

## Cover Page for Protocol

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## 16.1.1 Protocol and protocol amendments

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## Protocol

**Trial ID: NN1218-4131**

### **Efficacy and Safety of Faster-acting Insulin Aspart compared to NovoRapid® both in combination with Insulin Degludec in Adults with Type 1 Diabetes**

**onset® 8**

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

**Trial phase: 3b**

#### **Protocol originator**

[REDACTED], [REDACTED]

Clinical Operations, Insulin, GH & Devices-2

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## Table of Appendices

Appendix A Titration Guideline
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## List of abbreviations

ADA	American Diabetes Association
AE	adverse event
ANOVA	Analysis of variance
BG	blood glucose
BMI	body mass index
CRF	case report form
DUN	dispensing unit number
ECG	electrocardiogram
eCRF	electronic case report form
eDiary	electronic diary
EMA	European Medicines Agency
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FPFV	first patient first visit
FPG	fasting plasma glucose
GCP	Good Clinical Practice
HbA <sub>1c</sub>	glycosylated haemoglobin
hCG	human chorionic gonadotropin
HDL	high density lipoprotein
IB	Investigator's Brochure
ICH GCP	International conference on harmonisation-Good Clinical Practice
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee
IMP	investigational medicinal product
IRB	institutional review board
IV/WRS	interactive voice/web response system
LDL	low density lipoprotein

LOCF	last observation carried forward
LPFV	last patient first visit
LPLV	last patient last visit
MAR	missing at random
MCAR	missing completely at random
MESI	medical event of special interest
MMRM	mixed effect model for repeated measurements
NDeSAE	near device serious adverse event
PG	plasma glucose
PP	per protocol
PPG	postprandial glucose
PRO	patient reported outcome
SAE	serious adverse event
SAP	statistical analysis plan
s.c.	subcutaneous(ly)
SmPC	summary of product characteristics
SMPG	self-measured plasma glucose
SUSAR	suspected unexpected serious adverse reaction
T1DM	Type 1 Diabetes Mellitus
UTN	Universal Trial Number

# 1 Summary

## Objectives and endpoints:

### Primary objective

To confirm efficacy in terms of glycaemic control of treatment with mealtime faster-acting insulin aspart in combination with insulin degludec in adults with Type 1 Diabetes Mellitus.

### Secondary objectives

To confirm efficacy in terms of glycaemic control of treatment with postmeal faster-acting insulin aspart in combination with insulin degludec in adults with Type 1 Diabetes Mellitus.

To confirm superiority of mealtime faster-acting insulin aspart compared to mealtime NovoRapid<sup>®</sup> both in combination with insulin degludec in adults with Type 1 Diabetes Mellitus in terms of:

- Postprandial glucose regulation (meal test)
- Postprandial glucose excursions (1,5-anhydroglucitol)
- Overall glycaemic control (HbA<sub>1c</sub>)

To compare other efficacy and safety endpoints across mealtime faster-acting insulin aspart, postmeal faster-acting insulin aspart and mealtime NovoRapid<sup>®</sup>, all in combination with insulin degludec in adults with Type 1 Diabetes Mellitus.

### Primary endpoint

Change from baseline in HbA<sub>1c</sub> after 26 weeks of treatment

### Key secondary endpoints

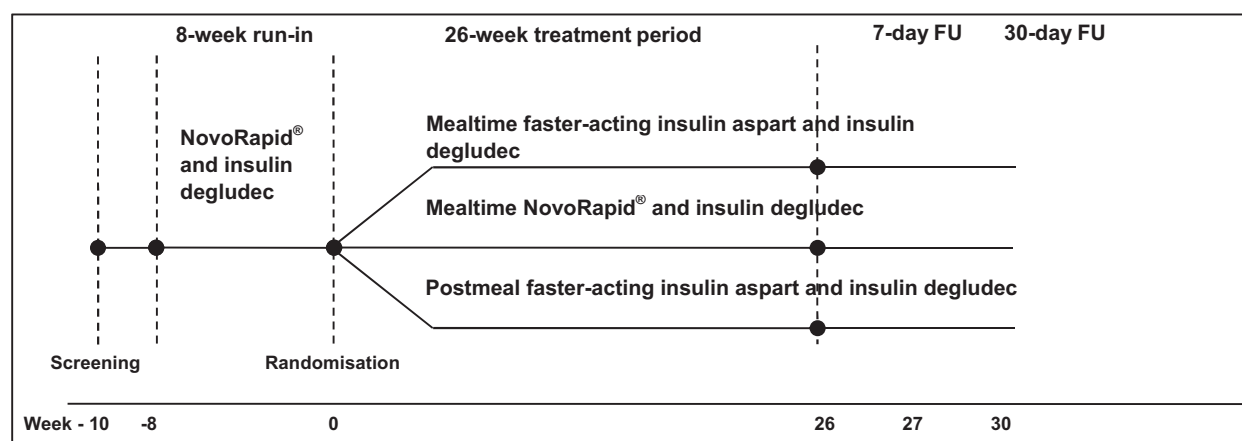
Confirmatory secondary endpoints

- Change from baseline in 1-hour post prandial glucose increment after 26 weeks of treatment (meal test)
- Change from baseline in 1,5-anhydroglucitol after 26 weeks of treatment

### Trial design:

This is a phase 3b, 26-week, multicentre, multinational, partly double-blind, randomised, active controlled, treat-to-target, three-armed parallel trial with an 8-week run-in period comparing the efficacy and safety of faster-acting insulin aspart with NovoRapid<sup>®</sup>, both in combination with insulin degludec in a basal-bolus regimen. The trial includes two blinded dosing arms - mealtime

faster-acting insulin aspart and mealtime NovoRapid® and an open-label postmeal faster-acting insulin aspart dosing arm.



**Figure 1-1 Trial design**

### **Trial population:**

A total of 1130 subjects with Type 1 Diabetes Mellitus are planned to enter the run-in period and 999 are expected to be randomised.

### **Key inclusion criteria:**

1. Male or female, age  $\geq 18$  years (for Japan and Taiwan: age  $\geq 20$  years) at the time of signing informed consent
2. Type 1 Diabetes Mellitus (based on clinical judgement and/or supported by laboratory analysis as per local guidelines)  $\geq 12$  months prior to screening
3. Currently treated with a basal-bolus insulin regimen for at least 12 months prior to screening (Visit 1)
4. Currently treated with a basal insulin analogue for at least 4 months prior to screening (Visit 1)
5. HbA1c 7.0-9.5% (53-80 mmol/mol) (both inclusive) as assessed by central laboratory
6. Body Mass Index  $\leq 35.0$  kg/m<sup>2</sup>

### **Key exclusion criteria:**

1. Within the past 180 days any of the following: myocardial infarction, stroke or hospitalization for unstable angina and/or transient ischemic attack
2. Subjects presently classified as being in New York Heart Association (NYHA) Class IV  
 Currently planned coronary, carotid or peripheral artery revascularisation

3. Diabetic ketoacidosis requiring hospitalisation within the last 180 days prior to screening (Visit 1)
4. Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria in a period of three months before screening (Visit 1)

### **Randomisation criterion**

Subjects eligible for randomisation must have:

HbA<sub>1c</sub> ≤ 9.5% (80 mmol/mol) measured by the central laboratory at Visit 9 (week -1).

### **Assessments:**

Key efficacy assessments

- HbA<sub>1c</sub>
- Overall PPG and PPG increment (meal test)
- 1,5-anhydroglucitol

Key safety assessments

- Hypoglycaemic episodes (nocturnal and day-time)
- Adverse events (AEs)

### **Trial product(s):**

- Faster-acting insulin aspart, 100 U/mL solution for injection for subcutaneous injection, 3 mL PDS290 pen injector (blinded)
- Faster-acting insulin aspart, 100 U/mL solution for injection for subcutaneous injection, 3 mL PDS290 pen injector (open for the postmeal arm)
- NovoRapid®, 100 U/mL solution for injection for subcutaneous injection, 3 mL PDS290 pen injector (blinded)
- Insulin degludec, 100U/mL solution for injection for subcutaneous injection, 3 mL PDS290 pen injector (open)

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Trial Periods	Protocol section	Screening	8 week run-in period						Randomisation	26 week treatment period														Follow-up period	
Visit (V) Phone contact (P)	<a href="#">8.1.7</a> <a href="#">8.1.8</a>	V1	V2	P3 P4	V5	P6 P7 P8	V9	V10	V11	P12 P13	V14	P15 P16 P17	V18	P19 P20 P21	V22	P23 P24 P25	V26	P27 P28 P29	V30	P31 P32 P33	V34	P35	V36	V37	P38
Timing of visit (weeks)		-10	-8	-7 -6	-5	-4 -3 -2	-1	0	1	2	4	5 6 7	8	9 10 11	12	13 14 15	16	17 18 19	20	21 22 23	24	25	26	7 days	30 days
Visit window (days)		+10	±3	±3	±3	±3	±3	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+5	+5
Diabetes treatment history	<a href="#">8.2.4</a>	x																					x	x	x
Diabetes complications	<a href="#">8.2.2</a>	x																							
Tobacco use	<a href="#">8.2.6</a>	x																							
EFFICACY																									
Meal test	<a href="#">8.3.1</a>							x															x		
Self measured plasma glucose	<a href="#">8.3.2</a>																								
4-point profile	<a href="#">8.3.2.1</a>			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
7-point profile	<a href="#">8.3.2.2</a>							x							x								x		
9-point profile	<a href="#">8.3.2.2</a>							x							x								x		
Glucose metabolism																									
1,5-anhydroglucitol	<a href="#">8.5.1.1</a>							x			x		x		x		x		x		x		x		
Fasting plasma glucose	<a href="#">8.5.1.2</a>							x							x						x		x		

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**Novo Nordisk**

Trial Periods	Protocol section	Screening	8 week run-in period						Randomisation	26 week treatment period																Follow-up period	
Visit (V) Phone contact (P)	<a href="#">8.1.7</a> <a href="#">8.1.8</a>	V1	V2	P3 P4	V5	P6 P7 P8	V9	V10	V11	P12 P13	V14	P15 P16 P17	V18	P19 P20 P21	V22	P23 P24 P25	V26	P27 P28 P29	V30	P31 P32 P33	V34	P35	V36	V37	P38		
Timing of visit (weeks)		-10	-8	-7 -6	-5	-4 -3 -2	-1	0	1	2	4	5 6 7	8	9 10 11	12	13 14 15	16	17 18 19	20	21 22 23	24	25	26	7 days	30 days		
Visit window (days)		+10	±3	±3	±3	±3	±3	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+5	+5		
Dispensing visit	<a href="#">9</a>		x					x			x		x		x				x								
New dose of trial insulin	<a href="#">8.3.3.1</a>		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x					
Dose of trial insulin, day(s) before visit	<a href="#">8.3.3</a>			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x				
Start/stop date of trial insulin (dosing)	<a href="#">8.3.3.1</a>			x					x														x				
Drug accountability	<a href="#">9.4</a>							x			x		x		x				x				x				
REMINDERS																											
Handout ID card	<a href="#">8.1.1</a>	x																									
Attend visit fasting	<a href="#">8.1.9</a>							x							x						x		x				
Training in diabetes and carbohydrate counting	<a href="#">8.6.2</a>		x		x		x	x																			
3x24-hour meal record	<a href="#">8.6.2</a>				x		x																				
Handout direction for use	<a href="#">9.2</a>		x					(x)			(x)		(x)		(x)				(x)								

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### 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)<sup>1</sup> and applicable regulatory requirements, and in accordance with the Declaration of Helsinki<sup>2</sup>.

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 UK 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)<sup>3,4</sup>.

Postprandial hyperglycaemia contributes significantly to the glycosylated haemoglobin (HbA<sub>1c</sub>) level and its control is thus essential for achieving HbA<sub>1c</sub> target level<sup>5</sup>. Basal-bolus insulin therapy aims at approaching the physiological insulin secretion profile in the healthy state to the largest possible extent. For that purpose, rapid-acting insulin analogues have been developed to more effectively control the post prandial 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 action<sup>6</sup>. However, unmet needs exist within prandial insulin therapy. The current rapid-acting insulins are not able to match the speed of the physiological postmeal insulin secretion, and a faster onset of action is preferred for improved PPG control. In addition, a more rapid delivery of the exogenous insulin to meet post prandial needs is likely to offer increased convenience and dosing flexibility for the patient<sup>7</sup>.

For an assessment of benefits and risks of the trial, see section [18.1](#).

#### 3.2 Therapeutic area

T1DM is a chronic disorder characterised by insulin deficiency and progressive complications due to hyperglycaemia. In T1DM a common treatment regimen is a basal-bolus therapy which was confirmed to be effective in reducing the incidence of late diabetic complications in the Diabetes Control and Complication Trial (DCCT)<sup>3</sup>.

The American Diabetes Association (ADA) recommends an HbA<sub>1c</sub> target of less than 7.0% (< 53 mmol/mol), without substantial hypoglycaemia<sup>8</sup>.

#### 3.3 Faster-acting insulin aspart

Faster-acting insulin aspart (also called faster aspart) is insulin aspart in a new formulation. Faster-acting insulin aspart is being developed with the objective of achieving an increased early

absorption of insulin aspart compared to NovoRapid<sup>®</sup> thereby providing a faster insulin action. Faster-acting insulin aspart aims at approaching the physiological prandial insulin secretion pattern better than currently available treatment and thereby more effectively controlling the PPG excursions and achieving a better PPG control and increased flexibility in the time of dosing around meals compared with NovoRapid<sup>®</sup>. Results from clinical pharmacology trials in adults comparing pharmacokinetic and pharmacodynamic properties of faster-acting insulin aspart and NovoRapid<sup>®</sup> have shown that faster-acting insulin aspart elicited an earlier onset of appearance and a greater early exposure to insulin aspart than NovoRapid<sup>®</sup> 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<sup>®</sup>, but no statistically significant difference between faster-acting insulin aspart and NovoRapid<sup>®</sup> in total glucose-lowering effect.

In a therapeutic confirmatory basal-bolus trial in adult subjects with T1DM, faster-acting insulin aspart taken with the meal in combination with Levemir<sup>®</sup> effectively improved glycaemic control and the reduction in HbA<sub>1c</sub> was statistically significantly larger than with NovoRapid<sup>®</sup>. Mealtime faster-acting insulin aspart provided superior PPG control compared to NovoRapid<sup>®</sup> based on 2-hour PPG increment during a meal test. A statistically significant difference was also demonstrated for 1-hour PPG increment (meal test) in favour of mealtime faster-acting insulin aspart. 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<sup>®</sup>. The rate during the first one hour after start of a meal, constituting a smaller fraction of all severe or BG confirmed hypoglycaemic episodes, was statistically significantly higher for faster-acting insulin aspart compared to NovoRapid<sup>®</sup>. The overall safety profile for faster aspart and NovoRapid<sup>®</sup> was similar and as expected for insulin aspart.

The safety profile of faster-acting insulin aspart is expected to be similar to that of NovoRapid<sup>®</sup>. The insulin aspart molecule has a well-known safety profile based on more than 15 years of clinical experience. Compared to NovoRapid<sup>®</sup>, 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 from 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)<sup>9</sup> and any updates hereof.

### **3.4 NovoRapid<sup>®</sup> (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 post prandial glycaemic control

by means of lowering total glucose excursion following a meal, both in subjects with T1DM [10](#) and in subjects with T2DM [11-13](#). This also allows insulin aspart to be injected immediately before a meal, in contrast to regular human insulin which should be injected 30 minutes prior to the meal.

For further details, please refer to the current version of the NovoRapid® EU Summary of Product Characteristics (SmPC) [14](#) and the U.S. NovoLog® Label Information [15](#).

### 3.5 Insulin degludec

Insulin degludec (marketed as Tresiba®) is a basal insulin with an ultra-long duration of action for once-daily s.c. administration at any time of the day, preferably at the same time every day. After s.c. injection, soluble and stable multi-hexamers are formed creating a depot of insulin in the s.c. tissue. Insulin degludec monomers gradually separate from the multi-hexamers thus resulting in a slow and continuous delivery of insulin degludec into the circulation, leading to the observed ultra-long pharmacokinetic and pharmacodynamic profiles and thereby a flat and stable glucose-lowering effect. The duration of action of insulin degludec is beyond 42 hours within the therapeutic dose range.

