator and the Novo Nordisk Global Safety department. If IV/WRS is not accessible at the time of code break the IV/WRS helpdesk should be contacted. Contact details are listed in [Attachment I](#).

If the code has been broken the Subject must be discontinued from trial product and a discontinuation session must be completed in IV/WRS.

12 Adverse events, technical complaints and pregnancies

12.1 Definitions

12.1.1 Adverse events

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

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a product, whether or not considered related to the product.

An AE includes:

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

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

- Pre-existing conditions, including those found as a result of screening procedures (pre-existing conditions should be reported as medical history or concomitant illness)
- Pre-planned procedures unless the condition for which the procedure was planned has worsened from signing the SI/IC
- Non-serious hypoglycaemia is an AE but is reported on a Hypoglycaemic Episode Form instead of on an AE Form; please see section [8.3.3.1](#)
- Non-serious unexplained hyperglycaemias are AEs, but are reported on a Unexplained Hyperglycaemic Form instead of on an AE Form; please see section [8.3.3.2](#)

The following three definitions are used when assessing an AE:

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

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

- **Probable** - good reason and sufficient documentation to assume a causal relationship
- **Possible** - a causal relationship is conceivable and cannot be dismissed
- **Unlikely** - the event is most likely related to aetiology other than the trial product
- **Final outcome:**
 - **Recovered/resolved** - the Subject has fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity after the Subject signed the informed consent
 - **Recovering/resolving** - the condition is 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 sequela meets an SAE criterion, the AE must be reported as an SAE
 - **Not recovered/not resolved** - the condition of the Subject has not improved and the symptoms are unchanged, or the outcome is not known
 - **Fatal** - this term is only applicable if the Subject died from a condition related to the reported AE. Outcomes of other reported AEs in a Subject before he/she died should be assessed as "recovered/resolved", "recovering/resolving", "recovered/resolved with sequelae" or "not recovered/not resolved". An AE with fatal outcome must be reported as an SAE
 - **Unknown** - this term is only applicable if the Subject is lost to follow-up

12.1.2 Serious adverse events

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

- Death
- A life-threatening^a experience
- In-patient hospitalisation^b or prolongation of existing hospitalisation
- A persistent or significant disability or incapacity^c
- A congenital anomaly or birth defect
- Important medical events that may not result in death, be life threatening^a or require hospitalisation^b may be considered an SAE when - based on appropriate medical judgement - they may jeopardise the Subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition of SAE^d

The following adverse events must always be reported as a Serious Adverse Event using the important medical event criteria if no other seriousness criteria are applicable:

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

- a. The term "life threatening" in the definition of SAE 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 was more severe
- b. The term "hospitalisation" is used when a Subject:
- Is admitted to a hospital or in-patient, irrespective of the active of physical stay, or
 - Stays at the hospital for treatment or observation for more than 24 hours

Medical judgement must always be exercised, and when in doubt, the hospital contact should be regarded as a hospitalisation. 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

- c. A substantial disruption of a Subject's ability to conduct normal life functions (e.g. following the event or clinical investigation the Subject has significant, persistent or permanent change, impairment, damage or disruption in his/her body function or structure, physical activity and/or quality of life)
- d. For example intensive treatment in an emergency room or at home of allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse

12.1.3 Non-serious adverse events

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

12.1.4 Medical events of special interest

A MESI is an event which, in the evaluation of safety, has a special focus. A MESI is an AE (SAE or non-serious AE) which fulfils the below defined MESI criteria.

- Medication errors concerning trial products:
 - Administration of wrong drug (Note: Use of wrong DUN is not considered a medication error.)
 - Wrong route of administration, such as intramuscular instead of s.c.
 - Administration of an overdose with the intention to cause harm (e.g. suicide attempt)

- Accidental administration of a lower or higher dose than intended. The administered dose must deviate from the intended dose to an extent where clinical consequences for the trial Subject were likely to happen as judged by the Investigator, although not necessarily did happen

12.1.5 Technical complaint

A technical complaint 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.

Examples of technical complaints:

- The physical or chemical appearance of trial products in the vials (e.g. discoloration, particles or contamination)
- The 10 mL vial packaging material (e.g. leakage, cracks, rubber membrane issues or errors in labelling text)

However, colour change, particle or crystal formation in the infusion set and reservoir are not considered as a technical complaint and thereby not to be reported to Customer Complaint Centre, Novo Nordisk.

12.2 Reporting of adverse events

All events meeting the definition of an AE must be collected and reported. This includes events from the first trial-related activity after the Subject has signed the SI/IC until the last phone contact/site visit. The events must be recorded in the applicable eCRF form in a timely manner; see timelines below and in [Figure 12-1](#).

During each contact with the trial site staff, the Subject must be asked about AEs and technical complaints, for example by asking: "Have you experienced any problems since the last contact?"

All AEs, observed by the Investigator or Subject, must be reported by the Investigator and evaluated. Novo Nordisk assessment of expectedness is performed according to the following reference documents:

- Faster-acting insulin aspart: IB, current version⁷ and updates thereof
- Insulin aspart (NovoRapid[®]): Company Core Data Sheet (CCDS) Current version

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

For SAEs, a SIF must be completed in addition to the AE Form. If several symptoms or diagnoses occur as part of the same clinical picture, one SIF can be used to describe all the SAEs.

MESIs, regardless of seriousness, must be reported using the AE Form, the SIF and a MESI Form. The MESI Form is a form tailored to collect specific information related to the individual MESI.

The AE Form for a non-serious AE not fulfilling the MESI criteria should be signed when the event is resolved or at the end of the trial.

12.2.1 Timelines for initial reporting of adverse events

The Investigator must complete the following forms in the eCRF within the specified timelines:

- **SAEs** - The AE Form **within 24 hours** and the SIF **within five calendar days** of the Investigator's first knowledge of the SAE

Both forms must be signed within seven calendar days from the date the information was entered in the eCRF:

- **SAEs fulfilling the MESI criteria** - In addition to above, the MESI Form **within 14 calendar days** of the Investigator's first knowledge of the AE
- **Non-serious AE fulfilling the MESI criteria** - The AE Form, SIF and MESI Form **within 14 calendar days** of the Investigator's first knowledge of the event

If the eCRF is unavailable, the concerned AE information must be reported on paper forms and sent to Novo Nordisk by fax, e-mail or courier within the same timelines as stated above. When the eCRF becomes available, the Investigator must transcribe the information on the appropriate forms in the eCRF.

Contact details (fax, telephone, e-mail and address) are provided in the Investigators trial file.

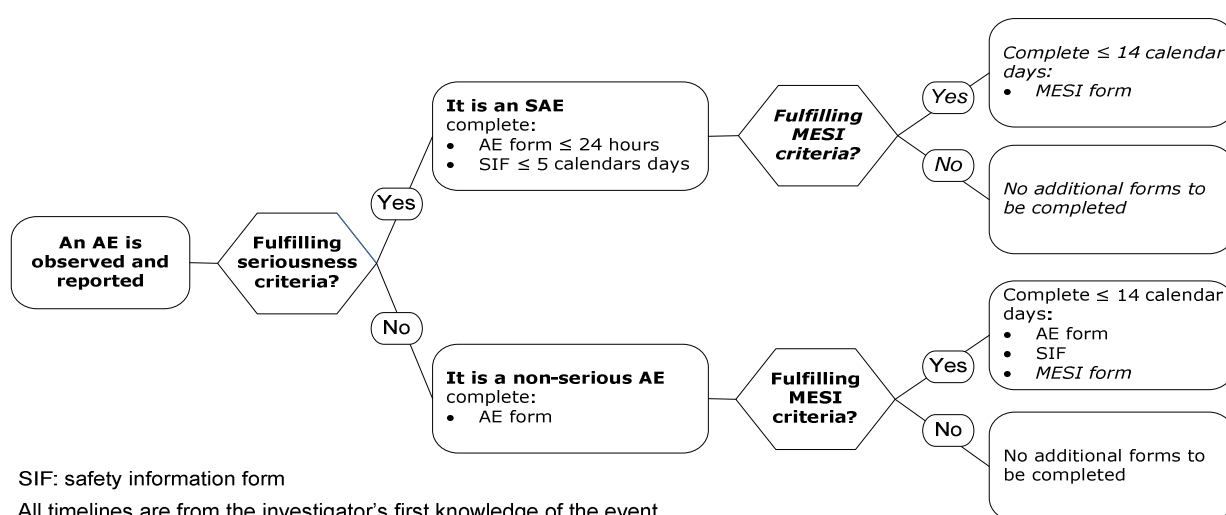


Figure 12–1 Initial reporting of AEs

12.2.2 Reporting of trial product-related SUSARs by Novo Nordisk

Novo Nordisk will notify the Investigator of trial product-related suspected unexpected serious adverse reactions (SUSARs) in accordance with local requirements and GCP¹. In addition, the Investigator will be informed of any trial-related SAEs that may warrant a change in any trial procedure.

In accordance with regulatory requirements, Novo Nordisk will inform the regulatory authorities, including EMA, of trial product-related SUSARs. In addition, Novo Nordisk will inform the Institutional Review Boards/Independent Ethics Committees (IRBs/IECs) of trial product-related SUSARs in accordance with local requirement and GCP¹, unless locally this is an obligation of the Investigator.

12.2.3 Novo Nordisk products used as concomitant medication

If a SAE and/or MESI 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 AE to relevant regulatory authorities.

12.3 Follow-up of adverse events

The Investigator must record follow-up information by updating the forms in the eCRF.

Follow-up information must be reported to Novo Nordisk according to the following:

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

- **Non-serious AE fulfilling the MESI criteria** - Non-serious AE fulfilling the MESI criteria must be followed as specified for non-serious AEs. Follow-up information on MESIs should only include new (e.g. corrections or additional) information and must be reported **within 14 calendar days** of the Investigator's first knowledge of the information. This is also the case for previously reported non-serious AEs which subsequently fulfil the MESI criteria.
- The Investigator must ensure that the worst case severity and seriousness of an event is kept throughout the trial. A worsening of an unresolved AE must be reported as follow-up with re-assessment of severity and/or seriousness of the event.

Queries or follow-up requests from Novo Nordisk must be responded to **within 14 calendar days** from the date of receipt of the request, unless otherwise specified in the follow-up request.

12.4 Technical complaints, and technical complaint samples

12.4.1 Reporting of technical complaints

All technical complaints on any of the following trial products:

- Faster-acting insulin aspart, 100 U/mL, 10 mL vial
- Insulin aspart (NovoRapid[®]), 100 U/mL, 10 mL vial

which occur from the time of first usage of the product until the time of the last usage of the product in the treatment period must be collected and sent to Customer Complaint Centre, Novo Nordisk.

Contact details (fax, e-mail and address) are provided in [Attachment I](#) to the protocol.

The Investigator must assess whether the technical complaint is related to any AEs, SAEs, and/or MESI.

Technical complaints must be reported on a separate Technical Complaint Form in the eCRF for each product listed. If the technical complaint involves more than one batch/code number or more than one DUN, a Technical Complaint Form for each batch/code number or for each DUN must be completed in the eCRF.

The Investigator must complete the Technical Complaint Form within the following timelines of the trial site obtaining knowledge of the technical complaint:

- Technical complaint assessed as related to an SAE **within 24 hours**
- All other technical complaints within **five calendar days**

If the eCRF is unavailable or when reporting a technical complaint that is not Subject-related, the information must be provided on a paper form by fax, e-mail or courier to Customer Complaint

Centre, Novo Nordisk, within the same timelines as stated above. When the eCRF becomes available, the Investigator must re-enter the information on the appropriate forms in the eCRF.

Technical complaints related to pumps should be addressed to the pump manufacturer, please see section [8.3.2.4](#).