For further details please refer to the current version of the Tresiba® SmPC [16](#). If not approved in the country of interest detailed information for insulin degludec is available in the current edition and any updates of the IB [17](#).

At the time of this protocol issuance, insulin degludec is approved in more than 60 countries including all EU countries and Japan.

### 3.6 Rationale for the trial

The purpose of this trial is to confirm the efficacy and safety of faster-acting insulin aspart as mealtime insulin as well as postmeal injected insulin in combination with insulin degludec in subjects with T1DM. The results will be used in the registration file in Japan and label updates globally on use of faster aspart in combination with insulin degludec.

In the European Medicines Agency (EMA) and FDA note for guidance on clinical investigation of medicinal products for the treatment of diabetes, HbA<sub>1c</sub> is considered the most widely accepted measure of overall, long-term glucose control. Consequently, HbA<sub>1c</sub> will be included as the primary endpoint [18,19](#).

The trial is also intended to confirm that faster-acting insulin aspart, with its faster onset of action, is capable of demonstrating superior control of post prandial glycaemic excursion. In addition, this trial includes a postmeal faster-acting insulin aspart dosing arm in order to confirm that postmeal administration could prove effective in achieving glucose control to offer a clinically acceptable treatment option. There are instances when it is challenging for patients to dose bolus insulin before a meal. Patients dose a rapid-acting insulin analogue after the start of a meal for reasons such as not

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being able to predict the volume of a meal that will be consumed (children, old people, sick days etc.), or if pre-meal dosing is not possible (including missed injections). Therefore it is considered that there is a true clinical need for a rapid-acting insulin analogue product which can be administered after a meal.

## 4 Objectives and endpoints

### 4.1 Objectives

#### 4.1.1 Primary objective

To confirm efficacy in terms of glycaemic control of treatment with mealtime faster-acting insulin aspart in combination with insulin degludec in adults with Type 1 Diabetes Mellitus.

#### 4.1.2 Secondary objectives

To confirm efficacy in terms of glycaemic control of treatment with postmeal faster-acting insulin aspart in combination with insulin degludec in adults with Type 1 Diabetes Mellitus.

To confirm superiority of mealtime faster-acting insulin aspart compared to mealtime NovoRapid<sup>®</sup> both in combination with insulin degludec in adults with Type 1 Diabetes Mellitus in terms of:

- Postprandial glucose regulation (meal test)
- Postprandial glucose excursions (1,5-anhydroglucitol)
- Overall glycaemic control (HbA1c)

To compare other efficacy and safety endpoints across mealtime faster-acting insulin aspart, postmeal faster-acting insulin aspart and mealtime NovoRapid<sup>®</sup>, all in combination with insulin degludec in adults with Type 1 Diabetes Mellitus.

### 4.2 Endpoints

Baseline is defined as randomisation (Visit 10).

#### 4.2.1 Primary endpoint

- Change from baseline in HbA<sub>1c</sub> after 26 weeks of treatment

#### 4.2.2 Secondary endpoints

##### 4.2.2.1 Confirmatory secondary endpoints

- Change from baseline in 1-hour post prandial glucose increment after 26 weeks of treatment (meal test)
- Change from baseline in 1,5-anhydroglucitol after 26 weeks of treatment



#### **4.2.2.2 Supportive secondary endpoints**

##### **Supportive secondary efficacy endpoints**

- Change from baseline in fasting plasma glucose after 26 weeks of treatment
- HbA<sub>1c</sub> responder after 26 weeks of treatment:
  - HbA<sub>1c</sub> < 7.0%
  - HbA<sub>1c</sub> < 7.0% without severe hypoglycaemia
  - HbA<sub>1c</sub> < 7.0% without severe hypoglycaemia and minimal weight gain (<3.0%)
- Change from baseline in 30- min, 1- hour, 2- hour, 3- hour and 4- hour PPG and 30- min, 2- hour, 3- hour and 4- hour PPG increment after 26 weeks of treatment (meal test)
- Change from baseline in 7-9-7-point self-measured plasma glucose after 26 weeks of treatment:
  - Mean of the 7-9-7-point profile
  - Post prandial glucose and post prandial glucose increment (mean, breakfast, lunch, main evening meal)
  - Fluctuation in 7- 9-7-point profile
  - Change in the nocturnal self-measured plasma glucose measurements
- Post prandial glucose responders (overall mean of daily post prandial glucose measurements in self-measured plasma glucose ) after 26 weeks of treatment:
  - Overall post prandial glucose (1 hour) ≤7.8 mmol/L [140 mg/dL]
  - Overall post prandial glucose (1 hour) ≤7.8 mmol/L [140 mg/dL] without severe hypoglycaemia
  - Overall post prandial glucose (1 hour) ≤ 7.8 mmol/L [140 mg/dL] and HbA<sub>1c</sub> < 7.0% and minimal weight gain (<3.0%) without severe hypoglycaemia
- Insulin dose (basal insulin dose, total and individual meal insulin dose) after 26 weeks of treatment.
- Change from baseline in lipids-lipoproteins profile after 26 weeks of treatment (total cholesterol, high density lipoproteins, low density lipoproteins)

##### **Supportive secondary safety endpoints**

- Number of adverse events during 26 weeks of treatment
- Number of injection site reactions during 26 weeks of treatment
- Number of hypoglycaemic episodes classified both according to the American Diabetes Association definition and Novo Nordisk definition during 26 weeks of treatment
  - 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

- Change from baseline after 26 weeks of treatment in clinical evaluations:
  - Physical examination
  - Vital signs
  - Electrocardiogram
  - Fundoscopy/fundus photography
- Change from baseline after 26 weeks of treatment in central laboratory assessments:
  - Haematology
  - Biochemistry
  - Urinalysis
- Total insulin aspart antibodies (amount of antibodies specific for insulin aspart and cross-reacting with human insulin)
- Change from baseline after 26 weeks of treatment in weight and body mass index

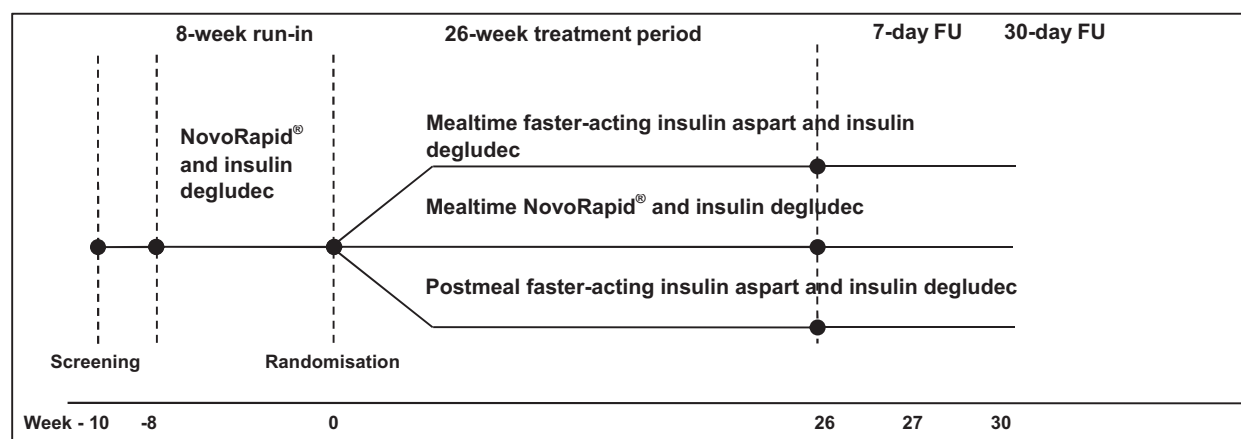
## 5 Trial design

### 5.1 Type of trial

This is a phase 3b, 26-week, multicentre, multinational, partly double-blind, randomised, active controlled, treat-to-target, three-armed parallel trial with an 8-week run-in period comparing the efficacy and safety of faster-acting insulin aspart with NovoRapid<sup>®</sup>, both in combination with insulin degludec in a basal-bolus regimen. The trial includes two blinded dosing arms - mealtime faster-acting insulin aspart and mealtime NovoRapid<sup>®</sup> and an open-label postmeal faster-acting insulin aspart dosing arm. See [Figure 5-1](#).

The total duration of the trial is approximately 40 weeks divided into the following periods:

- An approximate 2-week screening period
- An 8-week run-in period primarily for optimisation of the basal insulin and subject training
- An 26-week treatment period
- An 30-day follow-up period



**Figure 5-1 Trial design**

The trial includes a screening period followed by weekly visits/phone contacts during the trial. At Visit 2 all eligible subjects will be enrolled in an 8-week run-in period and start treatment with NovoRapid<sup>®</sup> and insulin degludec. After the run-in period, subjects with an  $HbA_{1c} \leq 9.5\%$  (80 mmol/mol) will be randomised (1:1:1) to mealtime NovoRapid<sup>®</sup> or to receive either mealtime faster-acting insulin aspart or postmeal faster-acting insulin aspart in addition to insulin degludec.

All subjects will have a standardised meal test at baseline (Visit 10) and at end of treatment (Visit 36). The meal test will be described in more details in section [8.3.1](#).

After the 26-week treatment period, each subject will have a 30-day safety follow-up period.

## **5.2 Rationale for trial design**

The 8-week run-in period has been included to ensure the subjects are being trained in the trial procedures and that the basal insulin titration is optimised. A 26-week treatment period is needed to obtain valid and adequate efficacy and safety data.

The inclusion of a postmeal treatment arm is done in order to investigate the influence of postmeal dosing in relation to meal-related glucose excursions, as in certain situations the content or amount of food is unknown before the meal. A 26-week period of postmeal dosing is considered sufficient to assess the overall glycaemic control when using postmeal dosing. It was not considered feasible to blind the postmeal arm due to the high number of injections required to make a double-blind, double dummy trial and increased burden on the subjects.

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

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®.

The 7-day follow-up visit and 30-day follow up visit are introduced in order to collect information on AEs occurring in the follow-up period.

## **5.3 Treatment of subjects**

At Visit 2 all eligible subjects will be enrolled in a run-in period where the subjects will be switched from their previous insulin treatment to insulin degludec once daily, and NovoRapid® as the mealtime bolus insulin. No other anti-diabetic medication or initiation or change in concomitant medications in excess of two weeks known to affect weight or glucose metabolism is allowed after Visit 2. During the run-in period the Investigator will focus on optimising the basal insulin treatment by using a treat-to-target approach. The subjects should continue to use the same method for adjusting the bolus insulin as they did before the trial. NovoRapid® will not be titrated during the run-in period unless the Investigator finds it necessary to adjust the bolus insulin for safety reasons. All subjects will receive diabetes training regarding carbohydrate counting in the run-in period.

In the treatment period, the Investigator should focus on optimising the bolus insulin. At randomisation the Investigator should evaluate whether subjects using flexible dosing based on the meal carbohydrate content are adequately trained in this method. If so the subject should continue this method for bolus adjustments. For those not adequately trained a pre-defined bolus dosing algorithm as described in [Appendix A](#) will be used. The Novo Nordisk insulin titration group will review progress of treatment.

### 5.3.1 Basal insulin titration

At Visit 2 subjects will be switched from their previous basal insulin analogue to insulin degludec, as described in the titration guideline ([Appendix A](#)). Insulin degludec should be administered once daily at any time of the day, preferably at the same time every day. During the 8-week run-in period the basal insulin will be titrated by the Investigator on a weekly basis to the pre-breakfast glycaemic target of 4.0 - 5.0 mmol/L [71 - 90 mg/dL] in accordance with the titration guideline ([Appendix A](#)). Further adjustments of the basal insulin dose during the treatment period should be done at the discretion of the Investigator, if needed.

### 5.3.2 Bolus insulin titration

At Visit 2 subjects will be switched from their pre-trial bolus insulin to mealtime NovoRapid<sup>®</sup>, as described in the titration guideline ([Appendix A](#)). NovoRapid<sup>®</sup> will not be titrated during the run-in period unless the Investigator finds it necessary to adjust the bolus insulin for safety reasons.

At randomisation subjects will be randomised to continue using mealtime insulin aspart, to receive mealtime faster-acting insulin aspart or to receive postmeal faster-acting insulin aspart. Timing of the bolus insulin injection must rely on randomisation, and must be injected as described below:

**Mealtime dosing** is defined as injecting 0-2 minutes before the meal

**Postmeal dosing** is defined as injecting the bolus insulin at the end of the meal but no later than 20 minutes after the start of the meal

In the 26 week treatment period, the Investigator should focus on optimising the bolus insulin. The bolus insulin will be titrated to the glycaemic target of fasting and pre-prandial plasma glucose between 4.0-6.0 mmol/L [71 - 108 mg/dL] in a treat-to-target fashion.

Throughout the trial the bolus insulin (faster-acting insulin aspart or NovoRapid<sup>®</sup>) will be administered at each three main meals (i.e. breakfast, lunch and main evening meal). Additional bolus dosing is allowed at the discretion of the Investigator.

## 5.4 Treatment after discontinuation of trial product

When discontinuing trial products, the subject should be switched to a suitable marketed product at the discretion of the Investigator.

## 5.5 Rationale for treatment

Based on the currently available pharmacokinetic data on faster-acting insulin aspart, it is anticipated that treatment with faster-acting insulin aspart as a mealtime insulin will enable insulin therapy to more closely approach a physiologic insulin secretory pattern. Consequently, the PPG

excursions may be more effectively controlled. For further details, please refer to the current version of the faster-acting insulin aspart IB [9](#).

NovoRapid<sup>®</sup> will be used as a comparator to faster-acting insulin aspart in order to compare the efficacy and safety of faster-acting insulin aspart to the currently marketed insulin aspart formulation. As this is a partly double-blind trial, NovoRapid<sup>®</sup> and faster-acting insulin aspart will be titrated following the same recommendations.

Insulin degludec has been chosen as the basal insulin because it is a once-daily basal insulin and as efficacy and safety has been confirmed in adult subjects. The flat and stable glucose-lowering effect of insulin degludec makes it an optimal insulin when assessing the properties of bolus insulin (faster-acting insulin aspart compared to NovoRapid<sup>®</sup>).

## 6 Trial population

### 6.1 Number of subjects

Number of subjects planned to be screened: 1487

Number of subjects planned to be included in the run-in period: 1130

Number of subjects planned to be randomised: 999

A screening failure rate of approximately 24 % and a run-in failure rate of approximately 11.5% are anticipated 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  $\geq 18$  years (for Japan and Taiwan: age  $\geq 20$  years) at the time of signing informed consent
3. Type 1 Diabetes Mellitus (based on clinical judgement and/or supported by laboratory analysis as per local guidelines)  $\geq 12$  months prior to screening
4. Currently treated with a basal-bolus insulin regimen for at least 12 months prior to screening (Visit 1)
5. Currently treated with a basal insulin analogue for at least 4 months prior to screening (Visit 1)
6. HbA<sub>1c</sub> 7.0-9.5% (53-80 mmol/mol) (both inclusive) as assessed by central laboratory
7. Body Mass Index  $\leq 35.0$  kg/m<sup>2</sup>
8. Ability and willingness to adhere to the protocol including performing of self-measured plasma glucose profiles and meal test
9. Ability and willingness to take at least three mealtime boluses a day every day during the trial
10. Not currently using real time continuous glucose monitoring system and/or willing not to use a real time continuous glucose monitoring system during the trial

### 6.3 Exclusion criteria

For an eligible subject, all exclusion criteria must be answered "no".