12.4.2 Collection, storage and shipment of technical complaint samples

The Investigator must collect the technical complaint sample and notify the monitor **within five calendar days** of obtaining the sample at trial site. The monitor must coordinate the shipment to Customer Complaint Centre, Novo Nordisk (the address is provided in [Attachment I](#)) and ensure that the sample is sent as soon as possible. A print or copy of the Technical Complaint Form must be sent with the sample.

The Investigator must ensure that the technical complaint sample contains the batch/code number and, if available, the DUN.

If the technical complaint sample is unobtainable, the Investigator must specify on the Technical Complaint Form in the eCRF why it is unobtainable.

Storage of the technical complaint sample must be done in accordance with the conditions prescribed for the product. The shipment of the technical complaint sample should be done in accordance with the same conditions as for storage, as detailed in section [9](#).

12.5 Pregnancies

12.5.1 Pregnancies in female Subjects

Female Subjects must be instructed to notify the Investigator immediately if they become pregnant during the trial (e.g. from start of the run-in period (Visit 2) until end of treatment (Visit 22)). The Investigator must report any pregnancy in Subjects who have received trial product(s).

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

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

The following must be collected and reported by the Investigator to Novo Nordisk electronically (e.g. in PDF format) or by fax or courier:

- **Reporting of pregnancy information** - Information about the pregnancy and pregnancy outcome/health of the new-born infant(s) has to be reported on Maternal Form 1A and 1B, respectively.

When the pregnancy outcome is abnormal (i.e. congenital anomalies, foetal death including spontaneous abortion and/or any anomalies of the foetus observed at gross examination or during autopsy), and/or when a congenital anomaly is diagnosed within the first month, further information has to be reported for the female Subject on Maternal Form 2. In addition, information from the male partner has to be reported on the Paternal Form, after an informed consent has been obtained from the male partner.

Initial reporting and follow-up information must be reported **within 14 calendar days** of the Investigator's first knowledge of initial or follow-up information

- **Reporting of AE information** - The Investigator has to report AEs in connection with the pregnancy as well as in the foetus and new-born infant(s). The SAEs that must be reported include abnormal outcome, such as foetal death (including spontaneous abortion), and congenital anomalies (including those observed at gross examination or during autopsy of the foetus), as well as other pregnancy complications fulfilling the criteria of an SAE

Forms and timelines for reporting AEs:

- Non-serious AEs:
 - Paper AE Form* **within 14 calendar days** of the Investigator's first knowledge of the initial or follow-up information to the non-serious AE
- SAEs:
 - Paper AE Form* **within 24 hours** of the Investigator's first knowledge of the SAE
 - Paper SIF **within five calendar days** of the Investigator's first knowledge of the SAE
 - **SAE follow-up information** to the AE Form and/or SIF **within 24 hours** of the Investigator's first knowledge of the follow-up information

* It must be clearly stated in the AE diagnosis field on the AE Form if the event occurred in the Subject, foetus or new-born infant.

Any queries or follow-up requests from Novo Nordisk to non-serious AEs, SAEs and Pregnancy Forms must be responded to by the Investigator **within 14 calendar days** from the date of receipt of the request, unless otherwise specified in the follow-up request.

12.6 Precautions and/or overdose

During treatment with insulin, there is a risk of hypoglycaemia (see section [8.3.3.1](#)). Symptoms of hypoglycaemia usually 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, spasms, and/or unconsciousness and, in extreme cases, death.

Asymptomatic hypoglycaemia and symptoms of hypoglycaemia should be treated with carbohydrates. Mild to moderate symptoms can be treated by ingestion of carbohydrate (for example, juice). Severe hypoglycaemia resulting in the loss of consciousness should be treated with parenteral glucose, glucagon or dextrose.

For further details, please refer to the current version of faster-acting insulin aspart IB⁷ and for NovoRapid[®] EU Summary of product characteristics, please refer to the current versions of the SmPC¹⁴ or U.S. Novolog[®] Label Information¹⁵.

12.7 Committees related to safety

12.7.1 Novo Nordisk safety committee

Novo Nordisk will constitute an internal faster-acting insulin aspart safety committee to perform ongoing safety surveillance. The faster-acting insulin aspart safety committee may recommend unblinding 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.

12.7.2 Data monitoring committee

The independent data monitoring committee (DMC) is established to review and evaluate accumulating data from an ongoing clinical trial in order to protect the safety of the Subjects and to evaluate the evolving risk-benefit if required. The DMC will perform an interim evaluation of the relevant safety data on an ongoing basis including possible infusion set occlusions.

The DMC is composed of permanent members who are independent of Novo Nordisk and will cover relevant medical and biostatistics specialities, and they may request assistance from additional ad hoc members, if needed. The DMC will review relevant safety data on an ongoing basis, and will recommend to Novo Nordisk whether to continue, modify, or terminate the trial, as necessary. The composition of the DMC, objectives of the surveillance, meeting frequency, data to be analysed at the meetings, time-point for interim evaluations and responsibilities with regard to information (such as meeting minutes) will be described in a DMC charter.

The DMC members will only have direct contact with the Novo Nordisk Global Safety department through the safety surveillance representatives, and will have no direct interaction with those in trial management. The DMC recommendations should be addressed directly to the Novo Nordisk Global Safety department and the internal Novo Nordisk safety committee for faster aspart. It is the responsibility of the Novo Nordisk internal safety committee for faster aspart to take action(s) for Subject safety based on the DMC recommendations. DMC concerns relating to trial processes should be communicated to trial management via the Novo Nordisk Global Safety department.

13 Case report forms

Novo Nordisk will provide a system for an eCRF. This system and support services to the system will be supplied by an external supplier.

Ensure that all relevant questions are answered, and that no empty data field exists. If a test or an assessment has not been done and will not be available, or if the question is irrelevant (e.g. is not applicable), indicate this according to the data entry instructions.

The following will be provided as paper CRFs:

- Pregnancy Form
- Technical Complaint Form

In addition paper AE Forms, Safety Information Form will be provided. These must only be used when access to the eCRF is revoked.

Print legibly on the paper CRF forms using a ballpoint pen. Ensure that all questions are answered, and that no empty data blocks exist. Ensure that no information is recorded outside the data blocks. If a test/assessment has not been done and will not be available, indicate this by writing "ND" (not done) in the appropriate answer field in the CRF. If the question is irrelevant (e.g. is not applicable) indicate this by writing "NA" (not applicable) in the appropriate answer field. Further guidance can be obtained from the instructions in the CRF.

The Investigator must ensure that all information is consistent with the source documentation. By electronically signing the case book in the eCRF, the Investigator confirms that the information in the eCRF and related forms is complete and correct.

13.1 Corrections to case report forms

13.1.1 Electronic case report form

Corrections to the eCRF data may be made by the Investigator or the Investigator's delegated staff. An audit trail will be maintained in the eCRF application containing as a minimum: the old and the new data, identification of the person entering the data, date and time of the entry and reason for the correction.

If corrections are made by the Investigator's delegated staff after the date the Investigator has signed the case book, the case book must be signed and dated again by the Investigator.

13.1.2 Paper case report form

Corrections to the data in CRFs may only be made by drawing a straight line through the incorrect data and then writing the correct entry next to the data that was crossed out. Each correction must be initialled, dated and explained (if necessary).

Corrections necessary after the CRFs have been removed from the trial site must be documented on a Data Clarification Form (DCF) or on a Monitor-Initiated Discrepancy Form (MIDF).

13.2 Case report form flow

The Investigator must ensure that data is recorded in the eCRF/paper CRF as soon as possible, preferably within five days after the visit. Once data has been entered, it will be available to Novo Nordisk for data verification and validation purposes.

Site specific eCRF data (in an electronic readable format) will be provided to the trial site before access to the eCRF is revoked. This data must be retained at the trial site.

14 Monitoring procedures

During the course of the trial, the monitor will visit the trial site to ensure that the protocol is adhered to, that all issues have been recorded, to perform source data verification (SDV) and to monitor drug accountability. The first monitoring visit will be performed as soon as possible after FSFV at the trial site and no later than four weeks after. The monitoring visit intervals will depend on the outcome of the remote monitoring of the eCRFs, the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP¹, but will not exceed 8 weeks.

14.1 Source data verification

The monitor must be given direct access to source 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).

Further, it must be possible to verify the Subject's diabetes history (diagnosis of diabetes and diabetes treatment) in source documents as Subject's medical record. If a Subject is not from the Investigators own practice; the Investigator must make reasonable effort to obtain a copy of Subject's medical records from relevant party e.g. primary physician or diabetes clinic.

All data must be verifiable in source documentation other than the eCRF.

Unless specified otherwise all data recorded in the PRO and the Subject diary is considered source data including:

- Hypoglycaemic episodes
- Unexplained hyperglycaemic episodes (including any urine/blood ketone values measured, if available)
- Change of infusion set and reservoir
- Meal dates and times (breakfast, lunch, main evening meal)

CareLink Clinical is considered source for all data captured from the pump and the BG meter.

All data recorded in the CGM is considered source including:

- Sensor time, sequence no.
- IG, calibrated
- Calibration value
- Serial no.

For all data recorded, the source document must be defined in a source document agreement at each trial site. There should only be one source defined at any time for any data element.

Source data generated by the trial site can be corrected by another person than the person entering the source data if accepted by local regulations; any correction must be explained, signed and dated by the person making the correction.

The original diaries and/or PROs must not be removed from the trial site.

The monitor will ensure that the eCRF is completed and that paper CRFs are collected.

Monitors must review the Subject's medical records and other source data (e.g. the diaries and PROs) to ensure consistency and/or identify omissions compared to the CRF. If discrepancies are found, the Investigator must be questioned about these.

A follow-up letter (paper or electronic) will be sent to the Investigator following each monitoring visit addressing any actions to be taken.

14.1.1 CGM source data verification

The following should be monitored from the diary data:

- Date and actual clock time of meals (breakfast, lunch, main evening meal and other meals)

The following should be monitored from the CGM reports:

- The CGM device status report has been printed, dated and signed by site staff
- The CGM data capture report has been printed, dated and signed by site staff
- The unblinded CGM trend reports have been printed, dated and signed by site staff
- The CGM receiver serial number in the CGM device status report has been recorded in the eCRF
- The CGM receiver mode in the CGM data capture report must be blinded
- Any SMPG values ≤ 3.9 mmol/L (70 mg/dL) in the CGM data capture report has been recorded as a hypoglycaemic episode in the eCRF

14.2 Continuous glucose monitoring procedures

During the course of the trial, the monitor will ensure that: (a) the CGM procedures have been adhered to, (b) all issues have been recorded and (c) monitoring and SDV has taken place. The monitor will have to verify that CGM data has been recorded and uploaded in accordance with the CGM manufacturer's user guide.

15 Data management

Data management is the responsibility of Novo Nordisk. Data management may be delegated under an agreement of transfer of responsibilities to an external Clinical Research Organisation (CRO).

Appropriate measures, including encryption of data files containing person identifiable data, will be used to ensure confidentiality of Subject data, when they are transmitted over open networks.

Data from central laboratories will be transferred electronically from the laboratory performing the analyses. In cases where data is transferred via non-secure electronic networks, data will be encrypted during transfer.

The Subject and any biological material obtained from the Subject will be identified by Subject number and trial identification number. Appropriate measures such as encryption or leaving out certain identifiers will be enforced to protect the identity of Subjects in all presentations and publications as required by local, regional, and national requirements.

Data collection

Insulin pumps, BG meters and CGM devices have made it possible to collect and transfer data electronically. The technology has been developed with the aim of ensuring optimal treatment and data driven decision between patient and physician. However, these devices create and collect many data designed for the surveillance and adjustment of patient's treatment that are not specified for collection of data specifically for this clinical trial.