1. Known or suspected hypersensitivity to trial product(s) 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 Japan only: Adequate contraceptive measures are abstinence (not having sex), diaphragm, condom (by the partner), intrauterine device, sponge, spermicide or oral contraceptives.
4. Receipt of any investigational medicinal product within four weeks before screening (Visit 1)
5. Anticipated change in lifestyle (e.g. eating, exercise or sleeping pattern) during the trial
6. Within the past 180 days any of the following: myocardial infarction, stroke or hospitalization for unstable angina and/or transient ischemic attack
7. Subjects presently classified as being in New York Heart Association Class IV
8. Currently planned coronary, carotid or peripheral artery revascularisation
9. Inadequately treated blood pressure as defined as Class 2 hypertension or higher (Systolic  $\geq 160$  mmHg or diastolic  $\geq 100$  mmHg)
10. Impaired liver function, defined as alanine aminotransferase  $\geq 2.5$  times upper limit of normal
11. Renal impairment estimated glomerular filtration rate  $\leq 60$  mL/min/1.73 m<sup>2</sup> as assessed by central laboratory
12. Anticipated initiation or change in concomitant medications in excess of two weeks known to affect weight or glucose metabolism, such as weight loss/modifying (e.g. sibutramine, orlistat, thyroid hormones, corticosteroids)
13. Proliferative retinopathy or maculopathy requiring acute treatment as verified by fundus photography or dilated fundoscopy performed within three months before screening (Visit 1)
14. Diabetic ketoacidosis requiring hospitalisation within the last 180 days prior to screening (Visit 1)
15. Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria in a period of three months before screening (Visit 1)
16. Diagnosis of malignant neoplasms within the last five years (except basal and squamous cell skin cancer, polyps and in-situ carcinomas) prior to screening (Visit 1)
17. Any condition which, in the opinion of the Investigator might jeopardise subject's safety or compliance with the protocol
18. Anticipated initiation in use of real time continuous glucose monitoring system during the trial

#### **6.4 Randomisation criterion**

Subjects eligible for randomisation must have:

- HbA<sub>1c</sub>  $\leq 9.5\%$  (80 mmol/mol) measured by the central laboratory at Visit 9 (week -1).

To be randomised, the randomisation criterion must be answered "yes".



## 6.5 Withdrawal criteria

The subject may withdraw at will at any time.

The subject may be withdrawn from the trial at the discretion of the Investigator due to a safety concern.

The subject must be withdrawn from the trial if 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 another clinical trial throughout the trial

## 6.6 Subject replacement

Subjects who are withdrawn will not be replaced.

## 6.7 Rationale for trial population

The trial population consists of adult subjects with T1DM who have been treated with a basal/bolus insulin regimen for at least 12 months, but are not sufficiently controlled as demonstrated by an  $HbA_{1c} \geq 7.0\%$ , and may benefit from intensified insulin titration using a treat-to-target approach. Subjects with an  $HbA_{1c}$  greater than 9.5% are not included in this trial and are not eligible to be randomised into the treatment period of the trial. This is because the trial protocol requires strict adherence and good subject compliance and a likely cause of elevated  $HbA_{1c}$  in a diabetic subject is poor compliance with treatment regimens or an atypical course of the disease. The upper  $HbA_{1c}$  limit is also expected to select a population that can achieve adequate basal insulin coverage in the 8-week run-in basal insulin titration period. Subjects in good glycaemic control defined as  $HbA_{1c} < 7.0\%$  may not benefit from this trial and hence the lower cut-off value has been chosen.

The subjects need to be on a basal-bolus insulin regimen for at least 12 months in order to ensure that they have been adequately educated and are familiar with using the intensive regimen required in this trial. This will also help to avoid including newly diagnosed patients that could enter in the metabolic remission period. During the last 4 months prior to Visit 1 the subjects must have been treated with a basal analogue in order to ensure a stable switch from prior treatment to trial treatment, and to ensure that optimal adjustment of basal insulin can be done during the 8-week run-in period.

A body mass index (BMI) limit of  $\leq 35.0 \text{ kg/m}^2$  was chosen to exclude very obese and thereby potential insulin resistant individuals.

## 7 Milestones

Planned duration of recruitment period (first patient first visit (FPFV) – last patient first visit (LPFV)): 26 weeks

End of trial is defined as last patient last visit (LPLV).

### **Recruitment:**

The recruitment period will depend on the screening rate, and the screening and run-in failure rate. Recruitment will be closed as soon as the total number of randomised subjects is reachable, taking into account the number of subjects currently in screening/in the run-in period, and previous screening/run-in failure rate. All subjects who are in screening/run-in when recruitment closes will be randomised if eligible.

The screening and randomisation rate will be followed closely via the interactive voice/web response system (IV/WRS) in order to estimate when to stop screening. All Investigators will be notified immediately when the recruitment period ends, after which no further subjects may be screened and the IV/WRS will be closed for further screening. All subjects included in the screening period and eligible for randomisation can be randomised.

### **Trial registration:**

Information of the trial will be disclosed at [clinicaltrials.gov](http://clinicaltrials.gov) and [novonordisk-trials.com](http://novonordisk-trials.com) and the Clinical Trials Information JapicCTI site [clinicaltrials.jp](http://clinicaltrials.jp). According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure<sup>20</sup>, it will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE)<sup>21</sup>, the Food and Drug Administration Amendment Act (FDAAA)<sup>22</sup>, European Commission Requirements<sup>23,24</sup> 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. These are also included in the flow chart (see section [2](#)).

#### 8.1.1 Screening

Informed consent must be obtained before any trial related activity, see section [18.2](#). Trial-related activities are any procedures that would not have been performed during the normal management of the subject.

All subjects must be provided with a copy of their own signed and dated informed consent form.

Subjects will continue on their current diabetes treatment until start of run-in period (Visit 2) and they will not be supplied with any trial products until then.

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.

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

Each subject 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.

#### 8.1.2 Screening failures

For screening failures the screening failure form in the electronic case report form (eCRF) must be completed 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](#).

A screening failure session must be made in the IV/WRS and the case book must be signed.

#### 8.1.3 Re-screening

Re-screening is not allowed.

#### **8.1.4 Run-in**

If the subject is found eligible to continue in the trial the subject will enter an 8-week run-in period (Visit 2 to Visit 10). 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.

At start of the run-in period (Visit 2), the subject will receive trial products (Insulin degludec and Insulin aspart) and no other anti-diabetic treatment is allowed from visit 2 until the end of treatment visit (Visit 36). Start date of trial products must be recorded in the eCRF.

A run-in dispensing session must be performed in the IV/WRS when entering the run-in period.

The electronic diary (eDiary) should be provided to the subjects at Visit 2.

#### **8.1.5 Run-in failures**

If the subject is not eligible to be randomised (i.e. has met one of the withdrawal criteria or has not met the randomisation criterion) then the subject will be considered a run-in failure. Consequently, a run-in failure session must be made in the IV/WRS system and a run-in failure form must be completed in the eCRF together with the reason for not continuing in the trial. No follow-up visit should take place and no additional assessments are needed.

Medical events of special interest (MESIs), SAEs and non-serious AEs from run-in failures must be transcribed by the Investigator into the eCRF. The last date of trial product treatment must be captured. Follow-up of AEs 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.

#### **8.1.6 Randomisation**

Randomisation (Visit 10) must occur after 8 weeks ( $\pm 3$  days) of run-in. If the subject meets the randomisation criterion at Visit 10, then the subject will be randomised into one of the three treatment arms by using IV/WRS; please see details in section [10](#). Stop date of NovoRapid<sup>®</sup> and start date of the randomised trial product must be recorded.

The subject must attend randomisation (Visit 10) fasting. For definition of fasting, please see section [8.1.9](#).

### **8.1.7 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 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 product. Drug accountability should be performed at each dispensing visit from Visit 10 until end of treatment (Visit 36)

Review of patient reported outcome (PRO) questionnaires, laboratory reports etc. must be documented either on the documents and/or in the subject's medical record.

### **8.1.8 Phone visits**

Before any phone contact, both the Investigator and subject should agree on the 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.

### **8.1.9 Fasting visits**

The subjects must attend the visits specified in section [2](#) in a fasting condition. Fasting is defined as at least eight hours without drink or food intake prior to the visit except for water.

Insulin dosing (including basal insulin) and medication which should be taken with or after a meal should be withheld until blood sampling has been performed. If a subject attends the visit non-fasting, then the subject's blood samples, meal test and body weight measurement must be re-scheduled within the visit window. For assessments performed at these visits, please see flowchart in section [2](#).

### **8.1.10 Rescheduled visits**

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).

### **8.1.11 Withdrawals**

If a subject is withdrawn from the trial, the Investigator must aim to undertake procedures similar to those for Visit 36 including the meal test, as soon as possible and the follow up visits (Visit 37 and 38).

The end of treatment/trial form must be completed and final drug accountability must be performed even if the subject is not able to come to the trial site. A withdrawal session must be made in the IV/WRS and the case book must be signed.

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.

### **8.1.12 End of treatment**

At end of treatment (Visit 36) the randomised treatment with trial product must be discontinued and a completion IV/WRS session must be performed. The subject should be switched to a suitable marketed product at the discretion of the Investigator and this product must be recorded on the Diabetes Treatment History form in eCRF, as described in section [8.2.4](#). For procedures to be performed at end of treatment (Visit 36); please see flowchart in section [2](#). At end of treatment the treatment-related part of the end of treatment/trial form must be completed.

### **8.1.13 Follow-up period**

The first follow-up visit (FU1) (Visit 37) is a site visit and must take place no earlier than 7 days after the actual date of the end of treatment visit (Visit 36). Follow-up Visit 2 (FU2) (Visit 38) is a phone contact and must take place no earlier than 30 days after the end of treatment visit.

#### **8.1.13.1 Follow-up visit 1 (Visit 37)**

The following data will be collected:

- AEs
- Concomitant medication
- Current diabetes medication
- Hypoglycaemic events
- Injection site reactions

The eDiary handed out at the run-in visit (Visit 2) should be returned by the subject.

### **8.1.13.2 Follow-up visit 2 (Phone contact 38)**

The following data will be collected during the phone contact:

- AEs
- Concomitant medication
- Current diabetes medication

At end of trial the second part of the end of treatment/trial form must be completed.

## **8.2 Subject related information**

### **8.2.1 Demography**

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

Date of birth (if not permitted according to local laws the year of birth will be collected)

- Ethnicity (if permitted according to local laws)
- Race (if permitted according to local laws)
- Sex

The Investigator must document whether females are of non-childbearing potential in the subject's medical record and in the eCRF.

### **8.2.2 Diagnosis of Type 1 Diabetes Mellitus and diabetes complications**

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.

#### **Hypoglycaemia unawareness:**

Information on hypoglycaemia unawareness must be recorded at screening according to Clarke's questionnaire, question 8<sup>25</sup>.

The investigator must ask the subject in the following way: "To what extent can you tell by your symptoms that your blood glucose is low?" The subject can answer never, rarely, sometimes, often or always.

Subjects answering 'never, rarely or sometimes' are considered as having reduced awareness of hypoglycaemia.

### 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 the first visit (Visit 1)) or found as a result of a screening procedure.

Diabetes complications should be reported separately in the Diabetes History/Diabetes Complications Form in the eCRF.

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

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

Any change to a concomitant illness should be recorded during the trial. A clinically significant worsening of a concomitant illness must be reported as an AE.

### 8.2.4 Diabetes treatment history

Any diabetes medication taken at screening, after end of treatment, or during any unplanned events (e.g. hospitalisation) must be recorded in the concomitant diabetes medication form in the eCRF including the trade name or generic name, total daily dose, start date and stop date or continuation. The history of hypoglycaemic episodes must also be recorded at visit 1. At the run-in visit (Visit 2) all diabetes medication should be discontinued and a stop date recorded. Start and stop date of the trial products will be recorded in separate forms in the eCRF.

### 8.2.5 Concomitant medication

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

Details of any concomitant medication must be recorded at Visit 1. Changes in concomitant medication must be recorded at each visit as they occur.

The information collected for each concomitant medication includes 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 reported according to section [12](#). If the change influences the subject's eligibility to continue in the trial, the monitor must be informed.

### 8.2.6 Tobacco use

Details of tobacco use must be recorded at 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, collect the stop date. If the subject smokes or has smoked, record the approximate duration of smoking and the average number per day.

### **8.3 Assessments for efficacy**

#### **8.3.1 Meal test**

The subjects will have their 30-min to 4-hour PPG measured at certain visits, as specified in the flowchart in section [2](#).

The subject should before the meal test be instructed to:

- Follow normal routine regarding eating and exercise habits 24 hours prior to the meal test
- Refrain from intake of alcohol and use of medications that affect motility (i.e. prokinetics, anticholinergics, tricyclic antidepressants) 24 hours prior to the meal test, unless the subject was on this medication at trial entry and does not change the product or product dose
- Remember to bring their trial bolus insulin, eDiary and BG (blood glucose) meter to the meal test visits

The subject must attend the meal test visits in a fasting condition. For definition of fasting, please refer to section [8.1.9](#).

The subject should achieve self-measured plasma glucose (SMPG) values within a range of 4.0-8.8mmol/L [71-160 mg/dL] before beginning the meal test. The SMPG value 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 test should be rescheduled within the visit window.

At Visit 10 (randomisation visit) the Investigator must evaluate if the subject is eligible to continue in the trial before the meal test is performed. Only subjects eligible for randomisation should have the Visit 10 meal test performed. Thus, this assessment should not be performed for run-in failure subjects. Randomisation should not take place until the meal test has ended.

The subject's body weight must be measured prior to the start of the meal test and a blood sample must be drawn two minutes before intake of the standardised meal.

The bolus insulin dose should be calculated by the Investigator based on the dose level of 0.1 units/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 subjects. The insulin should be administered subcutaneously in the abdomen in accordance with [Table 8-1](#).

Time point 0 is defined as the time when the subject starts the consumption of the liquid meal. The subject will have a carbohydrate-rich standardised liquid meal served. The standardised liquid meal must be consumed as quickly as possible and within 12 minutes. The Investigator should confirm that the subject consumed the required volume of the standardised meal in the eCRF and actual clock time of injection and of start 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 80 gram of carbohydrate. The amount of mL of the standardised meal may differ from country to country.

**Table 8–1 Meal test schedule**

Time point (minutes)	Blood sample	SMPG values	Standardised meal	Visit 10 Bolus insulin injection	Visit 36 Bolus insulin injection
<b>Before start of meal test</b>		X (within target range 4.0-8.8 mmol/L [71-160 mg/dL])			
<b>-2</b>	X				
<b>0</b>		X (as appropriate to ensure subject's safety)	X	X Insulin injection at the start of the meal	X Insulin injection at the start of the meal (if randomised to mealtime dosing)
<b>20</b>					<b>X- Insulin injection</b> (if randomised to postmeal dosing)
<b>30</b>	X				
<b>60</b>	X				
<b>120</b>	X				
<b>180</b>	X				
<b>240</b>	X				
<b>End of meal test</b>		X (for subject's safety)			

The subject should stay in the clinic to have the blood samples drawn after 30 min, 1, 2, 3 and 4 hours from the start of the standardised meal, as detailed in [Table 8–1](#).

For the meal test at visit 10 the subjects must receive the trial product that was also used in the run-in period at time point 0.

For the meal test at visit 36 the subjects should receive the trial product they are randomised to and have used throughout the treatment period. Depending on the randomisation to either mealtime or postmeal dosing, the subjects must be dosed at time point 0 or at time point 20 accordingly.

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

During the meal test the subject should be resting in a chair. No smoking or intake of food and liquids will be allowed during the meal test, except for water consumption which is allowed two hours after intake of the standardised meal.

If SMPG values  $\leq 3.9$  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, please see section [8.4.1.1](#).

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

- Fasting status
- SMPG value measured before the meal test and within allowed ranges and the time of the measurement
- Body weight
- Start and end time of standardised meal
- Volume of meal consumed
- Confirmation that the subject consumed the required volume of the standardised meal
- Batch number of the standardised meal
- Time and dose of bolus insulin
- Time of blood samples
- Hypoglycaemic episodes, if relevant
  - SMPG value, time of intervention and amount of glucose rescue treatment and hypoglycaemic episode form

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 at Visit 10 is completed, the subject will be instructed to discontinue NovoRapid<sup>®</sup> and start treatment with randomised trial product. When the meal test at the end of treatment (Visit 36) is completed, the subjects will be switched to a marketed insulin product according to Investigator's discretion as detailed in section [8.1.12](#).

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 LPLV (Visit 38).

### **8.3.2 Self-measured plasma glucose**

At Visit 2 subjects will be provided with a BG meter including lancets, plasma-calibrated test strips and control solutions as well as instructions for use. The subjects will be instructed in how to use the device and the instruction will be repeated as necessary during the trial.

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

Throughout the trial, only the BG meter provided by Novo Nordisk must be used to measure the plasma glucose values transferred to the diary.

Subjects should be instructed in how to record the results of the SMPG values in the eDiary. The record of each SMPG value should include date, time and value. SMPG measurements related to the 4-, 7- and 9-point SMPG profiles and hypoglycaemia episodes must be entered in the eDiary (see section [8.3.2.1](#) and [8.3.2.2](#) for SMPG profiles and [8.4.1.1](#) for hypoglycaemic episodes reporting).

#### **8.3.2.1 4-point self-measured plasma glucose profile**

The 4-point SMPG profile will be recorded for insulin titration purposes. Subjects will be instructed to perform 4-point profiles every day during the conduct of the trial for titration purposes. The measurements should be performed at the following time points:

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

SMPG values measured before breakfast, lunch, dinner (main evening meal), and at bedtime should be performed before any injection of bolus insulin and just before the start of the meal (breakfast, lunch or dinner). SMPG values measured before breakfast should be performed in a fasting condition. The 4-point profile is part of the 7- or 9-point profiles which are measured prior to selected site visits.

#### **8.3.2.2 7-9-7 point profile**

The 7- and 9-point SMPG profiles will be used for titration purposes and efficacy analysis of the trial. The subject will be instructed to perform a 7-9-7 point profile on the 3 consecutive days just before selected visits as outlined in the flowchart in section [2](#). See table [Table 8–2](#) (7-point profiles indicated as X and the 9-point profile indicated as √).

**Table 8–2 7-point SMPG profiles with additional 9-point SMPG profile**

Time point	Day -3 7-point profile	Day -2 9-point profile	Day -1 7-point profile
Before breakfast	X	✓	✓(X) <sup>a</sup>
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		✓	

<sup>a</sup>The last SMPG in the 9-point profile and the first SMPG of the 7-point profile on day -1 are overlapping.

For SMPG measurements actual clock time and date should be recorded in the eDiary for each measurement.

SMPG values measured before breakfast, lunch and dinner (main evening meal), and at bedtime should be performed before any insulin injection and just before the start of the meal (breakfast, lunch or dinner). SMPG values measured before breakfast should be performed in a fasting condition.

The measurements will be used to evaluate the glucose profile.

### 8.3.3 Insulin dose

During the trial, starting at the run-in visit (Visit 2), the subject should be instructed to report the following concerning dosing of trial products in the eDiary:

- Date, time point, and doses of bolus insulin on a daily basis throughout the trial.
- Duration of each of the main meals on the days of the 7-9-7 point profiles
- Time of injection (< 10 minutes or 10-20 minutes after start of meal) of bolus insulin on the days of the 7-9-7 point profiles for Visit 22 and 36 (postmeal arm only)
- Date and dose of basal insulin on a daily basis throughout the trial.

- Date, actual clock time, and dose for extra insulin boluses as well as time and type of previous meal and reason for the extra bolus

### **8.3.3.1 Dosing and dose adjustment**

Prescribed doses and I:Carb ratio and insulin correction factor (sensitivity factor) are entered in the eDiary. At each visit/phone contact the Investigator will titrate the subjects and make dose, I:Carb ratio and insulin correction factor adjustments if applicable. Subjects following the bolus dosing algorithm will furthermore perform self-titration between the scheduled visits/phone contacts. See titration guideline ([Appendix A](#)).

The Investigator should record the following in the eDiary (through the web portal):

- Prescribed doses of trial products, I:Carb ratio and insulin correction factor as applicable according to chosen titration method for the subject.
- Dose, I:Carb ratio and insulin correction factor adjustments
- Reason for deviating in dose adjustments from the bolus dosing algorithm, if applicable

The subject should report the following in the eDiary:

- Carbohydrate content per meal on a daily basis if the subject is carbohydrate counting
- Dose adjustment for subjects following the bolus dosing algorithm
- Reason for deviating from the titration method, if applicable.

Information on the first and last date of trial products must be recorded in the eCRF.

## **8.4 Assessments for safety**

### **8.4.1 Adverse events requiring special forms**

For some AEs special forms must be completed. The AEs that require special forms are:

- Hypoglycaemic episodes (captured in the eDiary)
- Injection site reactions(captured in the eCRF)
- Medication error (captured in the eCRF) (described in section [12.1](#))

#### 8.4.1.1 Hypoglycaemic episodes

Plasma glucose should always be measured and recorded when a hypoglycaemic episode is suspected.

All plasma glucose values:

- $\leq 3.9$  mmol/L (70 mg/dL) or
- $> 3.9$  mmol/L (70 mg/dL) occurring in conjunction with hypoglycaemic symptoms

should be reported in the eDiary according to the instructions below throughout the trial from Visit 2 to Visit 37.

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 guidelines [26](#).

A SMPG value  $\leq 3.9$  mmol/L (70 mg/dL) or hypoglycaemic symptoms must trigger a hypoglycaemic episode form to be completed by the subject. Repeated SMPG measurements and/or symptoms will per default be considered as one hypoglycaemic episode until a succeeding measurement 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 60 minutes, 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.

The e-diary will automatically link multiple values within 60 minutes to the same hypoglycaemic episode. 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 episode and a new hypoglycaemic episode form is to be filled in.

The record should include the following information:

- Start date and time of the hypoglycaemic episode
- The plasma glucose value before treating the episode (if available) and any follow up measurements.

The lowest value measured during the hypoglycaemic episode will be reported as the plasma glucose value for the episode, the remaining values will be kept as source data.

- Whether the episode was symptomatic (Yes/No)

A hypoglycaemic episode starting without symptoms should be updated to symptomatic if the subject experiences symptoms later during the episode. The subjects are therefore to be prompted whether there are changes to symptoms for each low SMPG value within the 60 minutes period.

- Whether the subject was able to treat him/herself

If the severity of a hypoglycaemic episode aggravates, only one hypoglycaemic episode should be reported reflecting the most severe degree of hypoglycaemia. The subjects are therefore to be prompted whether they are able to self-treat for each low SMPG value within the 60 minutes period.

- Date, time and dose of last basal insulin administration prior to the episode
- Date, time and dose of last bolus insulin administration prior to the episode
- Date and time of last main meal prior to the episode (breakfast, lunch, main evening meal)
- Whether the episode occurred in relation to physical activity
- Any sign of fever or other acute disease (e.g. gastrointestinal infections)
- Whether the subject was asleep when the episode occurred
  - If yes, whether the symptoms of the episode woke up the subject

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. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration <sup>26</sup>.

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

If the question "Was the subject able to treat him/herself?" is answered "No", the following information should be recorded by the subject:

- Who assisted in the treatment of the hypoglycaemic episode (i.e. medical person or non-medical person)
- Where the treatment was administered (in clinic/emergency room/ hospital or other. If the subject was treated in clinic/emergency room/hospital whether they were transported in an ambulance or not)
- Type of treatment provided by other person (i.e. oral carbohydrates, glucagon, IV glucose or other)
- Were symptoms alleviated after administration of treatment?



- 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)
- Did the subject experience seizure?
- Was the subject unconscious/comatose?
- Did the subject experience any of the following symptoms<sup>27</sup> (layman term used in the eDiary is specified in brackets if different from the protocol term)?
  - 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?

The Investigator must review the diary data for correct reporting of SMPGs and hypoglycaemic episodes at each contact. If the investigator experiences incomplete data in the diary, the subject must be questioned whether there have been any severe hypoglycaemic episodes since the last visit i.e. any hypoglycaemic episodes where the subject was not able to self-treat. Any severe hypoglycaemic episodes must be reported on a hypoglycaemic episode form.

Low SMPG values 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 due to decreased validity of such data <sup>28,29</sup>.

The subject must be re-trained in how to report hypoglycaemic episodes if the investigator identifies unreported hypoglycaemic episodes.

If the hypoglycaemic episode fulfils the criteria for an SAE then an AE form and a safety information form must also be filled in (see section [12](#)).

#### **8.4.1.2 Injection site reactions**

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

Possible injection site reactions related both to the bolus and/or basal insulin must be recorded as an AE on an AE form and on a specific injection site reaction form in the eCRF. The following information should be obtained:

- Type of reaction – local or generalised
- Symptoms associated to the event
- Treatment given for the event
- Association with the trial product(s)
- Risk factors associated to the event

The Investigator has to evaluate whether further actions are needed (e.g. extra visits, supervised injection, withdrawal, dermatologist consultation).

#### **8.4.2 Eye examination**

Fundus photography/dilated fundoscopy must be performed by the Investigator, a local ophthalmologist, or an optometrist according to local practice. The result of the fundus photography/dilated fundoscopy will be interpreted locally by the Investigator. To document this, the Investigator must sign and date the result page and write the interpretation in the subject's medical records.

The evaluation must follow the categories:

- normal
- abnormal
  - clinically significant? (Yes/No)

Any abnormal and clinically significant findings at screening (Visit 1) 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 [12.2](#).

If a fundus photography/dilated fundoscopy has been performed within three months before screening (Visit 1) and if the results are available at the screening visit, then the procedure does not need to be repeated. However, if clinically necessary the fundus photography/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/dilated fundoscopy performed within three weeks in advance of Visit 10 and Visit 36 is acceptable if the results are available at the scheduled visit.

### 8.4.3 Electrocardiogram – 12 lead

An electrocardiogram (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 subject's medical records.

The evaluation must follow the categories:

- normal
- abnormal
  - clinically significant? (Yes/No)

Any abnormal and clinically significant findings at screening (Visit 1) 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 [12.2](#).

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 necessary, the ECG-12 lead should be repeated within the screening period. 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 Visit 10 and Visit 36 are acceptable if the results are available at the scheduled visits.

### 8.4.4 Body measurements

**Height** (without shoes) will be measured at site in centimetres (cm) or inches (in) and recorded to one decimal place in the eCRF.

**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 weighing scale equipment throughout the trial, if possible.

**BMI** will automatically be calculated by the eCRF.

If the eCRF automatic calculation is not used to assess the BMI inclusion criteria then the Investigator should calculate the BMI manually. However, if there is a discrepancy between the

manual calculated BMI and the BMI in the eCRF then the assessment of the inclusion criteria should be based on the BMI calculated in the eCRF.

#### **8.4.5 Physical examination**

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 clinically significant findings at screening (Visit 1) must be recorded on the Medical History/Concomitant Illness Form, 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 clinically significant findings, must be reported as an AE in accordance with section [12.2](#).

#### **8.4.6 Vital signs**

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

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 used to assess the relevant exclusion criterion; please see section [6.3](#).

Any abnormal and clinically significant findings at screening (Visit 1) must be recorded on the Medical History/Concomitant Illness 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 [12.2](#).

#### **8.5 Laboratory assessments**

Except for urine pregnancy testing, 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 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.

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.

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 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 whether out of range results are clinically significant. Review of laboratory reports must be documented either on the documents and/or in the subject's medical record.

If any clinically significant abnormalities occur at screening (Visit 1) these must be recorded on the Concomitant Illness 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 [12.2](#).

The Investigator will not be able to review the meal test and antibody results for AEs as the antibody samples will be analysed after LPLV.

The laboratory equipment may provide analyses not requested in the protocol but produced automatically in connection with the requested analyses according to specifications in the laboratory standard operating procedures. Such data will not be transferred to the trial database, but abnormal values will be reported to the Investigator. The Investigator must review all laboratory results for concomitant illnesses and AEs and report these according to this protocol.

Laboratory samples will be destroyed on an ongoing basis.

Antibody samples may be retained until drug approval by U.S. Food and Drug Administration (FDA) and/or European Medicines Agency (EMA). The retained antibody samples may be used for further characterisation for antibody responses towards drug if required by health authorities or for safety reasons, see section [24.2](#).

## **8.5.1 Laboratory assessments of efficacy**

### **8.5.1.1 1,5-anhydroglucitol**

Blood samples will be drawn to determine the level of 1,5-anhydroglucitol in order to evaluate post prandial glycaemic fluctuations.

### **8.5.1.2 Fasting plasma glucose**

Fasting plasma glucose (FPG) is measured in order to evaluate metabolic control. The Subject must attend these visits fasting. For definition of fasting please refer to section [8.1.9](#).

FPG results  $\leq 3.9$  mmol/L (70 mg/dL) should not be reported as hypoglycaemic episodes but as an AE related to the procedure (e.g. a FPG result of 2.9 mmol/L (52 mg/dL), should be reported as 'low plasma glucose of 2.9 mmol/L (52 mg/dL)').

### **8.5.1.3 Glycosylated haemoglobin**

Blood samples will be drawn to determine the HbA<sub>1c</sub> level in order to evaluate metabolic control.

### **8.5.1.4 Lipids**

Blood samples for lipids will be analysed to determine:

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

## **8.5.2 Laboratory assessments of safety**

### **8.5.2.1 Biochemistry**

Blood samples for biochemistry will be analysed to determine:

- alanine aminotransferase
- aspartate aminotransferase
- albumin
- alkaline phosphatase
- creatinine
- potassium
- sodium
- total bilirubin
- total protein

eGFR will be calculated by the central laboratory based on the creatinine value using the CKD-EPI equation.<sup>30</sup>.

#### **8.5.2.2 Haematology**

Blood samples for haematology will be analysed to determine:

- erythrocytes
- haematocrit
- haemoglobin
- leucocytes
- thrombocytes

#### **8.5.2.3 Insulin antibodies**

The subject must be fasting according to section [8.1.9](#).

On the day of antibody measurement the subject must attend the visit without having taken any kind of insulin in the morning of the visit. Total insulin aspart antibodies (amount of antibodies specific for insulin aspart and cross-reacting with human insulin) will be measured.

#### **8.5.2.4 Pregnancy testing**

For females of childbearing potential, a blood human Chorion Gonadotropin (hCG) pregnancy test will be performed at the visits indicated 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 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.

For Austria only: A monthly pregnancy test is mandatory for female subjects of childbearing potential.

### **8.5.2.5 Urinalysis**

The following will be measured:

- Albumin/creatinine ratio
- Blood
- Protein
- Ketones

## **8.6 Other assessments**

### **8.6.1 Patient reported outcomes 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).

The questionnaire must be completed by the subject themselves and should preferably be completed after conclusion of all fasting related activities, if applicable, but before any other visit related activities.

It is the responsibility of the Investigator to review the questionnaires for completeness and possible AEs immediately following completion, as detailed in section [12](#). To confirm that this has been done, the review must be documented either on the front page of the documents when returned by the subject or in the subject's 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.

### **8.6.2 Training in diabetes and carbohydrate counting**

During the run-in period all subjects should have reinforced diabetes training regarding carbohydrate counting (e.g. sessions with a diabetes educator, dietician or qualified site staff).

It is the Investigator's responsibility to ensure that the subject is adequately trained 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 the carbohydrate content of a meal <sup>31</sup>

A 3x24-hour meal record representative for the meal habits should be filled in by the subject prior to the visits indicated in the flowchart in order to evaluate the subject's ability to count the carbohydrate content of the meal.

The Investigator should confirm that subjects who are capable of and willing to use the principle of flexible bolus dosing based on the meal carbohydrate content have hands-on experience in the above before the randomisation visit (Visit 10). Subjects who cannot demonstrate these skills will be allocated to follow the pre-defined insulin dose glucose algorithms described in the titration guideline ([Appendix A](#)) to adjust the bolus dose during the treatment periods.

### **8.6.3 Training in the pen system**

The subjects should be trained in how to handle the insulin pen system when handed out the first time. Training should be repeated during the trial if necessary. It is important to emphasise that the subject should remember the following:

- Always use a new needle for each injection as this will prevent contamination and blocked needles
- Priming the pen to ensure the insulin flow

The needle should be kept in the skin while counting slowly to 6 after the dose counter has returned to zero after injection. If the needle is removed too early then the full dose may not have been delivered.

### **8.6.4 eDiary**

At the run-in visit (Visit 2) the subjects will be provided with an eDiary. The eDiary should be returned by the subject at FU1 (Visit 37). The Investigator must carefully instruct the subject in how to use the eDiary. The eDiary is considered as source data for all data entered in the eDiary as described in sections [8.3.2](#), [8.3.3](#) and [8.4.1.1](#).

The Investigator should record the following administrative information in the eDiary/web portal:

- Time and date of next site visit and/or phone contact
- Subject ID
- Bolus dosing algorithm to be followed by subject
- Subject randomisation status (mealtime dosing or postmeal dosing)

All data from the eDiary will be transferred electronically to a trial database from where the Investigator must review all the data for the subjects belonging to the site through the web portal. The review of data must be performed before each visit/phone contact.