This has led to the necessity to specify:

- Which data points are collected by the device (insulin pump, BG meter and CGM device) that will be used for statistical analysis (inferential and descriptive) in order to address the objectives and endpoints of the trial
- Which data points are collected/transferred that are not required or used per protocol (and therefore not cleaned but only stored at a data repository)
- Which data points are collected by the device that are used for daily surveillance and adjustment of patient's treatment only (and therefore not cleaned but only stored at a data repository)
- Which data points required by the protocol will have to be captured in other sources if not captured by the device

Any required data points not captured by the device (insulin pump, BG meter or CGM device) will have to be collected from another source such as a paper diary. As paper diary data will be supportive to the data collected by the device it may require data points to be present in more than one location in order for the paper diary data to be linked with the device data.

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It has been defined for cases where the same data point exists in more than one location which data point should be considered the source. Additional details regarding collection and handling of data can be found in the Data collection and handling strategy document^{[34](#)}.

16 Computerised systems

Novo Nordisk will capture and process clinical data using computerised systems that are described in Novo Nordisk Standard Operating Procedures and IT architecture documentation. The use and control of these systems are documented.

Investigators working on the trial may use their own electronic systems to capture source data.

CareLink Clinical is a computerised system provided by Medtronic to be used to capture and process insulin pump data. This system is described in a data collection and handling strategy. The use and control of this system will be documented.

17 Statistical considerations

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.

General considerations

In general, for endpoints evaluated as a change from baseline and/or where a baseline adjustment is made, baseline is defined as information collected at randomisation (Visit 6). In case a measurement is not available at randomisation, the most recent measurement prior to randomisation will be used as baseline.

Two observation periods are defined, “in-trial” and “on-treatment”, and it will be specified which period each analysis will use.

- In-trial: the observation period from date of randomisation and until last trial-related Subject-site contact. The in-trial observation period includes data collected after discontinuation of randomised treatment.
- On-treatment: the observation period from date of first dose of randomised NovoRapid[®]/faster-acting insulin aspart and no later than 7 days after the day of last dose of randomised NovoRapid[®]/faster-acting insulin aspart. The on-treatment observation period includes data collected up to and including 7 days after discontinuation of randomised treatment.

All efficacy endpoints will be summarised and analysed using the full analysis set (FAS), unless otherwise stated. Safety endpoints will be summarised using the safety analysis set and analysed using the FAS.

Presentation of results from a statistical analysis will include the estimated mean treatment effects (LSMeans) for change from baseline, if applicable. Estimated mean treatment differences (or ratios) will be presented together with two-sided 95% confidence interval (CI) for all endpoints analysed statistically.

For endpoints measured over time, mean values will be plotted to explore the trajectory over time. For survival endpoints (e.g. drop-out pattern) Kaplan-Meier plots are presented for each treatment.

Data collected before randomisation (Visit 6) will only be summarised descriptively.

Estimands

The primary objective, to confirm the effect of CSII treatment with faster-acting insulin aspart in terms of glycaemic control by comparing it to CSII treatment with NovoRapid[®], in adults with T1DM, will be assessed by the change from baseline in HbA_{1c} using a non-inferiority approach.

More specifically the upper limit of the 95% confidence interval for the difference between faster-acting insulin aspart and NovoRapid[®] should be compared to a non-inferiority margin of 0.4%. If it is below or equal to 0.4% non-inferiority will be considered established and effect demonstrated.

The trial also aims to compare CSII treatment with faster-acting insulin aspart to NovoRapid[®] for a number of confirmatory secondary endpoints. The family-wise type I error rate will be controlled in the strong sense using a hierarchical (fixed sequence) testing procedure. This is based on a priority ordering of the null-hypotheses, and testing them in this order using the two-sided 95% confidence interval approach until an insignificant result appears. The effect is that rejection of a null hypothesis only will be considered for analyses where all previous null-hypotheses have been rejected in favour of faster-acting insulin aspart.

The steps in the hierarchical testing procedure are as follows:

Step 1 (Primary analysis): HbA_{1c} non-inferiority of faster-acting insulin aspart versus NovoRapid[®]

Step 2: 1-hour PPG increment (meal test) superiority of faster-acting insulin aspart versus NovoRapid[®]

Step 3: HbA_{1c} superiority of faster-acting insulin aspart versus NovoRapid[®]

Step 4: 1,5-Anhydroglucitol superiority of faster-acting insulin aspart versus NovoRapid[®]

Step 5: time spent in low IG (≤ 3.9 mmol/L [70 mg/dL]) superiority of faster-acting insulin aspart versus NovoRapid[®]

Primary estimand (de facto)

The primary estimand is defined as the treatment difference between Subjects randomised to CSII treatment with faster-acting insulin aspart and CSII treatment with NovoRapid[®] in adults with T1DM assessed by change from baseline in HbA_{1c} 16 weeks after randomisation for all randomised Subjects regardless of treatment discontinuation or use of ancillary therapies. This estimand is a de facto estimand addressing effectiveness.

The primary estimand assesses the expected benefit that a Subject can achieve if prescribed to CSII treatment with faster-acting insulin aspart as compared to CSII treatment with NovoRapid[®] in adults with T1DM. By not putting any restrictions on the randomised treatment adherence, this

estimand aims at a difference as close as possible to the one that can be expected in real-world clinical practice, provided that the treatment adherence and use of ancillary therapies reflects clinical practice. Thereby the primary estimand provides a clinically relevant treatment difference for clinicians concerning the glycaemic effect of CSII treatment with faster-acting insulin aspart as compared to CSII treatment with NovoRapid® in the day to day life in adults with T1DM.

Secondary estimand (de jure)

Unlike the primary estimand, the secondary estimand is defined as the treatment difference in change from baseline in HbA_{1c} 16 weeks after randomisation between CSII treatment with faster-acting insulin aspart and CSII treatment with NovoRapid® in adult Subjects with T1DM if Subjects continue on-treatment until 16 weeks. This estimand is a de jure estimand, addressing efficacy.

As an alternative to the primary estimand, this estimand provides a more hypothetical treatment difference, but may also be the most sensitive for a non-inferiority comparison, since the marketed product that Subjects discontinuing from randomised treatment are switched to may equalize the treatment effect.

The two estimands will be repeated for the endpoints:

- 1-hour PPG increment (meal test)
- 1,5-Anhydroglucitol
- time spent in low IG (≤ 3.9 mmol/L [70 mg/dL]) (CGM)

17.1 Sample size calculation

The primary objective of the trial is to confirm the effect of CSII treatment with faster-acting insulin aspart in terms of glycaemic control by comparing it to CSII treatment with NovoRapid® in adults with T1DM, using a non-inferiority approach. The non-inferiority margin of 0.4% (absolute) was chosen as described in section [5.2.1](#). The statistical evaluation will be done as described in section [17.3](#).

The trial also aims to confirm superiority of CSII treatment with faster-acting insulin aspart for a number of secondary confirmatory endpoints using the hierarchical testing procedure as described in section [17](#) (General considerations).

The sample size is determined to ensure sufficient power for the first step and second step in the hierarchical testing procedure.

In previous exploratory trials where CSII treatment with faster aspart has been investigated, the completion rates have been high. Therefore it will not be unexpected that treatment discontinuation might be as low as 4% where trial discontinuation constitutes half of these.

The power for the non-inferiority step is based on a t-statistic under the assumption of a one-sided test of size 2.5 %. A mean treatment difference of -0.1% for the comparison between faster-acting insulin aspart and NovoRapid[®] is expected. As trials in this population where Subjects are using insulin pumps and where data from treatment withdrawn subjects is retrieved is limited, a conservative estimate of the standard deviation (SD) in change from baseline in HbA_{1c} of 0.8% was chosen.

For determination of power in the second step in the hierarchical testing, where change from baseline in 1-hour PPG increment 16 weeks after randomisation is compared between faster-acting insulin aspart and NovoRapid[®] a t-statistic with a two-sided test of size 5.0% is used, where the treatment difference is expected to be at least 0.9 mmol/L [16 mg/dL]. The SD=3.4 mmol/L [62 mg/dL] in change from baseline in 1-hour PPG increments 16 weeks after randomisation based on laboratory analysed PG in a standardised meal test will be considered reasonable, based on prior trials.

The power calculation is done using proc power in SAS Version 9.4. Please refer to [Table 17-1](#) for assumption of the sample size calculation.

Table 17-1 Specifications assumed for sample size calculation

	Statistical test	Significance Level	Analysis Population	Non-inferiority Margin	SD	Mean Difference	Randomisation Scheme
Step 1	2-group t-test	One-sided 2.5%	FAS	0.4% (absolute)	0.8	-0.1	1:1
Step 2	2-group t-test	Two-sided 5.0%	FAS	NA	3.4	0.9	1:1

In [Table 17–2](#), the sensitivity of the sample size to the power in Step 1 and Step 2 is shown for three different sizes of FAS. Three different choices of the mean difference are used to calculate the power in Step 2.

Table 17–2 Sensitivity of sample size to power in step 1 and step 2

N Total FAS	N per arm FAS	Step 1			Step 2			
		Mean Diff	SD	Step 1 Power (%)	Null Diff	Mean Diff	SD	Step 2 Power (%)
300	150	-0.1	0.80	>99.9	0	0.8	3.4	52.8
		-0.1	0.80	>99.9	0	0.9	3.4	62.7
		-0.1	0.80	>99.9	0	1.0	3.4	71.9
450	225	-0.1	0.80	>99.9	0	0.8	3.4	70.2
		-0.1	0.80	>99.9	0	0.9	3.4	80.0
		-0.1	0.80	>99.9	0	1.0	3.4	87.6
600	300	-0.1	0.80	>99.9	0	0.8	3.4	82.0
		-0.1	0.80	>99.9	0	0.9	3.4	89.9
		-0.1	0.80	>99.9	0	1.0	3.4	94.9

In conclusion, with 450 Subjects in the FAS (225 Subjects per group) will ensure a power of >99.9% to conclude HbA_{1c} non-inferiority in the first step. This sample size gives 80.0% marginal power to conclude 1 hour PPG increment superiority in the second step.

Assuming a screening failure rate of 24% and run-in failure rate of 11%, 666 Subjects should be screened for inclusion in the trial.

17.2 Definition of analysis sets

The following analysis sets are defined in accordance with the ICH-E9 guidance¹:

- Full Analysis Set (FAS) includes all randomised Subjects. In exceptional cases, randomised Subjects may be excluded from the FAS. In such cases, the reason for exclusion will be justified and documented. Subjects in the FAS will contribute to the evaluation “as randomised”
- Per Protocol (PP) Analysis Set includes all Subjects in the full analysis set, excluding Subjects who:
 - Have violated any inclusion criteria
 - Have fulfilled any exclusion criteriaSubjects in the PP set will contribute to the evaluation “as treated”
- Safety Analysis Set includes all Subjects receiving at least one dose of the IMP or its comparator. Subjects in the safety analysis set will contribute to the evaluation “as treated”.

Randomised Subjects who are lost to follow-up, and where no exposure information of the trial product or its comparator is available after randomisation, will be handled as unexposed.

Before data are released for statistical review, a blinded review of all data will take place to identify serious non-adherence to the protocol that may potentially affect the results. Furthermore, extreme values and outliers will be identified by the statistician during programming and data review, according to ICH-E9¹. This will be performed by using a fake randomisation.

The Subjects or observations to be excluded, and the reasons for their exclusion must be documented and signed by those responsible before database lock. The Subjects and observations excluded from analysis sets, and the reason for this, will be described in the clinical trial report (CTR).

17.3 Primary endpoint

The primary endpoint is the change from baseline in HbA_{1c} 16 weeks after randomisation.