The eDiary should be collected by the Investigator at FU1 (Visit 37) and the subject should not be provided with a paper diary for the remaining follow up period. Consequently, source data for FU2 (Phone Contact 38) is the notes written in subject's medical record.

## **8.7 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.

To ensure treatment compliance, the Investigator will at each visit assess the subject's compliance by evaluating the glycaemic control, adherence to the visit schedule and completion of the subject's eDiary including the SMPG profiles.

## 9 Trial supplies

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

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

The following trial products will be provided by Novo Nordisk A/S, Denmark:

**Table 9–1 Trial Products**

<b>Trial product</b>	<b>Strength</b>	<b>Dosage form</b>	<b>Route of administration</b>	<b>Device</b>
Faster aspart (blinded for the mealtime arm) (IMP) <sup>a</sup>	100 U/mL	Solution for injection	Subcutaneously	3 mL PDS290 pen-injector
Faster aspart (open label for the postmeal arm) (IMP)	100 U/mL	Solution for injection	Subcutaneously	3 mL PDS290 pen-injector
Insulin aspart (NovoRapid®) (blinded for the mealtime arm and open label for the run-in period) (IMP)	100 U/mL	Solution for injection	Subcutaneously	3 mL PDS290 pen-injector
Insulin degludec (open label) (IMP)	100 U/mL	Solution for injection	Subcutaneously	3 mL PDS290 pen-injector

<sup>a</sup> Investigational medicinal product

The comparator and active drug are visually identical.

## **9.2 Labelling**

The trial products will be labelled in accordance with Annex 13 [32](#), 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.

The Investigator must document that direction for use is given to the subject orally and in writing at the first dispensing visit (Visit 2). Direction of use can be provided as needed at the following dispensing visits.

### 9.3 Storage

**Table 9–2 Storage of trial products**

<b>Trial product</b>	<b>Storage conditions (not-in-use)</b>	<b>In-use conditions</b>	<b>In-use time<sup>a</sup></b>
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 <sup>®</sup> )	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 degludec	Store in refrigerator (2°C – 8°C)  Do not freeze  Protect from light	Do not store above 30°C  Do not refrigerate  Protect from light	Use within 8 weeks

<sup>a</sup> In-use time starts when first dose is taken.

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).

For Japan only: The head of the study site or the trial product storage manager (if assigned by the head of the study site) must ensure the availability of proper storage conditions, record and evaluate the temperature.

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.

#### **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.

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.

Subjects are instructed to return all used, partly used and unused trial product at each dispensing visit after Visit 2, and then finally at Visit 36. Please refer to the flowchart in section [2](#) for timing of the dispensing visits.

The monitor will reconcile the drug accountability using the IV/WRS Drug Accountability module.

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

#### **9.5 Auxiliary supplies**

The following will be supplied by Novo Nordisk:

- Direction for use for the devices
- BG meters, and auxiliary supplies for BG meters
- Needles
- Liquid meal (for the meal test)

Needles with a length on 8 mm or less should be used.

For Japan only: The trial sites are allowed to purchase and supply themselves with auxiliary supplies, if possible. BG meters must be the same model as supplied by Novo Nordisk.

## 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:

- Medication arrival
- Screening
- Screening failure
- Run-in dispensing
- Run-in failure
- Randomisation
- Dispensing
- Withdrawal
- Completion
- Code break
- Drug accountability
- Data change

As the trial is blinded with regards to faster-acting insulin aspart and NovoRapid<sup>®</sup> it is important that, at all times during the trial, only DUNs allocated by the IV/WRS are dispensed to the subject.

If a subject requires additional trial product between dispensing visits, the site must perform an additional dispensing session in IV/WRS.

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

## 11 Randomisation procedure and breaking of blinded codes

At randomisation (Visit 10) the subject will be randomised to either faster-acting insulin aspart or Novo Rapid<sup>®</sup>, both in combination with once daily insulin degludec.

The randomisation will be carried out in a 1:1:1 manner to the 3 different intensification possibilities described below using the IV/WRS:

- Mealtime faster-acting insulin aspart and insulin degludec
- Mealtime NovoRapid<sup>®</sup> and insulin degludec
- Postmeal faster-acting insulin aspart and insulin degludec

### 11.1 Blinding

The bolus treatment is double blinded, except for the postmeal faster-acting insulin aspart treatment arm.

The Investigator, subject and Sponsor will be blinded to the treatment allocation for the mealtime arms.

### 11.2 Breaking of blinded codes

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

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.

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 withdrawn from the trial and a withdrawal session must be completed in IV/WRS.



## 12 Adverse events, and technical complaints and pregnancies

### 12.1 Definitions

#### Adverse event

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 adverse event (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 the first trial related activity after the subject has signed the informed consent.
- Non-serious hypoglycaemia is an AE, but is reported on a hypoglycaemic episode form instead of on an AE form, see section [8.4.1.1](#).

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**

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.

### Serious adverse event

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

- Death.
- A life-threatening<sup>a</sup> experience.
- In-patient hospitalisation<sup>b</sup> or prolongation of existing hospitalisation.
- A persistent or significant disability or incapacity<sup>c</sup>.
- A congenital anomaly or birth defect.
- Important medical events that may not result in death, be life threatening<sup>a</sup> or require hospitalisation<sup>b</sup> 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<sup>d</sup>.

Suspicion of transmission of infectious agents via the trial product must always be considered an SAE.

<sup>a</sup>. 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.

<sup>b</sup>. The term "hospitalisation" is used when a subject:

- Is admitted to a hospital or in-patient, irrespective of the duration 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.

- <sup>c</sup>. 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).
- <sup>d</sup>. 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.

### **Non-serious adverse event**

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

### **Medical event 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 one or more of the below defined MESI criteria.

#### **1. Medication errors concerning trial products:**

- Administration of wrong drug
  - For patients treated in the mealtime arms (blinded product) use of wrong DUN is not considered a medication error.
  - For patients treated in run-in and postmeal arm (open label) use of wrong DUN is not considered a medication error unless it results in administration of wrong drug
- Wrong route of administration, such as intramuscular instead of subcutaneous.
- Administration of an overdose with the intention to cause harm (e.g. suicide attempt).
- Accidental administration of a lower or higher dose than intended i.e. dose which may lead to significant health consequences, as judged by the Investigator, irrespective of whether the SAE criteria are fulfilled or not.

## **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 (e.g. discoloration, particles or contamination)
- The packaging material (e.g. leakage, cracks, rubber membrane issues or errors in labelling text)
- Problems related to devices (e.g. to the injection mechanism, dose setting mechanism, push button or interface between the pen and the needle)

## **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 informed consent until the end of the post-treatment follow-up period (Visit 38). The events must be recorded in the applicable eCRF forms in a timely manner, see timelines below and [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, either 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: Faster-acting insulin aspart IB. Current version and any updates hereof <sup>9</sup>
- NovoRapid®: Company Core Data Sheet. Current version and any updates hereof <sup>33</sup>
- Insulin degludec: Insulin degludec IB. Current version and any updates hereof <sup>17</sup>

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

MESIs, regardless of seriousness, must be reported using the AE form, the safety information form 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.

#### **Timelines for initial reporting of AEs:**

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

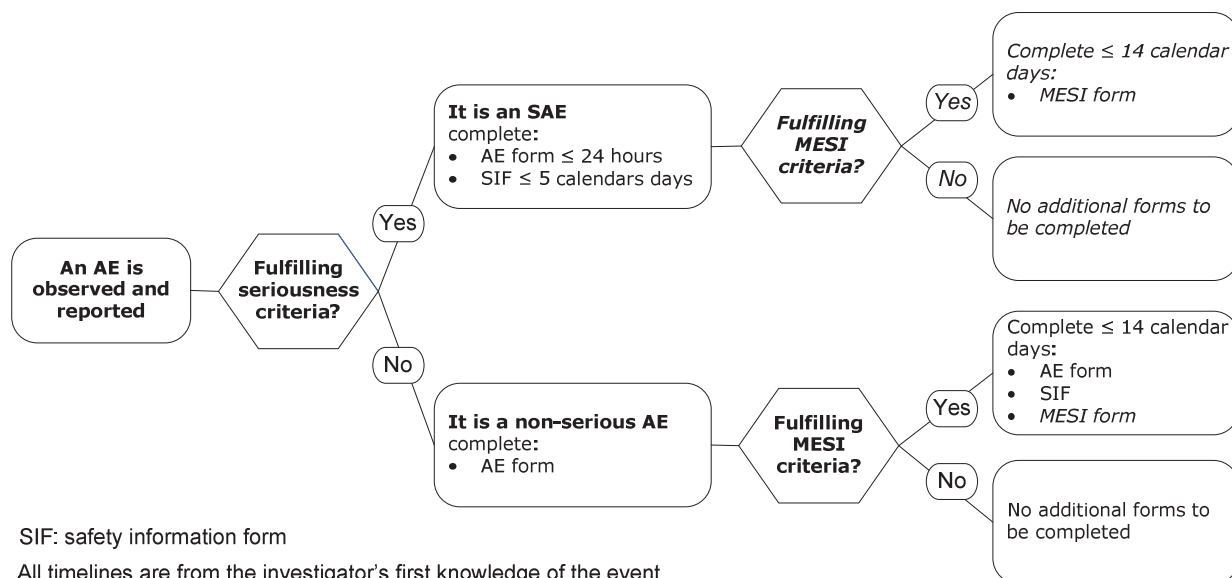
- **SAEs:** The AE form **within 24 hours** and the safety information form **within 5 calendar days** of the Investigator's first knowledge of the SAE.

Both forms must be signed within 7 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, safety information form 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 again, the Investigator must enter the information on the appropriate forms in the eCRF.

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



**Figure 12–1 Initial reporting of AEs**

### 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 ICH GCP <sup>1</sup>. 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 (IRBs)/independent ethics committees (IECs) of trial product-related SUSARs in accordance with local requirement and ICH GCP<sup>1</sup>, unless locally this is an obligation of the Investigator.

### 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 adverse event 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 products:

- Faster-acting insulin aspart, 100 U/mL solution for injection for s.c. injection, 3 mL PDS290 pen injector (blinded)
- Faster-acting insulin aspart, 100 U/mL solution for injection for s.c. injection, 3 mL PDS290 pen injector (open for postmeal arm)
- Insulin aspart, 100 U/mL solution for injection for s.c. injection, 3 mL PDS290 pen injector (blinded)
- Insulin aspart, 100 U/mL solution for injection for s.c. injection, 3 mL PDS290 pen injector (open)
- Insulin degludec, 100U/mL solution for injection for s.c. injection, 3 mL PDS290 pen injector (open)
- Novo Nordisk Needles

which occur from the time of first usage of the product until the time of the last usage of the product, must be collected and reported to Customer Complaint Center, 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. A technical complaint form for each batch, code or lot number or for each DUN must be completed.

The Investigator must complete the technical complaint form in the eCRF 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 **5 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 Center, Novo Nordisk, within the same timelines as stated above. When the eCRF becomes available again, the Investigator must enter the information on the technical complaint form in the eCRF.



#### **12.4.2 Collection, storage and shipment of technical complaint samples**

The Investigator must collect the technical complaint sample and notify the monitor **within 5 calendar days** of obtaining the sample at trial site. The monitor must coordinate the shipment to Customer Complaint Center, 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 or lot number and, if available, the DUN.

If the technical complaint sample is unobtainable, the Investigator must specify on the technical complaint form 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 (see section [9](#)).

#### **12.5 Pregnancies**

Female subjects must be instructed to notify the Investigator immediately if they become pregnant during the trial. 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 newborn infant is one month of age.

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

##### **1. Reporting of pregnancy information**

Information about the pregnancy and pregnancy outcome/health of the newborn 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.

## 2. Reporting of AE information

The Investigator has to report AEs in connection with the pregnancy as well as in the foetus and newborn 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 safety information form **within 5 calendar days** of the Investigator's first knowledge of the SAE.
- **SAE follow-up information** to the AE form and/or safety information form **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 newborn 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 [8.4.1.1](#)). 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 IB [9](#), Insulin degludec IB [17](#) and for NovoRapid<sup>®</sup>, please refer to the current versions of the SmPC [14](#) or U.S. Novolog<sup>®</sup> Label Information [15](#).

## **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.

## 13 Case report forms

Novo Nordisk will provide a system for the eCRF. This system and support services to the system will be provided 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 forms

In addition paper AE forms, safety information forms and technical complaint forms will be provided. These must be used when access to the eCRF is revoked or if the eCRF is unavailable.

On the paper CRF forms print legibly, 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

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.

### 13.2 Case report form flow

The Investigator must ensure that data is recorded in the eCRF as soon as possible, preferably within 5 days after the visit. Once data has been entered, it will be available to Novo Nordisk for data verification and validation purposes.

## 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 FPFV at the trial site and no later than 4 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 GCP, but will not exceed 12 weeks.

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).

All data must be verifiable in source documentation other than the eCRF except for all data that will be recorded directly in the eDiary and data entered in the web portal by the investigator that will be considered source data.

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

The original PRO questionnaires must not be removed from the trial site. After the trial has ended, the Investigator will receive an electronic copy of all the eDiary data belonging to the subjects at the Investigator's site.

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 Investigator's 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).

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 monitor will ensure that the eCRFs are completed and that paper CRFs are collected.

The following data will be source data verified for screening failures:

- Date for obtaining informed consent
- Screening failure form
- SAEs

Monitors must review the subject's medical records and other source data (eDiary data uploaded to the trial database and PRO questionnaires) to ensure consistency and/or identify omissions compared to the eCRF. 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. This should address any action to be taken.

## 15 Data management

Data management is the responsibility of Novo Nordisk. Data management may be delegated under an agreement of transfer of responsibilities to a contract research organisation.

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. 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 ID. 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.

## 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.

The eDiary software and hardware implementation are compliant with the requirements of FDA 21 CFR Part 11 and ICH E6 (EU directive for personal data protection). After trial finalisation, each site will be supplied with long-life DVDs. These DVDs will contain site-specific subject records including the subject's eDiary data and audit trail as well as any data additions and corrections made on each form. The eDiary vendor will furthermore retain and securely store copies of all archived documents and data for 50 years or as required by local data retention laws for trial data.



## 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 the randomisation visit (Visit 10). In case a measurement is not available at the randomisation visit, the most recent measurement prior to the randomisation visit will be used as baseline.

Analyses of efficacy endpoints will be based on the full analysis set (FAS). The primary objective, confirming the efficacy of treatment with mealtime faster-acting insulin aspart in combination with insulin degludec in adults with type 1 diabetes, will be assessed comparing the change from baseline HbA<sub>1c</sub> to NovoRapid<sup>®</sup> using a non-inferiority approach.

All secondary efficacy endpoints will be summarised and analysed using the FAS. Safety endpoints will be summarised using the safety analysis set (SAS) and analysed using the FAS.

The impact of protocol deviations and outliers may be investigated further in sensitivity analyses if deemed relevant.

All continuous endpoints will be summarised descriptively at each visit by treatment. Endpoints that are analysed untransformed, and endpoints that are not formally analysed are summarised by the arithmetic mean, standard deviation (SD), median, and minimum and maximum value. Endpoints that are analysed log-transformed are summarised by the geometric mean, coefficient of variation (CV%), median, minimum and maximum value.

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 intervals 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 will only be summarised descriptively.

### 17.1 Sample size calculation

The primary objective of this trial is to confirm efficacy of treatment with mealtime faster-acting insulin aspart in combination with insulin degludec. This is done by showing that mealtime faster-

acting insulin aspart is non-inferior to mealtime NovoRapid® both in combination with insulin degludec in terms of glucose lowering effect as assessed by mean change from baseline in HbA<sub>1c</sub> after 26 weeks of treatment using a non-inferiority margin of 0.4% (absolute). The non-inferiority margin of 0.4% (absolute) was chosen in accordance with the FDA guidance [19](#). The statistical evaluation will be done as described in section [17.3](#).

The trial also aims to confirm efficacy of treatment with mealtime faster-acting insulin aspart and postmeal faster-acting insulin aspart, for a number of secondary confirmatory endpoints using the hierarchical testing procedure as described in section [17.4.1](#). The sample size is determined to ensure a sufficient power for the first step (the primary objective : HbA<sub>1c</sub> non-inferiority of mealtime faster-acting insulin aspart) and the second step (HbA<sub>1c</sub> non-inferiority of postmeal faster-acting insulin aspart) in the hierarchical testing procedure .