Primary analysis

- 1) The primary estimand will be addressed by the below primary analysis based on all Subjects included in the FAS and using the in-trial observation period. Note that if Subjects withdraw consent to contribute additional information or are completely lost to follow-up, missing data will still occur. The primary analysis will be implemented as a statistical model using multiple imputations where the Subjects without any available HbA_{1c} measurements at scheduled visits will have their HbA_{1c} value imputed from the available information from the treatment the Subject has been randomised to. Note that this resembles in essence a mixed model of repeated measurements analysis, but Subjects without post-randomisation measurements contribute to the analysis, as the missing values will be imputed. The analysis will be implemented as follows:

- In the first step, intermittent missing values are imputed using a Markov Chain Monte Carlo (MCMC) method, in order to obtain a monotone missing data pattern. This imputation is done for each group separately and 100 copies of the dataset will be generated.
- In the second step, for each of the 100 copies of the dataset, an analysis of variance model with strata (two levels based on use of own CGM or not), previous insulin use (three levels: NovoRapid[®], Apidra[®] (insulin glulisin), Humalog[®] (insulin lispro) and region as factors, and baseline HbA_{1c} as a covariate is fitted to the change in HbA_{1c} from baseline to week 4 for each treatment group separately. The estimated parameters, and their variances, from these models are used to impute missing values at week 4 for Subjects in each treatment group, based on strata, previous insulin use, region and baseline HbA_{1c}.
- In the third step, for each of the 100 copies of the dataset, missing values at week 8 are imputed in the same way as for week 4. The imputations are based on an analysis of variance model with strata, previous insulin use and region as a factors and baseline HbA_{1c} and change from baseline in HbA_{1c} at week 4 as covariates.
- This stepwise procedure is then repeated sequentially for week 12 and 16
- For each of the complete data sets, the change from baseline to week 16 is analysed using an analysis of variance model with treatment, strata, previous insulin use and region as factors, and baseline HbA_{1c} as a covariate.
- The estimates and standard deviations for the 100 data sets are pooled using Rubin's formula:

$$m_{MI} = \frac{1}{100} \sum_{i=1}^{100} m_i ,$$

$$SD_{MI} = \sqrt{\frac{1}{100} \sum_{i=1}^{100} SD_i^2 + \left(1 + \frac{1}{100}\right) \left(\frac{1}{100-1}\right) \sum_{i=1}^{100} (m_i - m_{MI})^2}$$

where m_i and SD_i are the estimated means and standard deviations for the 100 copies of the dataset, and m_{MI} and SD_{MI} are the pooled estimates.

- From m_{MI} and SD_{MI} , the 95% confidence interval for the treatment differences is calculated.

Non-inferiority of faster-acting insulin aspart will be considered confirmed if the upper boundary of the two-sided 95% CI is below or equal to 0.4% or equivalent if the p-value for the one-sided test of

$H_0: D > 0.4\%$ against $H_A: D \leq 0.4\%$,

is less than or equal to 2.5%, where D is the mean treatment difference (faster-acting insulin aspart minus NovoRapid[®]).

Note that as the anticipated number of Subjects discontinuing treatment, but not trial is low, imputations based on such Subjects will not be suitable.

Provided that the hierarchical testing allows, the evaluation of superiority will be based on the same statistical model, as the primary analysis 1). The associated sensitivity analysis that follows will investigate the robustness of non-inferiority and superiority (analysis 3b and 3c) as well.

Sensitivity analyses for the primary analysis addressing the primary estimand

All sensitivity analyses for the primary analysis addressing the primary estimand will use the in-trial observation period.

- 2) First the primary analysis in 1) will be repeated, but excluding all factors except from treatment in the model. This analysis will explore the influence of the different factors.
- 3) The primary analysis approach chosen for this trial relies on the assumption that missing data is missing at random (MAR). This assumption implies that the HbA_{1c} for Subjects leaving the trial, after their withdrawal, develops in a similar way as the HbA_{1c} for similar Subjects that remain in the trial (not necessarily on treatment) and had similar development of HbA_{1c} before withdrawal. The MAR assumption may be questionable for Subjects withdrawing at own will. Therefore the statistical models using multiple imputation will be repeated with the following alterations:
 - a) Imputations will be done from the treatment arm that the Subject was randomised to and a value of 0.4% (non-inferiority margin) is added to the change from baseline in HbA_{1c} at week16 for Subjects randomised to faster-acting insulin aspart who withdrew from the trial³⁵.
 - b) Imputations will be done from the comparator arm (NovoRapid[®]). This will serve as a sensitivity analysis for the superiority analysis. It does not rely on the MAR assumption, but assumes that all Subjects who withdraw from the trial in the faster-

acting insulin aspart arm shift to NovoRapid[®]. The imputation will be done such that the treatment effect diminishes gradually after trial discontinuation (copy reference).

- c) Imputation will be done from the comparator arm (NovoRapid[®]). This will serve as a supplementary sensitivity analysis for the superiority analysis. It does not rely on the MAR assumption, but assumes that all Subjects that withdraw the trial in the faster-acting insulin aspart arms responded as if they had been on NovoRapid[®] for the entire trial. The imputation will be done such that the treatment effect diminishes immediately after trial discontinuation (jump to reference).

Analyses addressing the secondary estimand

All analyses addressing the secondary estimand will use the on-treatment observation period.

- 4) The secondary estimand will be analysed using the same statistical model using multiple imputations as the primary analysis in 1) except using the on-treatment observation period.
- 5) A tipping point analysis based on a statistical model using multiple imputation model similar to 1), using the on-treatment observation period, will be made. In this analysis observations for Subjects that discontinue randomised treatment are imputed based on the treatment arm they were randomised to and Subjects discontinuing treatment in the faster-acting insulin aspart group are given a penalty. This is done to investigate the robustness of the conclusion in the primary analysis with respect to the MAR assumption and mimics a scenario where the HbA_{1c} of the Subjects discontinuing treatment in the faster-acting insulin aspart groups evolve less favourably than predicted. As a first step imputations will be done without penalty assuming MAR in the treatment group. Second, the imputed values for week 16 in the faster-acting insulin aspart group will be added a penalty. This is done repeatedly, gradually increasing the penalty until the conclusion from the non-inferiority analysis no longer holds. This will serve as a sensitivity analysis for the non-inferiority analysis and the specific value of the penalty that changes the conclusion will be used to evaluate the robustness of the conclusion of the non-inferiority analysis.
- 6) A tipping point analysis based on a statistical model using multiple imputation, similar to 5) but with the modification that Subjects discontinuing treatment due to non-eligibility (Subjects discontinuing faster-acting insulin aspart/NovoRapid[®] prematurely due to criteria 1, 2, 3, and 4) in the faster-acting insulin aspart group will not have a penalty added. These analyses are motivated by the fact that data from Subjects prematurely discontinuing faster-acting insulin aspart/NovoRapid[®] due to non-eligibility can reasonably be assumed to be missing completely at random.
- 7) The same statistical model using multiple imputations as the analysis in 4), but using the PP analysis set and analysed using the on-treatment observation period. This analysis will

investigate the situation that Subjects might have deviated from the inclusion and exclusion criteria and will serve as sensitivity analysis for the non-inferiority analysis.

17.4 Secondary endpoints

17.4.1 Confirmatory secondary endpoints

If the effect of CSII treatment with faster-acting insulin aspart can be confirmed in the primary analysis, the trial also aims to confirm the superiority of CSII treatment with faster-acting insulin aspart, for a number of secondary confirmatory endpoints.

The steps used in the hierarchical testing procedure are as follows:

Step 1 (Primary analysis): HbA_{1c} non-inferiority of faster-acting insulin aspart versus NovoRapid[®]

Step 2: 1-hour PPG increment (meal test) superiority of faster-acting insulin aspart versus NovoRapid[®]

Step 3: HbA_{1c} superiority of faster-acting insulin aspart versus NovoRapid[®]

Step 4: 1,5-anhydroglucitol superiority of faster-acting insulin aspart versus NovoRapid[®]

Step 5: time spent in low IG (≤ 3.9 mmol/L [70 mg/dL]) superiority of faster-acting insulin aspart versus NovoRapid[®]

The primary estimand for the primary endpoint will be repeated for the confirmatory secondary endpoints, change from baseline in 1-hour PPG increment (meal test), change from baseline in 1,5-anhydroglucitol and change from baseline of time spent in low IG (≤ 3.9 mmol/L [70 mg/dL]) during CGM 16 weeks after randomisation. The analyses related to these estimands are defined below and will be used for the decisions to continue or not, throughout the hierarchical testing procedure. These analyses will be based on the FAS and use the in-trial observation period.

As sensitivity analyses the secondary analysis associated with the secondary estimand for the primary endpoint will also be repeated for the confirmatory secondary endpoints. The analyses will be based on the FAS and using the on-treatment observation period.

Change from baseline in 1-hour PPG increment 16 weeks after randomisation (meal test) (Step 2)

As the second step of the hierarchical testing procedure, change from baseline in 1-hour PPG increment 16 weeks after randomisation will be tested for superiority of faster-acting insulin aspart compared to Novo Rapid[®].

The 1-hour PPG increment will be analysed based on the laboratory measured values in the meal test.

The 1-hour PPG increment endpoint will be analysed using the FAS and the in-trial observation period based on a multiple imputation technique where the change from baseline in 1-hour PPG increment at week 16 for subjects withdrawn from trial are imputed based on data from completers in the NovoRapid[®] arm. Multiple copies (100 copies) of the full dataset will be generated by imputing missing values based on estimated parameters as follows:

- An analysis of variance model with strata (two levels based on use of own CGM or not), previous insulin use (three levels: NovoRapid[®], Apidra[®], Humalog[®]), and region as factors and baseline 1-hour PPG increment as covariate is fitted to the change from baseline in 1-hour PPG increment at week 16 for the NovoRapid[®] group only. The estimated parameters, and the variance, from this model are used to impute missing values using stochastic simulation at week 16 for subjects in both treatment groups in order to generate 100 complete datasets.
- For each of the complete data sets, the change from baseline to week 16 is analysed using an analysis of variance model with treatment, strata (two levels based on use of own CGM or not), previous insulin use (three levels: NovoRapid[®], Apidra[®], Humalog[®]), and region as factors, and baseline 1-hour PPG increment as covariate.
- The estimates and standard deviations for the 100 data sets are pooled to one estimate and associated standard deviation using Rubins formula. From this, the pooled estimates and 95% confidence interval for the treatment difference is calculated.

The superiority will be assessed by comparing the upper limit of the 95% CI to 0. If the upper 95% CI is below 0 then superiority will be confirmed.

Change from baseline in HbA_{1c} 16 weeks after randomisation (Step 3)

As the third step in the hierarchical testing, superiority of HbA_{1c} 16 weeks after randomisation with faster-acting insulin aspart compared to NovoRapid[®] is to be confirmed.

The confidence interval from the primary analysis 1) will be used to determine superiority. Superiority will be confirmed if the upper boundary of the two-sided 95% confidence interval of the mean treatment difference (faster-acting insulin aspart minus NovoRapid[®]) is below 0%.

Change from baseline in 1,5-anhydroglucitol 16 weeks after randomisation (Step 4)

Step 4 in the hierarchical testing procedure is to confirm superiority of change from baseline in 1,5-anhydroglucitol 16 weeks after randomisation with faster-acting insulin aspart compared to NovoRapid[®].

The change from baseline in 1,5-anhydroglucitol will be analysed using a model similar to 1), but with baseline 1,5-anhydroglucitol as a covariate.

Superiority will be confirmed if the upper boundary of the two-sided 95% confidence interval of the mean treatment difference (faster-acting insulin aspart minus NovoRapid[®]) is below 0.

Change from baseline of time spent in low IG (≤ 3.9 mmol/L [70 mg/dL]) during CGM 16 weeks after randomisation (Step 5)

The time spent in low IG is defined for each Subject at each CGM period as the accumulated time in hours spent below or equal to 3.9 mmol/L [70 mg/dL] from the first valid sensor value divided by the actual duration of the profile. To report the endpoint in minutes per 24 hours the ratio is multiplied by 1440.

Step 5 of the hierarchical testing procedure is to confirm superiority of change from baseline of time spent in low IG (≤ 3.9 mmol/L [70 mg/dL]) during CGM 16 weeks after randomisation with faster-acting insulin aspart compared to NovoRapid[®].