Power for the non-inferiority steps are based on a t-statistic under the assumption of a one-sided test of size 2.5%. A zero mean treatment difference for the comparison between mealtime faster-acting insulin aspart and mealtime NovoRapid® is expected, and for the comparison of postmeal faster-acting insulin aspart and mealtime NovoRapid® a mean difference of 0.1% in favor of mealtime NovoRapid® is expected. Based on experience from previous phase 3 trials in subjects with T1DM treated with NovoRapid® a conservative estimate of the SD in change from baseline in HbA<sub>1c</sub> of 1.1% would be anticipated. The power calculation is done using proc power in SAS 9.3. 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%	PP	0.4% (absolute)	1.1	0.0	1:1
Step 2	2-group t-test	One-sided 2.5%	PP	0.4% (absolute)	1.1	0.1	1:1

As this is a non-inferiority trial, the power calculation is based on the anticipated number of subjects in the PP analysis set. It is assumed that 85% of the randomised subjects will be in the PP analysis set based on previous phase 3 trials in T1DM treated with insulin and sample size is sealed in the FAS to have integer sample size for each arm that adheres exactly to the arm allocation weights (1:1:1).

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

			Primary (Step 1)			Step 2			
N total	N per arm		Mean	SD	Power (step 1)	Mean	SD	Power (step 2)	Power (step 1 and 2)
FAS	FAS	PP	Diff		(%)	Diff		(%)	(%)
813	271	230	0	1.1	97.3	0.1	1.1	83.1	80.9
<b>999</b>	<b>333</b>	<b>283</b>	<b>0</b>	<b>1.1</b>	<b>99.1</b>	<b>0.1</b>	<b>1.1</b>	<b>89.9</b>	<b>89.1</b>
1176	392	333	0	1.1	99.7	0.1	1.1	94.0	93.7

From the [Table 17–2](#) it can be seen that, based on the previously defined assumptions, a total of 283 subjects per arm in the PP analysis set give 99.1% power to conclude HbA<sub>1c</sub> non-inferiority in the first step. This sample size gives 89.9% marginal power to conclude HbA<sub>1c</sub> non-inferiority in the second step. Under the assumption of independence between the hypothesis tests, this sample size results in a combined power for the 2 steps of 89.1%, which is considered sufficient. [Table 17–3](#) summarises the anticipated number of subjects in FAS and PP analysis set.

Table 17–3 Anticipated number of subjects in FAS and PP analysis set

	Mealtime faster-acting insulin aspart	Postmeal faster-acting insulin aspart	Mealtime NovoRapid®	Total
Number of subjects in the FAS	333	333	333	999
Number of subjects in the PP analysis set:	283	283	283	849

## 17.2 Definition of analysis sets

The following analysis sets are defined in accordance with the ICH-E9 guideline <sup>34</sup>.

- 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”
- PP analysis set includes all subjects in the full analysis set who fulfils the following criteria:
  - have not violated any inclusion criteria
  - have not fulfilled any exclusion criteria
  - have a non-missing HbA<sub>1c</sub> measurement at screening and/or randomisation
  - have at least 12 actual treatment weeks of exposure
  - have at least one non-missing HbA<sub>1c</sub> measurement after 12 actual weeks of exposure

Subjects in the PP analysis set will contribute to the evaluation “as treated”

- SAS includes all subjects receiving at least one dose of the investigational product or its comparator. Subjects in the SAS will contribute to the evaluation “as treated”.
- Completer set: includes subjects who completed the trial and with a valid measurement of primary endpoint (i.e. HbA<sub>1c</sub>) at end of treatment. Subjects in the completer set will contribute to the evaluation “as randomised”

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

Before data are released for statistical analysis, a blinded review of all data will take place to identify protocol deviations 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-E9 [34](#).

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.

### 17.3 Primary endpoint

The primary endpoint is change from baseline in HbA<sub>1c</sub> after 26 weeks of treatment.

Change from baseline in HbA<sub>1c</sub> after 26 weeks of treatment will be analysed using a mixed effect model for repeated measurements (MMRM) where all calculated changes in HbA<sub>1c</sub> from baseline at planned post-baseline visits until 26 weeks will be included in the analysis. This model will include treatment and region as fixed effects, HbA<sub>1c</sub> at baseline as a covariate and interactions between all fixed effects and visit, and between the covariate and visit. An unstructured covariance matrix will be used to describe the variability for the repeated measurements for a subject. From this model, contrasts will be set up to estimate the treatment difference after 26 weeks together with a 95% confidence interval.

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

$$H_0: D > 0.4\% \text{ against } H_A: D \leq 0.4\%$$

is less than or equal to 2.5%, where D is the mean treatment difference (mealtime faster-acting insulin aspart minus mealtime NovoRapid<sup>®</sup>).

The MMRM model is based on the assumption that the data are missing at random (MAR). For this trial the missing data are expected to be mainly due to subjects that are withdrawn from the trial.

The possible withdrawal reasons and criteria are described in section [6.5](#) Data from subjects that are withdrawn due to withdrawal criteria 1, 2, 3 and 4 can reasonably be assumed to be missing completely at random (MCAR). Data from subjects withdrawn due ineffective therapy may be MAR because the withdrawal may in these cases be predictable from the HbA<sub>1c</sub> values measured before withdrawal. It is expected that a limited amount of the missing data will be due to this criterion.

The sensitivity analyses described below will be used to investigate whether the results from the MMRM model are robust towards deviations from the assumption of MAR.

### Sensitivity analyses

Sensitivity analyses will be performed for change from baseline in HbA<sub>1c</sub> after 26 weeks of treatment to investigate the sensitivity of the results associated with the different confirmatory hypothesis associated with the primary analysis with regard to the handling of missing data, and with regard to the choice of analysis set. The sensitivity analyses will include:

1. A MMRM model similar to the primary analysis but based on the PP analysis set.
2. A MMRM model similar to the primary analysis but based on the completer set.
3. An analysis of variance (ANOVA) based on imputation of missing data using the last observation carried forward (LOCF) principle. The ANOVA will have change from baseline in HbA<sub>1c</sub> after 26 weeks of treatment (using LOCF) as dependent variable, treatment and region as factors, and baseline HbA<sub>1c</sub> as a covariate. This analysis is based on the FAS.
4. A pattern mixture model approach mimicking an ITT scenario, where withdrawn subjects in the mealtime or postmeal faster-acting insulin aspart groups are assumed to be switched to a treatment inferior to mealtime NovoRapid<sup>®</sup> after withdrawal. This analysis is based on the FAS. Multiple copies (100 copies) of the full dataset will be generated by imputing missing values based on estimated parameters for the mealtime NovoRapid<sup>®</sup> group. This will be done 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 treatment 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 ANOVA model with region as a factor, and baseline HbA<sub>1c</sub> as a covariate, is fitted to the change in HbA<sub>1c</sub> from baseline to visit 14 for the mealtime NovoRapid<sup>®</sup> group only. The estimated parameters, and their variances, from this model are used to impute missing values at visit 14 for subjects in all treatment groups, based on their region factor, and their HbA<sub>1c</sub> at baseline.
  - In the third step, for each of the 100 copies of the dataset, missing HbA<sub>1c</sub> values at visit 18 are imputed in the same way as for visit 14. Now the imputations are based

on an ANOVA model with region as a factor, and the HbA<sub>1c</sub> values at baseline and visit 14 as covariates, fitted to the mealtime NovoRapid<sup>®</sup> group.

- This stepwise procedure is then repeated sequentially for visits 22, 26, 30, 34 and 36.
- For each withdrawn subject in the mealtime or postmeal faster-acting insulin aspart group, a value of 0.4% (the non-inferiority limit) is added to the change in HbA<sub>1c</sub> at visit 36 (26 weeks). This step is included to mimic a scenario where withdrawn subjects in the mealtime or postmeal faster-acting insulin aspart group are switched to a treatment inferior to mealtime NovoRapid<sup>®</sup> after withdrawal.
- For each of the complete data sets, the change from baseline to visit 36 is analysed using an ANOVA model with treatment and region as factors and the baseline HbA<sub>1c</sub> value as a covariate.
- The estimates and standard deviations for the 100 data sets are pooled to one estimate and associated standard deviation using Rubin's formula:

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

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 intervals for the treatment differences are calculated.
5. The same analysis as in 4 above, but without adding the 0.4% to subjects withdrawing from the mealtime or postmeal faster-acting insulin aspart treatment. This will mimic a scenario where subjects withdrawing from mealtime or postmeal faster-acting insulin aspart treatment are switched to mealtime NovoRapid<sup>®</sup> after withdrawal. This analysis will in particular investigate the sensitivity of the superiority analysis (step 5 in the hierarchical testing procedure). This analysis is based on the FAS.
  6. The same analyses as in 4 and 5 above, with the modification that subjects withdrawn due to withdrawal criteria 1, 2, 3 and 4 in the mealtime or postmeal faster aspart group will have their imputations based on parameters estimated from the mealtime or postmeal faster aspart group (and not the mealtime NovoRapid<sup>®</sup> group). These analyses are motivated by the fact that withdrawals due to withdrawal criteria 1, 2, 3 and 4 can reasonable be assumed to be MCAR. This analysis is based on the FAS.

The results from the sensitivity analyses will be compared to the results of the MMRM method. Any marked difference concerning treatment differences between the missing-value-handling approaches above will be commented upon in the clinical trial report.



## 17.4 Secondary endpoints

### 17.4.1 Confirmatory secondary endpoints

If efficacy of mealtime faster-acting insulin aspart can be confirmed in the primary analysis, the trial also aims to compare treatment arms 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 the null hypothesis only, will be confirmed for endpoints where all previous null-hypotheses have been rejected in favour of faster-acting insulin aspart.

The steps in the hierarchical testing procedure are:

**Step 1 (Primary analysis):** Change from baseline in HbA<sub>1c</sub> after 26 weeks of treatment (non-inferiority of mealtime faster-acting insulin aspart versus mealtime NovoRapid<sup>®</sup>)

**Step 2:** Change from baseline in HbA<sub>1c</sub> after 26 weeks of treatment (non-inferiority of postmeal faster-acting insulin aspart versus mealtime NovoRapid<sup>®</sup>)

**Step 3:** Change from baseline in 1-hour PPG increments after 26 weeks of treatment (meal test) (superiority of mealtime faster-acting insulin aspart versus mealtime NovoRapid<sup>®</sup>)

**Step 4:** Change from baseline in 1,5-Anhydroglucitol after 26 weeks of treatment (superiority of mealtime faster-acting insulin aspart versus mealtime NovoRapid<sup>®</sup>)

**Step 5:** Change from baseline in HbA<sub>1c</sub> after 26 weeks of treatment (superiority of mealtime faster-acting insulin aspart versus mealtime NovoRapid<sup>®</sup>)

#### Change from baseline in HbA<sub>1c</sub> after 26 weeks of treatment (step 2)

Step 2 in the hierarchical testing procedure is to confirm efficacy of treatment with postmeal faster-acting insulin aspart in terms of glycaemic control by showing that postmeal faster-acting insulin aspart is non-inferior to NovoRapid<sup>®</sup> both in combination with insulin degludec in terms of glucose lowering effect as assessed by change from baseline in HbA<sub>1c</sub> after 26 weeks of treatment using a non-inferiority margin of 0.4%.

The non-inferiority will be evaluated as described in section [17.3](#) based on a two-sided 95% confidence interval of mean treatment difference (postmeal faster-acting insulin aspart minus mealtime NovoRapid<sup>®</sup>) obtained from the primary statistical analysis.

The sensitivity of the analysis will be addressed as described in section [17.3](#).

### **Change from baseline in 1-hour PPG increments after 26 weeks of treatment (meal test) (step 3)**

As the third step of the hierarchical testing procedure changes from baseline in 1-hour PPG increments (meal test) after 26 weeks of treatment will be tested for superiority of mealtime faster-acting insulin aspart compared to mealtime NovoRapid®.

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

The endpoint will be analysed using an ANOVA model including treatment and region as factors and 1-hour PPG increment at baseline as covariate. The superiority will be evaluated based on the comparison of mealtime faster-acting insulin aspart and mealtime NovoRapid®.

#### ***Sensitivity analysis***

To investigate the sensitivity of the analysis with regard to the handling of missing data, a sensitivity analysis based on a pattern mixture model will be made, using the FAS. This analysis is motivated by the fact that withdrawals due to non-eligibility can reasonable be assumed to be MCAR. Multiple copies (100 copies) of the full dataset will be generated by imputing missing values based on estimated parameters as follows:

- For each of the 100 copies of the dataset, an ANOVA model with treatment and region as factors and baseline 1-hour PPG increment as a covariate is fitted to the change in 1-hour PPG increment at week 26 for the mealtime NovoRapid® group only. The estimated parameters, and their variances, from this model are used to impute missing values at week 26 for subjects in all treatment groups. However, subjects withdrawn due to withdrawal criteria 1, 2, 3 and 4 in the mealtime faster aspart group will have their imputations based on parameters estimated from the mealtime faster aspart group.
- For each of the complete data sets, the change from baseline to week 26 is analysed using an ANOVA model with treatment and region as factors, and baseline 1-hour PPG increment as a covariate.
- The estimates and standard deviations for the 100 data sets are pooled to one estimate and associated standard deviation using Rubin's formula. From this, the pooled estimates and 95% confidence interval for the treatment difference is calculated.

### **Change from baseline in 1,5-Anhydroglucitol after 26 weeks of treatment (step 4)**

Change from baseline in 1,5-anhydroglucitol after 26 weeks of treatment will be analysed based on all planned post-baseline measurements until or at 26 weeks using a MMRM for repeated measurements, similar to the model used for analysis of the primary endpoint except with baseline



1,5-anhydroglucitol as covariate. The superiority will be evaluated based on the comparison of mealtime faster-acting insulin aspart and mealtime NovoRapid®.

The sensitivity of the analysis will be addressed using the pattern mixture models described in section 17.3. Only the sensitivity analyses 5) and 6) in section 17.3 will be applied excluding the analyses where the non-inferiority margin of 0.4% are added to subjects withdrawing in the faster-acting insulin aspart arm.

### **Change from baseline in HbA1c after 26 weeks of treatment (step 5)**

Step 5 in the hierarchical testing procedure is to confirm superiority of HbA1c after 26 weeks of treatment with mealtime faster-acting insulin aspart compared to NovoRapid®. The statistical analysis will be identical to the primary analysis. Superiority will be confirmed if the upper boundary of the two-sided 95% confidence interval of the mean treatment difference (mealtime faster-acting insulin aspart minus mealtime NovoRapid®) is below 0%.

The sensitivity of the analysis will be addressed using the pattern mixture models as described in section 17.3. Only the sensitivity analyses 5) and 6) in section 17.3 will be applied excluding the analyses where the non-inferiority margin of 0.4% are added to subjects withdrawing in the faster-acting insulin aspart arm.

## **17.4.2 Supportive secondary endpoints**

### **17.4.2.1 Efficacy endpoints**

#### **Change from baseline in FPG after 26 weeks of treatment**

Change from baseline in FPG after 26 weeks of treatment will be analysed based on all planned post-baseline measurements until or at 26 weeks using an MMRM similar to the model used for analysis of the primary endpoint, except with baseline FPG as covariate.

#### **HbA1c responder after 26 weeks of treatment:**

##### ***HbA1c < 7.0%***

A dichotomous (responder/non-responder) endpoint will be defined based on whether a subject has met the ADA HbA1c target (HbA1c <7.0%) after 26 weeks of treatment.

This responder endpoint will be analysed based on a logistic regression model using treatment and region as factors, and baseline HbA1c as covariate. Predicted values from the model used for the primary analysis will be used for all subjects with no HbA1c at the last visit.

### ***HbA1c < 7.0% without severe hypoglycaemia***

A dichotomous (responder/non-responder) endpoint will be defined based on whether a subject has met the ADA HbA1c target (HbA1c <7.0%) after 26 weeks of treatment without treatment emergent severe hypoglycaemic episodes. The withdrawals from their randomised treatment will be set to non-responders. This is based on the assumption that the subjects would experience a severe hypoglycaemia after the withdrawal. A predicted value from the model used for the primary analysis will be used if a treatment completer does not have HbA1c at the last visit.

This responder endpoint will be analysed based on a logistic regression model using treatment and region as factors and baseline HbA1c as covariate.

### ***HbA1c < 7.0% without severe hypoglycaemia and minimal weight gain (<3.0%)***

A dichotomous (responder/non-responder) endpoints will be defined based on whether a subject has met the ADA HbA1c target (HbA1c <7.0%) after 26 weeks of treatment without treatment emergent severe hypoglycaemic episodes, and minimal weight gain from baseline to 26 weeks of treatment (defined as less than a 3% increase). The withdrawals from their randomised treatment will be set to non-responders. This is based on the assumption that the subjects would experience a severe hypoglycaemia after the withdrawal. A predicted value from the MMRM model will be used if a treatment completer does not have HbA1c or body weight at the last visit.

This responder endpoint will be analysed based on a logistic regression model using treatment and region as factors and baseline HbA1c and baseline body weight as covariates. **Change from baseline in 30- min, 1- hour, 2- hour, 3- hour and 4- hour PPG and 30- min, 2- hour, 3- hour and 4- hour PPG increment after 26 weeks of treatment (meal test)**

Laboratory measured PG from the meal test will be analysed for 30, 60, 120, 180, and 240 minutes PPG separately. The corresponding PPG increments will be derived separately using each PPG measurement minus the pre-prandial PG.

Change from baseline after 26 weeks of treatment in PPG and PPG increment endpoints will be analysed separately using an ANOVA model including treatment and region as factors, and the corresponding baseline value as covariate.

### **Change from baseline in 7-9-7-point SMPG profile after 26 weeks of treatment:**

In general, analyses will be based on the entire 7-9-7-point profile except for the analyses of nocturnal endpoints where information in the 9-point profile will be utilised. Duration of main meals and time of injection of bolus insulin, which will be collected in connection with 7-9-7 point profiles, will be summarised descriptively.

### ***Mean of the 7-9-7-point profile***

The mean of the 7-9-7-point 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 mean of the 7-9-7-point profile will be analysed based on all planned post-baseline measurements until or at 26 weeks using a MMRM similar to the model used for analysis of the primary endpoint and the corresponding baseline value as covariate.

### ***PPG and PPG increment (mean, breakfast, lunch, main evening meal)***

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

PPG will be recorded by the patient as part of two 7-point and one 9-point SMPG profile prior to the 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-point and 9-point 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 PPG and PPG increment endpoints (mean and each separate meal) will be analysed based on all planned post-baseline measurements until or at 26 weeks using a MMRM similar to the model used for analysis of the primary endpoint and the corresponding baseline value as covariate.

### ***Fluctuation in 7-9-7-point profile***

The fluctuation in the 7-9-7-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 7-9-7-point profile will be logarithmically transformed and analysed in the same way as mean of the profile is analysed with log-transformed baseline values.

### ***Change in the nocturnal SMPG measurements***

Change in nocturnal PG values 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 in the nocturnal SMPG measurements will be analysed in the same way as mean of the profile is analysed.

### **PPG responders (overall mean of daily PPG measurements in SMPG) after 26 weeks of treatment:**

#### ***Overall PPG (1 hour) $\leq 7.8$ mmol/L [140 mg/dL]***

A dichotomous endpoint will be defined based on whether a subject has reached an overall mean 1-hour PPG  $\leq 7.8$  mmol/L [140 mg/dL] after 26 weeks of treatment, where PPG is derived from the 7- and 9-point profile.

This responder endpoint will be analysed based on a logistic regression model using treatment and region as factors, and baseline overall mean 1-hour PPG as covariate. Predicted values from the MMRM model for overall mean 1-hour PPG will be used for all subjects with no PPG at the last visit.

#### ***Overall PPG (1 hour) $\leq 7.8$ mmol/L [140 mg/dL] without severe hypoglycaemia***

A dichotomous endpoint will be defined based on whether a subject has reached an overall mean 1-hour PPG  $\leq 7.8$  mmol/L [140 mg/dL] after 26 weeks of treatment without any treatment emergent severe hypoglycaemic episodes. The withdrawals from their randomised treatment will be set to non-responders. This is based on the assumption that the subjects would experience a severe hypoglycaemia after the withdrawal. A predicted value from the MMRM model will be used if a treatment completer does not have overall mean 1-hour PPG at the last visit.

This responder endpoint will be analysed based on a logistic regression model using treatment and region as factors, and baseline overall mean 1-hour PPG as covariate.

#### ***Overall PPG (1 hour) $\leq 7.8$ mmol/L [140 mg/dL] and HbA<sub>1c</sub> < 7.0% and minimal weight gain (<3.0%) without severe hypoglycaemia***

A dichotomous endpoint will be defined based on whether a subject has reached an overall mean 1-hour PPG  $\leq 7.8$  mmol/L [140 mg/dL], have HbA<sub>1c</sub> < 7.0% and has had minimal weight gain

(increase in body weight from baseline  $<3.0\%$ ) after 26 weeks of treatment, and without any treatment emergent severe hypoglycaemic episodes. The withdrawals from their randomised treatment will be set to non-responders. This is based on the assumption that the subjects would experience a severe hypoglycaemia after the withdrawal. A predicted value from the MMRM model will be used if a treatment completer does not have overall mean 1-hour PPG, HbA<sub>1c</sub> or body weight at the last visit.

This responder endpoint will be analysed based on a logistic regression model using treatment and region as factors, and baseline overall mean 1-hour PPG, baseline HbA<sub>1c</sub> and baseline body weight as covariates.

#### **Insulin dose (basal insulin dose, total and individual meal insulin dose) after 26 weeks of treatment**

Basal and bolus insulin doses will be recorded throughout the trial. The insulin doses will be summarised descriptively by treatment week according to regimen, both by time point of administration and as total daily dose in units and units/kg (total daily and separately for each mealtime dose).

#### **Change from baseline in lipids-lipoproteins profile after 26 weeks of treatment (total cholesterol, high density lipoproteins, low density lipoproteins)**

Change from baseline in lipid endpoints (total cholesterol, HDL and LDL) after 26 weeks of treatment will be analysed based on all planned post-baseline measurements until or at 26 weeks using an MMRM similar to the model used for analysis of the primary endpoint, except with the corresponding baseline measurement as covariate.

#### **17.4.2.2 Safety endpoints**

##### **Number of AEs during 26 weeks of treatment**

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All AEs occurring during the 26 weeks of treatment 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 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, withdrawal 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 summarised and listed.

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

### **Number of injection site reactions**

Treatment emergent injection site reactions occurring during the trial will be summarised and listed. No formal statistical analysis will be made.

### **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.

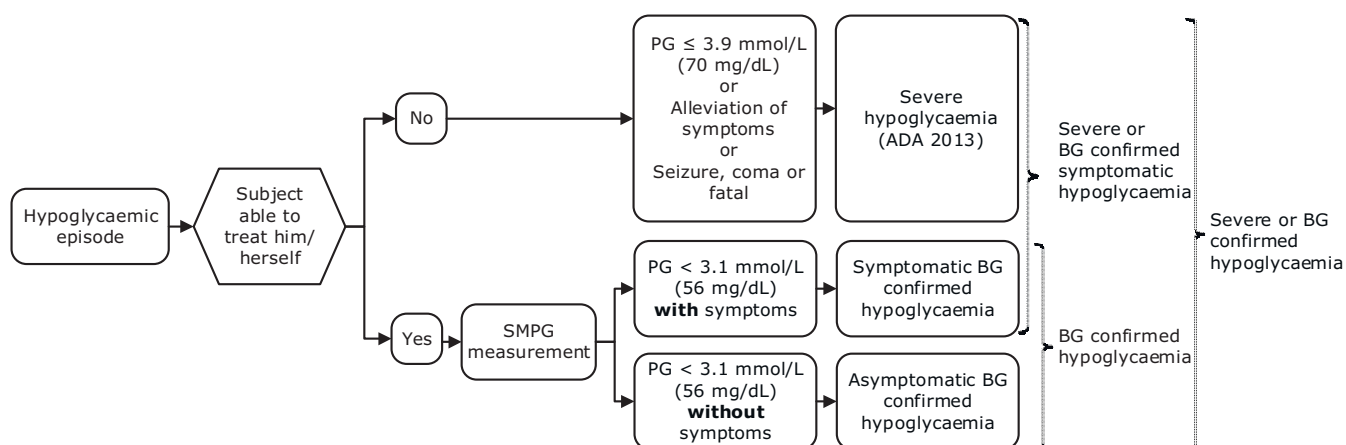
Hypoglycaemic episodes are classified according to the Novo Nordisk classification of hypoglycaemia (see [Figure 17-1](#) and the ADA classification of hypoglycaemia [Figure 17-2](#)).

### **Novo Nordisk classification of hypoglycaemia**

In normal physiology, symptoms of hypoglycaemia occur below a PG level of 3.1 mmol/L (56 mg/dL)<sup>35</sup>. Therefore, Novo Nordisk has included hypoglycaemia with PG levels below this cut-off point in the definition of BG confirmed hypoglycaemia.

Novo Nordisk uses the following classification ([Figure 17-1](#)) in addition to the ADA classification:

- Severe hypoglycaemia according to the ADA classification<sup>26</sup>.
- Symptomatic BG confirmed hypoglycaemia: An episode that is BG confirmed by plasma glucose value <3.1 mmol/L (56 mg/dL) **with** symptoms consistent with hypoglycaemia.
- Asymptomatic BG confirmed hypoglycaemia: An episode that is BG confirmed by plasma glucose value <3.1 mmol/L (56 mg/dL) **without** symptoms consistent with hypoglycaemia.
- Severe or BG confirmed symptomatic hypoglycaemia: An episode that is severe according to the ADA classification<sup>26</sup> or BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) **with** symptoms consistent with hypoglycaemia.
- BG confirmed hypoglycaemia: An episode that is BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) **with** or **without** symptoms consistent with hypoglycaemia.
- Severe or BG confirmed hypoglycaemia: An episode that is severe according to the ADA classification<sup>26</sup> or BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) **with** or **without** symptoms consistent with hypoglycaemia.



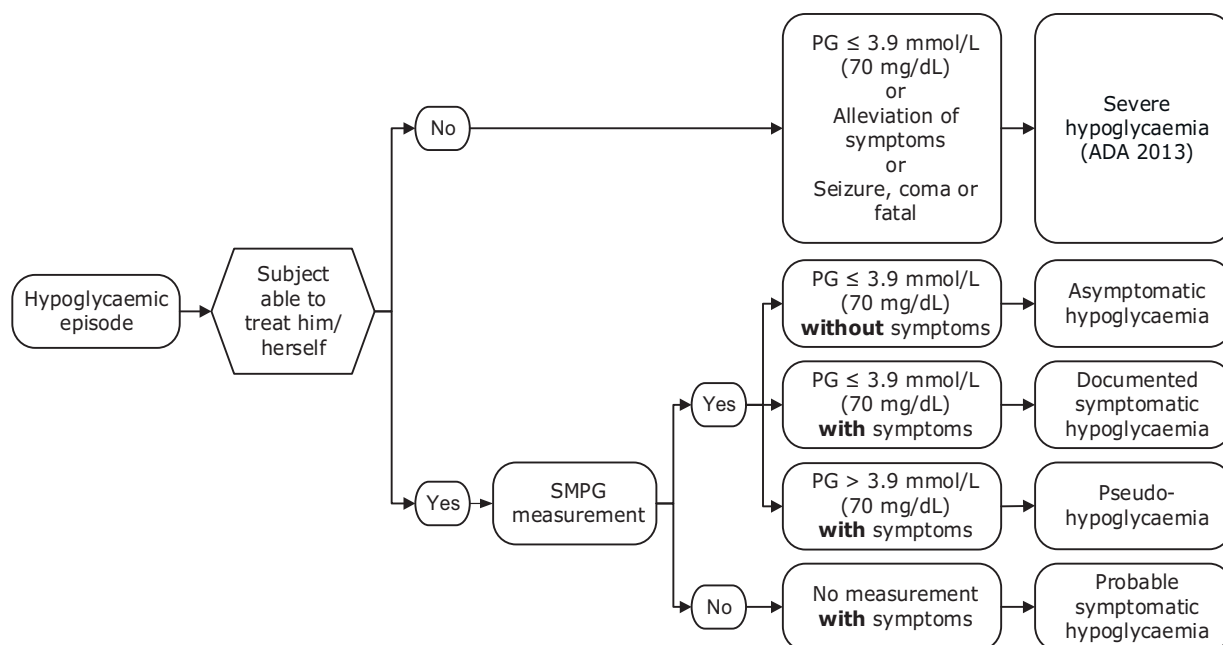
Note: Glucose measurements are performed with capillary blood calibrated to plasma equivalent glucose values

Figure 17–1 Novo Nordisk classification of hypoglycaemia



### ADA classification of hypoglycaemia<sup>26</sup>

- Severe hypoglycaemia: An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.
- Asymptomatic hypoglycaemia: An episode not accompanied by typical symptoms of hypoglycaemia, but with a measured plasma glucose concentration  $\leq 3.9$  mmol/L (70 mg/dL).
- Documented symptomatic hypoglycaemia: An episode during which typical symptoms of hypoglycaemia are accompanied by a measured plasma glucose concentration  $\leq 3.9$  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 plasma glucose 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 plasma glucose determination but that was presumably caused by a plasma glucose concentration  $\leq 3.9$  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. Episodes will also be summarised overall and by category in relation to time since start of meal, as occurring during first 1, 2, and 4 hours after start of meal, and from 2 hours (exclusive) to 4 hours (inclusive) after start of meal, respectively.

The number of treatment emergent severe or BG confirmed hypoglycaemic episodes (all, daytime, nocturnal, 1 hour, 2 hour, 4 hour and from 2 hours [exclusive] to 4 hours [inclusive] after start of meal) will be analysed using a negative binomial regression model with a log-link function and the logarithm of the time period for which a hypoglycaemic episode is considered treatment emergent as offset. The model will include treatment and region as factors. To the extent where data allow, separate analyses will be performed for severe episodes.

### **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 in shift tables. All findings will be listed.

### **Vital signs**

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 and the normal/abnormal not clinically significant/abnormal clinically significant categorisation in shift tables.

### **ECG**

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.

### **Fundoscopy/fundus photography**

Fundus photography/fundoscopy 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.

## **Clinical laboratory assessments**

Change from baseline after 26 weeks of treatment in central laboratory assessments:

Haematology  
Biochemistry  
Urinalysis

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

### **Total insulin aspart antibodies (amount of antibodies specific for insulin aspart and cross-reacting with human insulin)**

Change from baseline after 26 weeks of treatment in total insulin antibodies, antibodies specific for insulin aspart and antibodies cross-reacting with human insulin will be summarised descriptively.

### **Change from baseline in body weight and BMI after 26 weeks of treatment**

The measurements will be summarised descriptively using both the actual values and change from baseline.

Change from baseline in body weight will be analysed based on all planned post-baseline measurements until or at 26 weeks using an MMRM similar to the model used for analysis of the primary endpoint, except with baseline body weight as covariate.

## 18 Ethics

The trial will be conducted in compliance with ICH GCP<sup>1</sup> and applicable regulatory requirements, and in accordance with the Declaration of Helsinki<sup>2</sup>.

### 18.1 Benefit-risk assessment of the trial

All subjects included in the trial will be treated with insulin degludec as basal insulin in addition to either NovoRapid<sup>®</sup> or faster-acting insulin aspart. Insulin degludec will be titrated weekly by the Investigator during the initial 8-week run-in period. The bolus insulin will be adjusted daily or weekly during the treatment period of the trial depending on the methods used by the subject to adjust their bolus dose.

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 received at the time they entered the trial. However, subjects will have to use extra time as additional visits to the clinic are required and some of the assessments performed during the trial are done outside normal practice.

When treatment with trial products ends, 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 or insulin degludec trial products.

### Summary of clinical pharmacology

Results from clinical pharmacology trials comparing pharmacokinetic and pharmacodynamic properties of faster-acting insulin aspart and NovoRapid<sup>®</sup> have shown that faster-acting insulin aspart elicited an earlier onset of insulin exposure and a greater early exposure to insulin aspart than NovoRapid<sup>®</sup> 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<sup>®</sup>, but no statistically significant difference between faster-acting insulin aspart and NovoRapid<sup>®</sup> in total glucose-lowering effect<sup>9</sup>.

No safety concerns were raised during any of the trials<sup>9</sup>.