The change from baseline of time spent in low IG (≤ 3.9 mmol/L [70 mg/dL]) will be analysed with a model similar to 1), but with the baseline value of time in hypoglycaemia as covariate.

17.4.2 Supportive secondary endpoints

17.4.2.1 Efficacy endpoints

All endpoints except insulin dose and insulin pump parameters in this section will be assessed using the FAS and the in-trial observation period and repeated using the on-treatment observation period. Insulin dose and insulin pump parameters will be presented using the safety analysis set and will therefore only use the on-treatment observation period.

Change from baseline in FPG to 16 weeks after randomisation

Change from baseline in FPG 16 weeks after randomisation will be analysed on all planned post-baseline measurements until or at 16 weeks with a model similar to 1) except with baseline FPG as covariate.

Percentage of Subjects reaching HbA_{1c} target 16 weeks after randomisation:

HbA_{1c} < 7.0%

A dichotomous (responder/non-responder) endpoint will be defined based on whether a Subject has met the HbA_{1c} target (HbA_{1c} < 7.0% (53 mmol/mol)) 16 weeks after randomisation.

This responder endpoint will be analysed based on a logistic regression model using treatment, strata (two levels based on use of own CGM or not), previous insulin use (three levels: NovoRapid[®], Apidra[®], Humalog[®]), and region as factors, and baseline HbA_{1c} as covariate. In analysis of the in-trial observation period Subjects without an HbA_{1c} measurement at week 16 will be treated as non-responders. In the on-treatment observation period analysis both Subjects who discontinue faster-acting insulin aspart/NovoRapid[®] or withdraw from trial is included as non-responders.

HbA_{1c} <7.0 % without severe hypoglycaemia

A dichotomous (responder/non-responder) endpoint will be defined based on whether a Subject has met the HbA_{1c} target (HbA_{1c} <7.0% (53 mmol/mol)) 16 weeks after randomisation without treatment emergent severe hypoglycaemic episodes.

This responder endpoint will be analysed based on a logistic regression model using treatment, strata (two levels based on use of own CGM or not), previous insulin use (three levels: NovoRapid[®], Apidra[®], Humalog[®]), and region as factors and baseline HbA_{1c} as covariate. In the analysis of the in-trial observation period Subjects without an HbA_{1c} measurement at week 16 will be treated as non-responders. In the on-treatment observation period analysis both Subjects who discontinue faster-acting insulin aspart/NovoRapid[®] or withdraw from trial will be included as non-responders.

Change from baseline in 30- min, 1- hour, 2- hour, 3- hour and 4- hour PPG and in 30- min, 2- hour, 3- hour and 4- hour PPG increment after 16 weeks after randomisation (meal test)

Laboratory measured PG from the meal test will be analysed for 30 minutes, 1-hour, 2-hours, 3-hours and 4-hours PPG separately. The corresponding PPG increments will be derived separately using each PPG measurement minus the pre-prandial PG.

Change from baseline in PPG and PPG increment 16 weeks after randomisation will be analysed separately using a model similar to the model used in hierarchical testing procedure step 2 for 1-hour PPG increment 16 weeks after randomisation (meal test) except with the corresponding baseline value as covariate.

Change from baseline in endpoints derived from the 7-7-9 point SMPG profile 16 weeks after randomisation

PPG and PPG increments based on the 7-7-9-point SMPG profiles will be derived separately for PG measurements made 1 hour after the meal. In the following section this distinction will be considered implicit and without further explanation.

Pre-prandial PG and PPG will be recorded by the Subjects as part of the 7-7-9 point SMPG profile prior to three defined visits. Individual mean mealtime PPG (post-breakfast, post-lunch, post-main

evening meal) will be derived from the three profiles. Overall mean PPG will be derived from the individual derived mealtime PPG values.

PPG increment for each meal (breakfast, lunch, main evening meal) will be derived from the 7-7-9 point SMPG profile as the difference between PPG values and the PG value before meal in each separate profile. The mean of the derived increments will then be calculated separately for each meal. Mean 1 hour PPG increments over all meals will be derived as the mean of all corresponding mean meal increments.

- Change from baseline in mean of the 7-7-9-point SMPG profile

The mean of the 7-7-9-point SMPG profile is defined as the area under the curve profile divided by the measurement time, and is calculated using the linear trapezoidal technique.

Change from baseline in the mean of the 7-7-9-point SMPG profile 16 weeks after randomisation will be analysed using a model similar to 1) except with the corresponding baseline value as covariate.

- Change from baseline in mean pre-prandial PG, PPG and PPG increment over all three meals

Change from baseline in mean pre-prandial PG, PPG and PPG increment 16 weeks after randomisation will be analysed separately using a model similar to 1), except with the corresponding baseline value as covariate.

- Change from baseline in individual meal (breakfast, lunch and main evening meal) PPG, PPG increment and pre-prandial PG (pre-breakfast, pre-lunch, pre-main evening meal)

Change from baseline in PPG, PPG increment and pre-prandial PG endpoints 16 weeks after randomisation for the individual meals will be analysed separately using a model similar to 1) except with the corresponding baseline value as covariate.

- Change from baseline in fluctuation in 7-7-9-point profile

The fluctuation in the 7-7-9-point profile is defined as:

$$\frac{1}{T} \int_0^T |PG(t) - \overline{PG}| dt$$

where T , $PG(t)$ and \overline{PG} denotes the length of the profile, the PG value at time t and the mean of the profile, respectively.

Fluctuation in the 7-7-9-point profile will be logarithmically transformed and analysed in the same way as mean of the profile is analysed except with the corresponding log-transformed baseline value as covariate.

Estimated treatment means and the estimated treatment difference with corresponding 95% CI will be back-transformed to the original scale, resulting in estimated geometric means, a treatment ratio and a 95% CI for the treatment ratio.

- Change in nocturnal SMPG measurements

Change from baseline in nocturnal SMPG measurements will be assessed by considering the differences between PG values available at bedtime, at 4 AM and the before breakfast value the following day: (4 AM PG value minus at bedtime PG value), (before breakfast PG value minus at bedtime PG value) and (before breakfast PG value minus 4 AM PG value).

Change from baseline in nocturnal SMPG measurements 16 weeks after randomisation will be analysed in the same way as mean of the profile is analysed, except with the corresponding baseline values as covariate. .

PPG responders (based on mean of PPG measurements in SMPG) 16 weeks after randomisation:

- Overall PPG (1 hour) ≤ 7.8 mmol/L [140 mg/dL]

A dichotomous (responder / non-responder) endpoint will be defined based on whether a Subject has reached an overall mean 1 hour PPG ≤ 7.8 mmol/L [140 mg/dL] 16 weeks after randomisation, where PPG is derived from the 7-7-9 point SMPG profile.

This responder endpoint will be analysed based on a logistic regression model using treatment, strata (two levels based on use of own CGM or not), previous insulin use (three levels: NovoRapid[®], Apidra[®], Humalog[®]), and region as factors, and baseline overall 1-hour mean PPG as covariate. In analysis of the in-trial observation period Subjects without an overall mean 1 hour PPG at week 16 will be treated as non-responder. In the on- treatment observation period analysis both Subjects who discontinue faster-acting insulin aspart/NovoRapid[®] or withdraw from trial will be included as non-responders.

- Overall PPG (1-hour) ≤ 7.8 mmol/L [140 mg/dL] without severe hypoglycaemia

A dichotomous (responder / non-responder) endpoint will be defined based on whether a Subject has reached an overall 1-hour PPG ≤ 7.8 mmol/L [140 mg/dL] 16 weeks after randomisation without any treatment emergent severe hypoglycaemic episodes.

This responder endpoint will be analysed based on a logistic regression model using treatment, strata (two levels based on use of own CGM or not), previous insulin use (three levels: NovoRapid[®], Apidra[®], Humalog[®]) and region as factors, and baseline mean 1-hour PPG as covariate. In analysis of the in-trial observation period Subjects without an overall mean 1 hour PPG at week 16 will be treated as non-responders. In the on- treatment observation period analysis both Subjects who discontinue faster-acting insulin aspart/NovoRapid[®] or withdraw from trial will be included as non-responders.

Change from baseline in lipids-lipoproteins profile 16 weeks after randomisation

Change from baseline in lipid endpoints (LDL, HDL, and total cholesterol) will be analysed separately using a model similar to 1). The lipid endpoints will be log-transformed before they are analysed including the corresponding baseline measurement which is included in the analysis as a covariate. The treatment difference and associated 95% confidence intervals will be back-transformed providing results in terms of ratios of geometric means on the original scale.

Insulin dose (Units/day and Units/kg/day; total basal, total bolus, total daily insulin dose and individual meal insulin dose)

The insulin doses will be summarised descriptively by treatment week according to regimen, both by meal type and as total daily dose in units and units/kg (total daily and separately for each meal time dose). The total daily basal dose will be derived from the total daily dose and bolus doses including correction doses. Insulin doses will be summarised using the on-treatment observation period and using the safety analysis set.

Insulin delivery pump parameters

The insulin pump parameters including insulin carbohydrate ratio, glucose sensitivity factor and active insulin time will be summarised descriptively by treatment week. They will be summarised using the on-treatment observation period and using the safety analysis set.

Supportive secondary CGM-related endpoints

All following endpoints will be assessed 16 weeks after randomisation:

- Percentage of time spent with IG $\leq 2.5, 3.0, 3.5$ mmol/L [45, 54, 63 mg/dL]) and IG $> 10.0, 12.0$ mmol/L [180, 216 mg/dL])
- Incidence of episodes with IG $\leq 2.5, 3.0, 3.5, 3.9$ mmol/L [45, 54, 63, 70 mg/dL]) and IG $> 10.0, 12.0$ mmol/L [180, 216 mg/dL])
- Percentage of time spent within IG target range 4.0-10.0mmol/L (71-180 mg/dL)
- Change from baseline in mean of the IG profile

The mean of the IG profile will be defined as:

$$\overline{IG} = \frac{1}{T} \int_0^T IG(t) dt$$

where T is the time length of the profile and $IG(t)$ is the IG value at time t . (Here $t=0$ represents the time point for the start of the profile.) This mean will be calculated by means of the linear trapezoidal technique.

- Variation in the IG profile

The variation in the IG profile will be defined as:

$$\frac{1}{T} \int_0^T |IG(t) - \overline{IG}| dt$$

where T is the time length of the profile, $IG(t)$ is the IG value at time t , and \overline{IG} is the mean of the IG profile as defined above. (Again, here $t=0$ represents the time point for the start of the profile.) The integral will be calculated by the linear trapezoidal technique. The coefficient of variation (CV%) will also be calculated to describe the IG variation.

- Change from baseline in the AUC_(3.9-IG) for IG ≤ 3.9 mmol/L [70 mg/dL]

The AUC_(3.9-IG) is defined for each Subject at each CGM period as the AUC_(3.9-IG) when IG is below or equal to 3.9 mmol/L [70 mg/dL] from the first valid sensor value divided by the actual duration of the profile. The AUC will be calculated by the linear trapezoidal technique. If the profile has missing sensor values, then the AUC should be calculated for each profile part consisting of non-missing sensor values. The endpoint is then calculated as the sum of the AUCs for all profile parts divided by the sum of the duration of the profile parts for which AUC is calculated.

IG measurements during meal test will be excluded.

All CGM endpoints will be summarised descriptively by treatment.

Supportive secondary CGM and meal-characteristics endpoints

The following endpoints will be assessed 16 weeks after randomisation:

- Change from baseline in mean IG increment (0-30 min, 0-1 hour and 0-2 hours after start of the meal)

The mean IG (meal) increment will be defined as the mean across main meals of the prandial increments, i.e. the difference between IG 30 (1 or 2 hours, respectively) after the meal and IG before the meal

- Change from baseline in mean IG peak after start of meal

The mean IG peak after start of meal will be derived as mean across main meals of the IG maximum values within 4 hours after start of the meal.

- Change from baseline in mean time to the IG peak after meal

The mean time to the IG peak after meal is derived as the mean time to the IG peak across main meals.

These endpoints will also be derived for each main meal separately (breakfast, lunch and main evening meal). IG measurements during meal test will be excluded. All endpoints will be analysed separately, using a model similar to 1) except with the corresponding baseline value as covariate.

All CGM endpoints will be summarised descriptively by treatment.

Supportive secondary efficacy endpoints related to CGM and meal test

Endpoints listed below will be assessed during meal test and based on CGM measurements.

The following endpoints will be assessed 16 weeks after randomisation:

- Change from baseline in $AUC_{IG,0-15min}$
- Change from baseline in $AUC_{IG,0-30min}$
- Change from baseline in $AUC_{IG,0-1h}$
- Change from baseline in $AUC_{IG,0-2h}$
- Change from baseline in $AUC_{IG,0-4h}$
- Change from baseline in time to the IG peak after start of meal
- Change from baseline in IG peak after start of meal

$AUC_{IG,0-15 min}$, $AUC_{IG,0-30 min}$, $AUC_{IG,0-1h}$, $AUC_{IG,0-2h}$, and $AUC_{IG,0-4h}$ will be calculated as the AUC IG using the linear trapezoidal technique. The endpoint will be analysed using an analysis of variance model including treatment, previous insulin use (three levels: NovoRapid[®], Apidra[®], Humalog[®]), region and strata as factors, and the corresponding baseline value as covariate.

The IG peak after start of meal will be derived as the IG maximum values within 4 hours after start of the meal-test meal.

Change from baseline in IG peak and time to IG peak 16 weeks after randomisation will be compared separately between treatments using an analysis of variance model including treatment, strata (two levels based on use of own CGM or not), previous insulin use (three levels: NovoRapid[®], Apidra[®], Humalog[®]), and region as factors, and the corresponding baseline value as covariate.

17.4.2.2 Safety endpoints

All safety endpoints will be compared using the on-treatment observation period. In terms of adverse events, as a minimum, serious adverse events will be tabulated separately also using the in-trial observation period.

All events in the in-trial observation period will be listed with information about whether it appeared in the on-treatment observation period or not.

Number of treatment emergent Adverse Events (AEs)

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

A Treatment Emergent Adverse Event (TEAE) is defined as an event that has an onset date on or after the first day of exposure to randomised treatment, and no later than seven days after the last day of randomised treatment.

TEAEs are summarised descriptively, whereas AE's not defined as treatment emergent are presented in listings, including AEs reported in the 30-day follow-up period. The summaries of TEAEs are made displaying the number of Subjects with at least one event, the percentage of Subjects with at least one event, the number of events and the event rate per 100 patient years of exposure. These summaries are done by seriousness, severity, relation to insulin treatment, relation to device, premature treatment discontinuation due to AEs and outcome.

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

- All TEAEs
- Serious TEAEs
- Possibly or probably related TEAEs
- Severe TEAEs
- TEAEs with preferred term that are experienced by at least 5% of the Subjects in any treatment arm or by at least 5% of all Subjects

For AEs where additional information is recorded, this will be listed.

AEs occurring during the run-in period are considered non-treatment emergent and will be summarised separately.

Number of treatment emergent infusion site reactions

Infusion site reactions occurring during the trial will be summarised using the on-treatment observation periods, and listed.

Classification of Hypoglycaemia

Treatment emergent: hypoglycaemic episodes will be defined as treatment emergent if the onset of the episode occurs on or after the first day of IMP administration after randomisation and no later than one day after the last day on IMP.

Nocturnal hypoglycaemic episodes: are episodes occurring between 00:01 and 05.59 both inclusive.

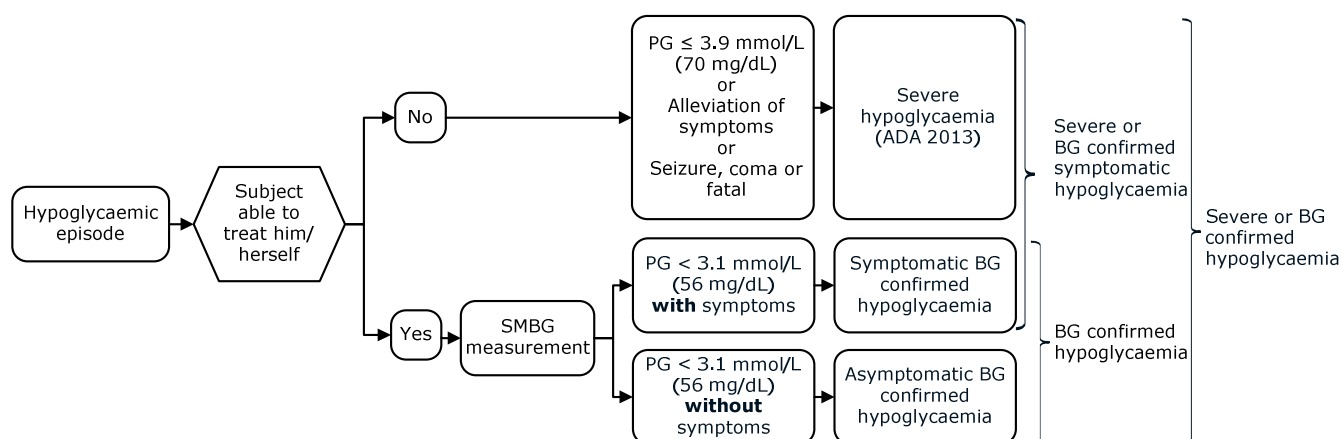
Hypoglycaemic episodes are classified according to the Novo Nordisk classification of hypoglycaemia (see [Figure 17-1](#)) and the American Diabetes Association (ADA) classification of hypoglycaemia (see [Figure 17-2](#)).

Novo Nordisk classification of hypoglycaemia

In normal physiology, symptoms of hypoglycaemia occur below a PG level of 3.1 mmol/L [56 mg/dL]³⁶. 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 (see [Figure 17–1](#)) in addition to the ADA classification:

- Severe hypoglycaemia according to the ADA classification²⁹
- Severe or BG confirmed hypoglycaemia: An episode that is severe according to the ADA classification²⁹ or BG confirmed by a PG value <3.1 mmol/L [56 mg/dL] **with** or **without** symptoms consistent with hypoglycaemia



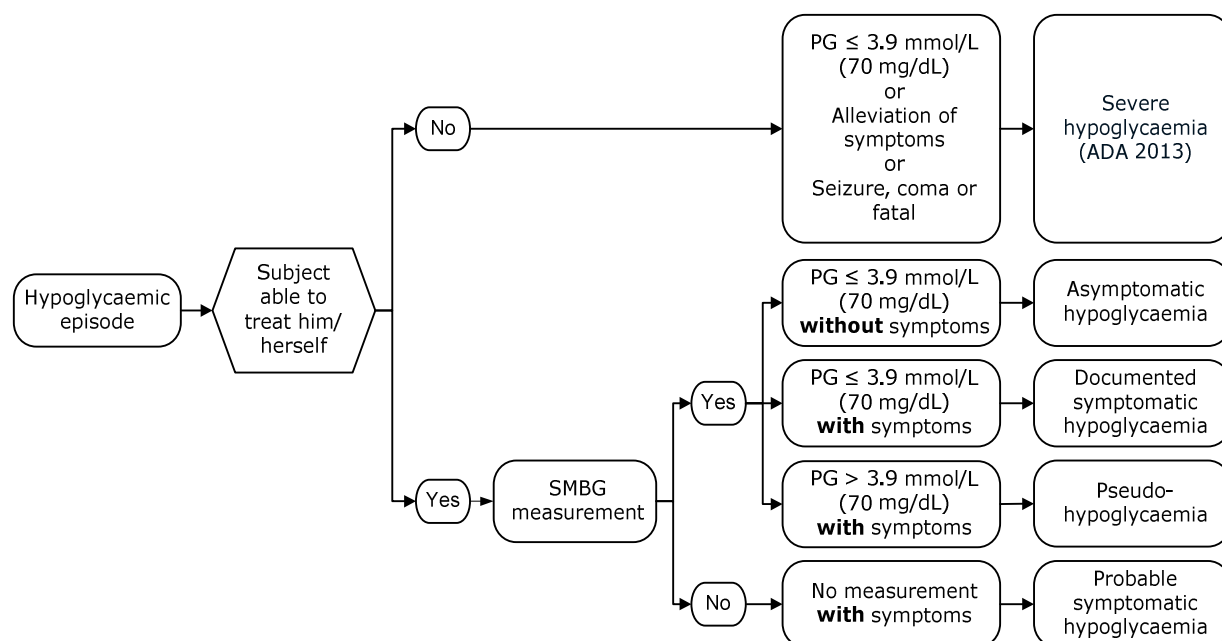
Note: Glucose measurements are performed with capillary blood calibrated to plasma equivalent glucose values

Figure 17–1 Novo Nordisk classification of hypoglycaemia

ADA classification²⁹ 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]



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

Figure 17–2 ADA classification of hypoglycaemia

Data on-treatment emergent hypoglycaemic episodes are 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). Separate summaries are made by severity considering all episodes, nocturnal and daytime episodes using Novo Nordisk and ADA classified episodes. All episodes will also be summarised by category, including summaries in relation to time since start of meal, as occurring during first 1, 2, and 2 (inclusive) to 4 hours

(exclusive) after start of meal, respectively. Non-treatment emergent hypoglycaemic episodes will be listed.

The number of treatment emergent severe or BG confirmed hypoglycaemic episodes (all, daytime, nocturnal, 1 hour, 2 hour, 4 hour and 2 (inclusive) to 4 hours (exclusive) after start of the meal) will be analysed based on the FAS using a negative binomial regression model with a log-link function and the logarithm of the time period in which a hypoglycaemic episode is considered treatment emergent as offset. The model will include treatment, strata (two levels based on use of own CGM or not), previous insulin use (three levels: NovoRapid[®], Apidra[®], Humalog[®]), and region as factors. To the extent where data allow, separate analyses will be performed for severe episodes.

Number of unexplained episodes of hyperglycaemia (confirmed by SMPG)

The number of unexplained episodes of hyperglycaemia will be summarised in a frequency table. Unexplained hyperglycaemia is defined as a confirmed PG value ≥ 16.7 mmol/L (300 mg/dL) and is unexplained (i.e. no apparent medical, dietary, insulin dosage or pump failure reason). The percentage of Subjects with unexplained hyperglycaemia will be presented.

Physical examination

The physical examination parameters (head, ears, eyes, nose, throat, neck, respiratory system, cardiovascular system, gastrointestinal system incl. mouth, musculoskeletal system, central and peripheral nervous system, skin), and their change from baseline, will be summarised descriptively. All findings will be listed.

Electrocardiogram

ECG findings will be summarised descriptively including summaries of the change from baseline. Change from baseline will be summarised as normal/abnormal not clinically significant/abnormal clinically significant categorisation in shift tables.

Vital signs (blood pressure, pulse)

Vital signs include diastolic blood pressure, systolic blood pressure and pulse. The measurements will be summarised descriptively using both the actual values as mean change.

Fundus photography/fundoscopy

Fundus photography/fundoscopy findings and the change from baseline will be summarised descriptively.

Clinical laboratory assessments

Change from baseline 16 weeks after randomisation in central laboratory assessments:

- Haematology (haemoglobin, haematocrit, erythrocytes, thrombocytes, and leucocytes)
- Biochemistry (total protein, creatinine, ALT, AST, AP, sodium, potassium, albumin, and total bilirubin)
- Urinalysis (albumin/creatinine ratio, erythrocytes, protein, and ketones)

Individual laboratory values will be compared to their relevant reference range (when existing) and flagged as being below or above the range. The measurements and their change from baseline will be summarised descriptively. Change from baseline will be summarised descriptively using both the actual values and the low/normal/high categorisation in shift tables.

Change from baseline in body weight and BMI 16 weeks after randomisation

The measurements will be summarised descriptively using the actual values as mean change.

Change from baseline in body weight will be analysed using a statistical model similar to 1), except with the corresponding baseline measurement as covariate. The analysis will be based on the safety analysis set and the on-treatment observation period.

Number of change-of-infusion-sets per week during 16 weeks after randomisation

For each Subject this is calculated as the total number of infusion sets used divided by the actual duration of the randomised treatment period in days, multiplied by seven. It will be summarised for each treatment using descriptive statistics.

Number of Subjects with at least one non-routine change categorised by reasons for change

The percentage of Subjects with at least one non-routine change will be presented, categorised by reasons for change, in a frequency table by treatment.

18 Ethics

The trial will be conducted in compliance with ICH GCP¹ and applicable regulatory requirements, and in accordance with the Declaration of Helsinki².

All Subjects included in the trial will be treated with their pre-trial insulin in the run-in period and thereafter be randomised to either faster-acting insulin aspart or NovoRapid[®].

The most common side effect of all available insulin preparations is hypoglycaemia. The Investigator will explain to the Subject how they should check their BG with the BG meter provided by Novo Nordisk, and what precautions to take.

Subjects randomised in the trial will be transferred to a treatment regimen anticipated to be either better than or equal to the treatment they receive at the time they entered the trial. However, participation in the study will mean additional visits to the clinic and additional assessments as some of the assessments required for the study are not performed in normal practice or are performed less frequently.

At the end of treatment (Visit 22), the Subject and Investigator will decide on the best available treatment on the market. It will not be possible for the Subjects to continue using faster-acting insulin aspart trial product.

18.1 Summary of clinical pharmacology

Results from clinical pharmacology trials comparing pharmacokinetic and pharmacodynamic properties of faster-acting insulin aspart and NovoRapid[®] have shown that faster-acting insulin aspart elicited an earlier onset of insulin exposure and a greater early exposure to insulin aspart than NovoRapid[®] in Subjects with T1DM, with the largest difference found within the first 15 minutes after injection⁷. Faster-acting insulin aspart also elicited a greater early glucose-lowering effect than NovoRapid[®], but no statistically significant difference between faster-acting insulin aspart and NovoRapid[®] in total glucose-lowering effect⁷.

In an exploratory insulin pump trial a greater BG lowering effect during 2 hours after a standardised meal test was seen. In this trial the mean prandial IG increments measured by CGM at 60 and 120 minutes after all meals were statistically significantly lower for faster aspart when compared to NovoRapid[®].

No safety concerns were raised during any of the trials.

18.2 Clinical benefits and risk considerations

The current trial will compare the effect and safety of faster-acting insulin aspart versus NovoRapid[®] in CSII. The currently available data demonstrate that treatment with faster-acting

insulin aspart results in an increased early absorption of faster-acting insulin aspart compared to NovoRapid[®], thereby providing a faster action.

For the individual Subjects, the personal health-related benefits are related to the medical examination and the benefit from an intensified insulin treatment regimen anticipated to be better than or equal to the treatment they receive at the time they enter the trial. However, they will have to spend some extra time monitoring and recording data and on additional visits to the clinic and phone contacts.

The very high frequency of contacts between the trial population and the Investigator and the thorough evaluation of basal rates, insulin sensitivity and insulin to carbohydrate-ratio will provide the opportunity for optimising the titration of basal and bolus insulin based on SMPG values and thereby may contribute to obtaining improved HbA_{1c} results. All Subjects will have reinforced pump and diabetes training regarding carbohydrate counting.

For the individual Subject, the anticipated risks include hypoglycaemia, hyperglycaemia, infusion site reactions, CGM related inconveniences, systemic allergic reactions and antibody development. Frequent site visits, close monitoring and supervision, as well as frequent measurement of BG levels will enable the site to react in a timely manner if the Subject should be affected by the described risks.

A consequence of the pharmacodynamics of rapid-acting insulin analogues is that if hypoglycaemia occurs, it may occur earlier after an injection than with soluble human insulin. Similarly, it should be kept in mind that the onset of action of faster aspart is expected to be faster than with NovoRapid[®].

The small s.c. depot at the infusion site could be seen as a potential risk leading to shortened time to hypoinsulinaemia, hyperglycaemia and potentially diabetic ketoacidosis in case of technical problems with the pump.

Infusion site reactions can occur. The nature of the infusion site reactions is expected to be mild, transient and more of a visual character and is not expected to be of concern to the Subject's safety.

In the periods where a blinded CGM is being worn, inconvenience from the CGM sensor due to local skin irritation or pain from the attached small recorder might happen but is considered to be transient and not to be of any safety concerns to the Subject.

The blood samples taken during meal tests might be inconvenient to the Subjects but is not of any safety concern.

No maximum dose of insulin is specified as doses are titrated individually. All Subjects will perform at least 4-point profiles on a daily basis throughout the trial for safety purposes and for the

purpose of insulin titration. More frequently sampled SMPG profiles can be expected in a shorter period after randomization for adjustment of the basal rates and pump adjustments.

All Subjects will have diabetes training regarding carbohydrate counting and handling of the insulin pump including training in use of the Bolus Wizard[®] and assessment of the basal rates.

Insulin aspart is marketed as NovoRapid[®]. NovoRapid[®] is approved for pump use. Please refer to the local labelling for a description of risks and benefits.

All treatments are contraindicated in case of hypersensitivity to the active substances or any of the excipients.

When discontinuing trial treatment, the Subject will be switched to a suitable marketed product at the discretion of the Investigator.

18.2.1 Conclusion on clinical benefits and risk considerations

Subjects in this trial will benefit from an intensified insulin treatment in a CSII regimen in a treat-to-target setting under close supervision.

The safety profile of insulin aspart is well established from the market use of NovoRapid[®]. The data available for faster-acting insulin aspart in non-clinical and clinical studies taken together with review of the additional excipients in the faster-acting insulin aspart formulation have not revealed any safety issues that would prohibit the administration of faster-acting insulin aspart formulations in accordance with the planned trial.

It is therefore concluded that the clinical benefits from the trial as well as the contribution to the development of a new faster-acting insulin aspart outweigh the potential risks of participating in the trial.

18.3 Informed Consent

In seeking and documenting SI/IC, the Investigator must comply with applicable regulatory requirement(s) and adhere to ICH GCP¹ and the requirements in the Declaration of Helsinki².

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

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

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

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

If information becomes available that may be relevant to the Subject's willingness to continue participating in the trial, the Investigator must inform the Subject in a timely manner, and revised SI/IC must be provided and a new SI/IC must be obtained.

18.4 Data handling

If the Subject is discontinued from treatment, withdraws consent, or is lost to follow-up, then the Subject's data will be handled as follows:

- Data already collected and data collected at the EoT visit will be retained by Novo Nordisk, entered into the database and used for the trial report
- Safety events will be reported to Novo Nordisk and regulatory authorities according to local/national requirements

If data is used, it will always be in accordance with local regulations and IRBs/IECs.

18.5 Information to Subject during trial

The site will be offered a communication package to the Subject during the conduct of the trial. The package content is issued by Novo Nordisk. The communication package will contain the letters intended for distribution to the Subjects. The letters will be translated and adjusted to local requirements and distributed to the Subject by discretion of the Investigator. The Subject may receive a "welcome to the trial letter" and a "thank for your participation letter" at the end of the trial. Further the Subject may receive trial letters during the trial period.

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

18.6 Premature termination of the trial and/or trial site

Novo Nordisk, the IRBs/IECs, or a regulatory authority may decide to stop the trial, part of the trial or a trial site at any time, but agreement on procedures to be followed must be obtained.

If a trial is suspended or prematurely 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 IRBs/IECs and provide a detailed written explanation. The relevant regulatory authorities must be informed.

If, after the termination of the trial, the risk/benefit analysis changes, the new evaluation must be provided to the IRBs/IECs in case it has an impact on the planned follow-up of Subjects who have participated in the trial. If it has an impact, the actions needed to inform and protect the Subjects should be described.

19 Protocol compliance

19.1 Protocol deviation

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 edit checks in the eCRF or via listings from the trial database.

Documentation on protocol deviations must be kept in the Investigator's trial master file and Novo Nordisk trial master file.

19.2 Prevention of Missing Data

A significant proportion of missing data can be potential source of bias when analysing data in clinical trials leading to a risk of misinterpretation of the trial results. Missing data may affect both estimation of treatment effect and the confidence interval that surrounds it as well as the representativeness of the sample size in relation to the target population.

The run-in period in this trial will reduce the likelihood of drop-outs as only those who adhere to the protocol requirements will undergo randomisation. Subjects will during the run-in period get an understanding of what is expected from them when taking part in the trial and thereby minimise discontinuation from trial product post randomisation. In addition, only absolutely necessary criteria for premature discontinuation of trial product primarily focusing on Subjects safety are included and thereby reducing the number of discontinuations and securing maximum amount of data.

Close surveillance of retention rate will be performed throughout the trial by Novo Nordisk with focus on reasons for premature discontinuation of trial product or withdrawal from trial (e.g. adverse events, Subject withdrawing consent or due to any of the criteria for premature discontinuation of trial product). In case of decreasing retention rate at a site, the site will be re-trained in the importance of emphasising to the Subject the importance of continuing in the trial and adhering to trial procedures.

Investigators must make every effort to ensure all assessments are performed and data are collected. If missing data does occur the reason will be collected via the protocol deviation process (see section [19.1](#)) and trends will be monitored on an on-going basis throughout the trial followed by appropriate actions (e.g. training of Subjects and site staff).

It should be noted that there is no universal best statistical method for handling missing data. The assumptions that go into the primary statistical analysis will be investigated by further sensitivity analysis. Considerably consistent results from sensitivity analyses and from the primary analysis will provide assurance of the overall trial conclusions. In the final clinical trial report, results for all pre-specified analyses and any substantial differences between the analyses will be the Subject of explicit discussion.

20 Audits and inspections

Any aspect of the clinical trial may be Subject to audits conducted by Novo Nordisk or inspections from domestic or foreign regulatory authorities or from IRBs/IECs. Audits and inspections may take place during or after the trial. The Investigator and the site staff as well as Novo Nordisk staff have an obligation to cooperate and assist in audits and inspections. This includes giving auditors and inspectors direct access to all source documents and other documents at the trial site relevant to the clinical trial. This includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are relevant to the evaluation of the trial.

21 Critical documents

Before a trial site is allowed to start screening Subjects, the following documents must be available to Novo Nordisk:

- Regulatory approval and/or acknowledgement of notification as required
- Approval/favourable opinion from IRBs/IECs clearly identifying the documents reviewed as follows: protocol, any protocol amendments, SI/IC, any other written information to be provided to the Subject and Subject recruitment materials
- List of IRB/IEC members and/or constitution(or a general assurance number/statement of compliance)
- Curricula vitae of Investigator and sub-Investigator(s) (current, dated and signed - must include documented GCP training or a certificate)
- Signed receipt of Investigator's Brochure
- SMPC for NovoRapid®
- Signed and dated Agreement on Protocol
- Signed and dated agreement on protocol amendment, if applicable
- Contract, signed by the Investigator and/or appropriate parties on behalf of the Investigator's site and Novo Nordisk
- Source document agreemeazxsnt
- Central laboratory certification and normal ranges
- Insurance statement, if applicable
- Financial Disclosure Form from Investigator and sub-Investigator(s)
- For US trial sites: verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest
- For US trial sites: FDA Form 1572 must be completed and signed by the Investigator at each site

FDA Form 1572

For US sites:

- Intended for US sites
- Conducted under the Investigational New Drug (IND)
- All US Investigators, as described above, will sign FDA Form 1572

For sites outside the US:

- Intended for participating sites outside of the US
- Not conducted under the IND
- All Investigators outside the US will not sign the FDA Form 1572

Novo Nordisk will analyse and report data from all sites together.

By signing the protocol, each Investigator agrees to comply fully with ICH GCP¹, applicable regulatory requirements and the Declaration of Helsinki².

By signing the protocol, each Investigator also agrees to allow Novo Nordisk to make Investigator's name and information about site name and address publically available if this is required by national or international regulations.

22 Responsibilities

All staff (Novo Nordisk, site, laboratory, CRO etc.) will conduct the trial in compliance with ICH GCP¹, applicable regulatory requirements and the Declaration of Helsinki².

22.1 Investigator responsibilities

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

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

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

The Investigator will follow instructions from Novo Nordisk when processing data.

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 of the data produced) in the Investigator's trial file. The documents including the subject identification code list should be kept in a secure locked facility, so 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 tasks.

22.2 Novo Nordisk responsibilities

Novo Nordisk will be responsible for the preparation of the protocol and any updates, the eCRF, the supply of trial products and auxiliary supplies as defined in section [9](#), monitoring, data management, and statistics, the CTR as documented by Novo Nordisk procedures and internal specific agreements as well as the current GCP guidelines¹.

Novo Nordisk will provide an electronic system for electronic data capture (EDC). This system, and the support services to the system, will be supplied by a clinical services vendor. The activities of the clinical services vendor will be under the direction and supervision of Novo Nordisk. Furthermore, Novo Nordisk will be responsible for the IV/WRS.

Surveillance of insulin titration will be performed by Novo Nordisk. The titration deviations will be reviewed by titration surveillance consultants from Novo Nordisk.

A central laboratory will be responsible for providing all laboratory supplies for the analysis of all blood and urine samples taken during the trial.

23 Reports and publications

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 physicians 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.

One Investigator will be appointed by Novo Nordisk to review and sign the CTR (signatory Investigator) on behalf of all participating Investigators. The signatory Investigator will be appointed based upon the criteria defined by the ICMJE for research publications³⁷.

23.1 Communication of results

Novo Nordisk commits to communicating, and otherwise making available for public disclosure, results of trials regardless of outcome. Public disclosure includes publication of a paper in a 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, as reflected in the Novo Nordisk Code of Conduct for Clinical Trial Disclosure.

Novo Nordisk reserves the right to defer the release of data until specified milestones are reached, for example when the CTR 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. All authors will be given the relevant

statistical tables, figures, and reports needed to evaluate the planned publication. 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.

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.

Novo Nordisk maintains the right to be informed of plans by any Investigator to publish and to review any scientific paper, presentation, communication or other information concerning the investigation described in this protocol. Any such communication must be submitted in writing to Novo Nordisk before submission for comments. Comments will be given within one month from receipt of the planned communication.

23.1.1 Authorship

Authorship of publications should be in accordance with the Uniform Requirements of the International Committee of Medical Journal Editors (ICMJE³⁷, sometimes referred to as the Vancouver Criteria).

The Investigator(s) offered authorship will be asked to comment and approve the publication.

23.1.2 Site-specific publication(s) by Investigator(s)

For a multi-centre clinical trial, analyses based on single-site data usually have significant statistical limitations and frequently do not provide meaningful information for healthcare professionals or Subjects, and therefore may not be supported by Novo Nordisk. It is a Novo Nordisk policy that such individual reports do not precede the primary manuscript and should always reference the primary manuscript of the trial.

Novo Nordisk reserves the right to prior review of such publications. Further to allow for the primary manuscript to be published as the first, Novo Nordisk asks for deferment of publication of individual site results until the primary manuscript is accepted for publication. As Novo Nordisk wants to live up to the industry publication policy, submission of a primary publication will take place no later than 18 months after trial completion.

23.2 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.

24 Retention of clinical trial documentation

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

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. Site-specific CRFs and other Subject data (in an electronic readable format or as paper copies or prints) will be provided to the Investigator before access is revoked to the systems and/or electronic devices supplied by Novo Nordisk. These data must be retained by the trial site. If the provided data (e.g. the CD-ROM) is not readable during the entire storage period, the Investigator can request a new copy. A copy of all data will be stored by Novo Nordisk.

Novo Nordisk will maintain Novo Nordisk documentation pertaining to the trial for as long as the product is on the market plus 20 years.

The files from the trial site/institution must be retained for 15 years after the completion of the trial, or longer if required by local regulations or Novo Nordisk. In any case trial files cannot be destroyed until the trial site/institution is notified by Novo Nordisk. The deletion process must ensure confidentiality of data and must be done in accordance with local regulatory requirements.

25 Institutional Review Boards/Independent Ethics Committees and regulatory authorities

Institutional Review Boards/Independent Ethics Committees

Written approval or favourable opinion must be obtained from IRB/IEC prior to commencement of the trial.

During the trial, the Investigator or Novo Nordisk, as applicable, must promptly report the following to the IRB/IEC, in accordance with local requirements: updates to IB, unexpected SAEs where a causal relationship cannot be ruled out, protocol amendments according to local requirements, deviations to the protocol implemented to eliminate immediate hazards to the Subjects, new information that may affect adversely the safety of the Subjects or the conduct of the trial (including new benefit-risk analysis in case it will have an impact on the planned follow-up of the Subjects), annually written summaries of the trial status, and other documents as required by the local IRB/IEC.

The Investigator must ensure submission of the CTR synopsis to the IRB/IEC.

Protocol amendments must not be implemented before approval or favourable opinion according to local regulations, unless necessary to eliminate immediate hazards to the Subjects.

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

Regulatory Authorities

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

26 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.

Novo Nordisk accepts liability in accordance with:

For **Belgium**: Law concerning experiments on the human person of 07 May 2004 – Article 29: § Even if without fault, the sponsor is liable for the damage which the Subject and/or his rightful claimants sustain and which shows either a direct or an indirect connection with the trial

For **Netherlands**: Wetgeving betreffende geneesmiddelen; geneesmiddelenwet 1 juli 2007 (Medicines Law, 1 July 2007).

De Wet Medisch-wetenschappelijk Onderzoek met mensen (WMO), 1 maart 2006 (Medical Research Involving Human Subjects Act, 1 March 2006).

Besluit verplichte verzekering bij medisch-wetenschappelijk onderzoek met mensen 2015, 24 november 2014 (Decree compulsory insurance in medical research involving human Subjects 2015, 24 November 2014).

For **France**: The French Public Health Code article L 1121-10 (law n° 2004-806 of 9 August 2004 art. 88 I, IX, Journal Officiel of 11 August 2004.

"The sponsor is responsible for identification of the harmful consequences of the biomedical the research for the person lending himself thereto and for indemnification of his beneficiaries, except in case of proof, incumbent on it, that the prejudice is not attributable to his fault or if the fault of any intervening party, without the sponsor's being entitled to call on acts by a third party or the voluntary withdrawal of the person who had initially consented to cooperating in the research".

For **Russia**: Federal law "On Medical Products" #86-FZ dated 22 June 1998 (last amendments dated 30 December 2008. Federal Law of 12 April 2010 No. 61-FZ "On Medicinal Drugs' Circulation".

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Protocol
Trial ID: NN1218-3854
UTN: U1111-1118-2480
EudraCT no.: 2010-024054-11

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Date: 04 February 2016
Version: 4.0
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Fast-acting insulin aspart
Trial ID: NN1218-3854
Clinical Trial Report
Appendix 16.1.1

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Date:
Version:
Status:

08 February 2018
1.0
Final

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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, final version 4
dated 04 February 2016

Trial ID: NN1218-3854

Efficacy and Safety of Continuous Subcutaneous Insulin Infusion of
Faster-acting Insulin Aspart compared to NovoRapid® in Adults with
Type 1 Diabetes

onset® 5

Trial phase: 3b

Applicable to Russia

Amendment originator:



TrialOps 5 , Insulin & Devices

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1 Introduction including rationale for the protocol amendment

This local protocol amendment is being generated for Russia to ensure that it is clear to all parties involved in the execution of this trial that the blood glucose meter Ascensia Contour® Next Link used in this trial is not approved in Russia and will therefore be used as a device for investigational use in Russia.

Further, this protocol amendment specifies how the technical complaints for this device for investigational use will be collected in Russia.

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 8.3.2.2 Self-measured plasma glucose

At the start of the run-in visit (Visit 2), the Subject will be provided with a BG meter, including lancets, *the corresponding lancing device* and plasma calibrated test stripes for BG meters. The Subject will be instructed verbally on how to use the device according to the manufacturer's instructions. The Subject will also be provided with written instructions *in local language*. Sites will, as necessary, go through the instructions of use with the Subject during visits to the site. *It is the site's responsibility to ensure that the subject is familiar with the use of the device, as the device's display will be in English.*

The BG meter used in this trial will be the Ascensia Contour® Next Link blood glucose monitoring system (Ascensia Diabetes Care, Basal, CH). The Ascensia Contour® Next Link blood glucose monitoring system is CE marked in the European Union, but is not marketed, licensed or approved in Russia. Accordingly, the device will be marked as "for investigational use only" in Russia.

Novo Nordisk A/S will be responsible for ensuring subjects' safety when using this device for investigational use during this trial.

All technical complaints, AEs and SAEs related to the BG meters must be reported to Novo Nordisk using a separate Technical Complaint Form for BG meters and on the AE Form and SIF according to the process and reporting timelines specified in Section 12. The Investigator must inform the local Ethics Committees of such events according to local legislation.

Section 8.3.2.6 Back-up kit

- Glucagon for injection (reimbursed by Novo Nordisk affiliate, or supplied by the *Novo Nordisk affiliate-central lab* in Russia)

Section 9.5.1 Auxiliaries supplied by Novo Nordisk

- ~~Bayer~~ *Ascensia Contour® Next Link meters blood glucose monitoring system (CE-approved marked in EU) marked as “for investigational use only”, and strips, lancets and control solution for BG meters*

9.5.2 Auxiliaries supplied by site

- Glucagon for injection (reimbursed by Novo Nordisk affiliate, supplied by the *Novo Nordisk affiliate-central lab* in Russia)

12.1.5 Technical complaint

A technical complaint is any written, electronic, or oral communication that alleges product (medicine or device *for investigational use in Russia*) defects. The technical complaint may be associated with an AE, but does not concern the AE itself.

Examples of technical complaints:

- The physical or chemical appearance of trial products in the vials (e.g. discoloration, particles or contamination)
- The 10 mL vial packaging material (e.g. leakage, cracks, rubber membrane issues or errors in labelling text)
- *Any technical malfunction of the BG meter*

12.4.1 Reporting of technical complaints

All technical complaints on any of the following trial products *and devices for investigational use*:

- Faster-acting insulin aspart, 100 U/mL, 10 mL vial
- Insulin aspart (NovoRapid®), 100 U/mL, 10 mL vial
- *Ascensia Contour® Next Link blood glucose monitoring system (BG meter)*

Technical complaints must be reported on a separate Technical Complaint Form in the eCRF for each *Novo Nordisk* product listed. If the technical complaint involves more than one batch/code

number or more than one DUN, a Technical Complaint Form for each batch/code number or for each DUN must be completed in the eCRF.

Technical complaints concerning the BG meters must be reported using the paper based Technical Complaint Form for BG meters.

12.4.2 Collection, storage and shipment of technical complaint samples

The Investigator must collect the technical complaint BG meter and notify the monitor within five calendar days of obtaining the sample at trial site. The monitor must coordinate the shipment to Ascensia, (the address is provided in Attachment I) and ensure that the BG is sent as soon as possible. A print or copy of the Technical Complaint Form for BG meters must be sent with the sample.

13 Case report forms

The following will be provided as paper CRFs:

- Pregnancy Form
- Technical Complaint Form
- *Technical Complaint Form for BG meters*

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