### Clinical benefits and risk considerations for the trial

The purpose of this trial is to confirm the efficacy and safety of faster-acting insulin aspart as mealtime insulin as well as postmeal injected insulin in combination with a basal insulin in subjects with T1DM.

For the individual subjects, the personal health-related benefits are related to the medical examination and the benefit from an intensified 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 subject and the Investigator and the thorough evaluation of SMPG values and for the group of subjects who adjust their bolus insulin based on the method of flexible dosing the thorough evaluation of insulin sensitivity and I:Carb 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<sub>1c</sub> results. All subjects will have reinforced diabetes training including carbohydrate counting.

For the individual subjects, the anticipated risks include hypoglycaemia, hyperglycaemia, systemic allergic reactions, injection site reactions, and antibody development. The risks will be mitigated by the close supervision of the subjects and the frequent measurements of BG levels.

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<sup>®</sup>.

Injection site reactions can occur. The nature of the injection 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.

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

Subjects in this trial will be using bolus and basal insulin administered via two differently coloured pre-filled pens. This colour difference will help the subject to distinguish between the pens and thereby minimise the risk of medication errors with regard to mixing up the pens used for basal and bolus injection. It is expected that the risk of mixing up basal and bolus insulin in this trial is similar to other clinical trials.

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

All treatments are contraindicated in case of hypersensitivity to the active substances or any of the excipients.

## Conclusion

Subjects in this trial will benefit from an intensified insulin treatment in a basal-bolus 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 this 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 this trial.

### 18.2 Informed consent

In seeking and documenting informed consent, the Investigator must comply with applicable regulatory requirement(s) and adhere to ICH GCP<sup>1</sup> and the requirements in the Declaration of Helsinki<sup>2</sup>.

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 ample time to come to a decision whether or not to participate in the trial.

A voluntary, signed and personally dated informed consent must be obtained from the subject before any trial-related activity.

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

If information becomes available that may be relevant to the subject's willingness to continue participating in the trial, the Investigator must inform the subject in a timely manner, and a revised written subject information must be provided and a new informed consent must be obtained.

### **18.3 Data handling**

If the subject is withdrawn from the trial or lost to follow-up, then the subject's data will be handled as follows:

- Data already collected and data collected at the end of treatment visit and the follow-up visits 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.

### **18.4 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 at the discretion of the Investigator. The subject may receive a "welcome to the trial letter" and a "thank you for your participation letter" after completion of the trial. Further the subject may receive letters during the trial.

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

### **18.5 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 regulatory authorities and IRBs/IECs and provide a detailed written explanation.

If, after the termination of the trial, the benefit-risk 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

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 clinical database.

Documentation on protocol deviations must be kept in the Investigator's trial master file and sponsor trial master file.

### 19.1 Missing data

A significant proportion of missing data is a 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. In addition, only absolutely necessary withdrawal criteria to ensure the safety of subjects are included and thereby reducing the number of withdrawals and securing maximum number of data.

Surveillance of withdrawal rate and withdrawal reasons will be performed throughout the trial by Novo Nordisk with focus on withdrawal reason (e.g. AEs, subject withdrawing consent or withdrawals due to any of the withdrawal criteria) to secure early mitigations in collaboration with the trial sites. Withdrawn subjects will be completed according to section [8.1.11](#).

The importance of subject retention will be addressed by Novo Nordisk in the communication with the trial sites. The subjects will be carefully informed about the trial procedures before signing informed consent so they know the implication by participating in the trial.

The subjects must be instructed to complete their diary ongoing according to the protocol. Missing data will not be recorded retrospectively due to the decreased validity of such data [28,29](#); however a 7 days' timeline is applied for reporting of missing hypoglycaemic episode, see section [8.4.1.1](#). The subject will be retrained in correct completion of the diary if missing data is identified.

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 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. 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, subject information/informed consent form, 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 IB and SmPC or similar labelling as appropriate
- 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 agreement
- 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 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 of the US will not sign FDA form 1572

Novo Nordisk will analyse and report data from all sites together if more than one site is involved in the trial.

By signing the protocol, each Investigator agrees to comply fully with ICH GCP<sup>1</sup>, applicable regulatory requirements and the Declaration of Helsinki<sup>2</sup>.

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.

For Japan only: In Japan a seal is accepted as signature.

## 22 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 log of appropriately qualified persons to whom he/she has delegated specified 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 trial master 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 task(s).

## 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.

Two Investigators will be appointed by Novo Nordisk to review and sign the clinical trial report (signatory Investigators) on behalf of all participating Investigators. The signatory Investigators will be appointed based upon the criteria defined by the International Committee of Medical Journal Editors for research publications<sup>2</sup>.

### 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 <sup>20</sup>.

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

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

In all cases the trial results will be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations. 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 four weeks 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 <sup>36</sup> (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.

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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 and human biospecimens**

### **24.1 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 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.

### **24.2 Retention of human biospecimens**

Blood samples will be collected to measure insulin antibodies. The total volume of blood that will be obtained from a subject during the trial for antibody analysis is approximately 4.5 mL. The blood samples will be stored at a central archive for later analysis and will be destroyed after marketing approval. If requested by the Regulatory Authorities antibody samples may be stored for a longer period until drug approval by FDA and/or EMA.



## **25 Institutional Review Boards/Independent Ethics Committees and regulatory authorities**

### **IRB/IEC:**

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 clinical trial report 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 clinical trial report 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:

Austria: Arzneimittelgesetz (BGBl. Nr. 185/1983) last amended with BGBl. Nr. 162/2013

## 27 References

- 1 International Conference on Harmonisation. ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6 (R1), Step 4 including Post Step 4 errata. 10 Jun 1996.
- 2 World Medical Association. Declaration of Helsinki: Ethical principles for medical research involving human subjects - Last amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013.
- 3 The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *New Engl J Med* 1993; 329(14):977-986.
- 4 UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; 352(9131):837-853.
- 5 Woerle HJ, Neumann C, Zschau S, Tenner S, Irsigler A, Schirra J et al. Impact of fasting and postprandial glycemia on overall glycemic control in type 2 diabetes. Importance of postprandial glycemia to achieve target HbA<sub>1c</sub> levels. *Diabetes Res Clin Pract* 2007; 77:280-285.
- 6 Brange J, Owens DR, Kang S, Vølund A. Monomeric insulins and their experimental and clinical implications. *Diabetes Care* 1990; 13(9):923-954.
- 7 Lindholm A, McEwen J, Riis AP. Improved postprandial glycemic control with insulin aspart. A randomized double-blind cross-over trial in type 1 diabetes. *Diabetes Care* 1999; 22:801-805.
- 8 American Diabetes Association. Standards of Medical Care in Diabetes 2015 ed. *Diabetes Care*. 38 Suppl:S33-40. doi: 10.2337/dc15-S009., S33-S40.
- 9 Novo Nordisk A/S. Investigator's brochure. Faster-acting insulin aspart. Current version.
- 10 Home PD, Lindholm A, Riis A. Insulin aspart vs. human insulin in the management of long-term blood glucose control in type 1 diabetes mellitus: a randomized controlled trial. *Diabet Med* 2000; 17(11):762-770.
- 11 Bretzel RG, Arnolds S, Medding J, Linn T. A direct efficacy and safety comparison of insulin aspart, human soluble insulin, and human premix insulin (70/30) in patients with type 2 diabetes. *Diabetes Care* 2004; 27(5):1023-1027.
- 12 Gallagher A, Home PD. The effect of improved post-prandial blood glucose control on post-prandial metabolism and markers of vascular risk in people with type 2 diabetes. *Diabetes Res Clin Pract* 2005; 67(3):196-203.

- 13 Perriello G, Pampanelli S, Porcellati F, Avogaro A, Bosi E, Petrella G et al. Insulin aspart improves meal time glycaemic control in patients with type 2 diabetes: a randomized, stratified, double-blind and cross-over trial. *Diabet Med* 2005; 22(5):606-611.
- 14 NovoRapid<sup>®</sup> Summary of Product Characteristics - current version 27-Mar-2014.
- 15 NovoLog<sup>®</sup> US Label Information - current version 31-Oct-2013.
- 16 Tresiba<sup>®</sup> Summary of Product Characteristics - current version 26-Jun-2014.
- 17 Novo Nordisk A/S. Investigator's Brochure, Insulin degludec (10th Edition). 16 Dec 2014.
- 18 Guideline on clinical investigation of medicinal products in the treatment of diabetes mellitus, Committee for Medicinal Products for Human Use (CHMP). 20 Jan 2010. European Medicines Agency.
- 19 U.S.Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER. Guidance for Industry, Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention, U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) February 2008. 2008.
- 20 Novo Nordisk. <http://novonordisk-trials.com/website/content/how-we-disclosetrial-information.aspx>.
- 21 De Angelis C, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. *New Engl J Med* 2004; 351(12):1250-1251.
- 22 Food and Drug Administration. Food and Drug Administration Amendments Act. 2007.
- 23 The European Parliament and the Council of the European Council. Directive 2001/20/EC of the European Parliament and the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, article 11. *Official Journal of the European Communities*. May. 2001.
- 24 The European Parliament and the Council of the European Council. Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, article 57. *Official Journal of the European Communities*. April. 2001.

- 25 Clarke WL, Cox DJ, Gonder-Frederick LA. Reduced awareness of hypoglycemia in adults with IDDM: a prospective study of hypoglycemic frequency and associated symptoms. *Diabetes Care* 1995; 18:517-522.
- 26 Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L et al. Hypoglycemia and Diabetes: A Report of a Workgroup of the American Diabetes Association and The Endocrine Society. *Diabetes Care* 2013; 36(5):1384-1395.
- 27 McAulay V, Deary IJ, Frier BM. Symptoms of hypoglycaemia in people with diabetes. *Diabet Med* 2001; 18(9):690-705.
- 28 U.S.Department of Health and Human Services - FDA. Guidance for Industry, Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. Dec 9 A.D.
- 29 Stull DE, Leidy NK, Parasuraman B, et al. Optimal recall periods for patient-reported outcomes: challenges and potential solutions. *Current Medical Research and Opinion* 25[4], 929-942.
- 30 KDIGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Official Journal of the International Society of Nephrology* 2012; 3(1).
- 31 Watts S.A., Anselmo J.M., et al. Validating the AdultCarbQuiz: A Test of Carbohydrate-Counting Knowledge for Adults With Diabetes. *Diabetes Spectrum* 2011; 24(3):154-160.
- 32 European Union. The rules governing medicinal products in the European Union, volume 4, Annex 13, Manufacture of Investigational Medicinal Products. Feb 2010.
- 33 Novo Nordisk A/S. Company core data sheet (CCDS), NovoRapid (Version 15). 2013.
- 34 International Conference on Harmonisation. ICH Harmonised Tripartite Guideline. Statistical principles for clinical trials E9. International Conference on Harmonisation E9 Expert Working Group. September 1998.
- 35 Schwartz NS, Clutter WE, Shah SD, Cryer PE. Glycemic thresholds for activation of glucose counterregulatory systems are higher than the threshold for symptoms. *J Clin Invest* 1987; 79(3):777-781.
- 36 International Committee of Medical Journal Editors. Uniform Requirements for Manuscripts submitted to Biomedical Journals. 2012.

## **Appendix A: Titration Guideline**

**NN1218-4131**

# **Efficacy and Safety of Faster-acting Insulin Aspart compared to NovoRapid<sup>®</sup> both in combination with Insulin Degludec in Adults with Type 1 Diabetes**

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# 1 Introduction

The goal of insulin therapy is to achieve near normoglycaemia, i.e. to reach a pre-defined HbA<sub>1c</sub> level with a low rate of hypoglycaemic episodes and as little weight gain as possible. Several trials have shown that this is difficult to achieve, unless plasma glucose (PG) values are intensively monitored and the insulin dose(s) frequently adjusted [1-6](#)

To ensure treatment uniformity between the sites, as well as to ensure that subjects receive an optimal treatment, titration algorithms have been developed specifying recommended dose adjustments at different PG levels.

It is recognised that treatments differ between different regions and countries. Likewise, specific titration guidelines may not be applicable in certain clinical situations. It is important that other information, such as symptoms of hypo/hyperglycaemia, previous response to dose adjustments, other glucose measurements and other indicators of the subject's level of glycaemic control, is taken into consideration when decisions on dosing are made. The investigator should always use his clinical judgement to avoid safety hazards. The investigator is responsible for the treatment of the subjects and can therefore overrule the guideline.

To optimise and maintain glycaemic control, the Investigator should, throughout the trial be at least in weekly contact with the subjects to assist the subjects in adjusting insulin doses and to ensure the subject's welfare.



## 2 Treatment regimens

All subjects will be treated with insulin degludec and NovoRapid<sup>®</sup> /faster-acting insulin aspart in a basal-bolus regimen.

At Visit 2 eligible subjects will be transferred from their previous basal insulin dose to insulin degludec once daily according to Section [3.1](#).

During the following 8 weeks the Investigator will focus on adjusting the basal insulin dose according to Section [3.2](#).

In addition, the subjects will be transferred to NovoRapid<sup>®</sup> at Visit 2 as bolus insulin and adjusted according to Section [3.3](#) and Section [3.4](#).

At randomisation (after 8 weeks) eligible subjects will be randomised 1:1:1 into three parallel treatment groups:

1. mealtime faster-acting insulin aspart + insulin degludec
2. mealtime NovoRapid<sup>®</sup> + insulin degludec
3. postmeal faster-acting insulin aspart + insulin degludec

### 2.1 Injection area

Insulin degludec should be injected subcutaneously into the thigh, or upper arm (deltoid area).

Faster-acting insulin aspart or NovoRapid<sup>®</sup> should be injected subcutaneously into the abdominal wall.

Rotation of injection sites within a given region is recommended.

### 2.2 Time of injection

Insulin degludec should be administered once daily at any time of the day, preferably at the same time every day.

For the blinded mealtime arms, faster-acting insulin aspart or NovoRapid<sup>®</sup> should be given 0-2 minutes prior to meals.

For open-label postmeal faster-acting insulin aspart dosing arm, faster-acting insulin aspart will be injected at the end of the meal but no later than 20 minutes after the start of the meal.

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Main meals are defined as breakfast, lunch and main evening meal. Extra bolus dosing is allowed at the Investigator's recommendation.

### 3 Initiation and titration of insulin degludec, faster-acting insulin aspart and NovoRapid®

#### 3.1 Initiation of insulin degludec (Visit 2)

For subjects previously receiving once daily basal insulin, and having HbA1c  $\geq 8.0\%$ , the pre-trial basal insulin should be transferred to insulin degludec once daily on unit-to-unit by the Investigator's discretion.

For subjects taking twice daily basal insulin or having HbA1c  $< 8.0\%$ , the dose of once daily insulin degludec should be determined on an individual basis, and dose reduction needs to be considered by the Investigator.

#### 3.2 Titration of insulin degludec

Insulin degludec dose will be adjusted weekly by the Investigator in the run-in period in connection with the scheduled visit/phone contacts.

The dose of insulin degludec should be titrated based on the mean of three pre-breakfast SMPG values measured on the three days prior to the contact in accordance with [Table 1](#).

If one or more SMPGs values are missing, the adjustment should be performed on the remaining SMPG value(s).

If one of the SMPG values is below target ( $< 4.0$  mmol/L or 71 mg/dL) then the insulin degludec dose should be reduced in accordance with [Table 2](#).

**Table 1 Increase of insulin degludec Dose**

Mean Pre-breakfast SMPG Values		Increase of insulin degludec dose
mmol/L	mg/dL	U
<b>4.0 – 5.0</b>	<b>71 – 90</b>	<b>No adjustment</b>
5.1 – 10.0	91 – 180	+ 2
10.1 – 15.0	181 – 270	+ 4
> 15.0	> 270	+ 6

**Table 2 Reduction of insulin degludec Dose**

Lowest Pre-breakfast SMPG Value		Reduction of insulin degludec dose
mmol/L	mg/dL	U
3.1 – 3.9	56 – 70	- 2 (for a dose of >45 U, suggest a dose reduction of 5%)
<3.1	< 56	- 4 (for a dose of >45 U, suggest a dose reduction of 10%)

### 3.3 Initiation of NovoRapid® (Visit 2)

Subjects should be switched to trial NovoRapid® unit-to-unit from previous mealtime bolus doses at Visit 2, and should continue to use the same method for adjustment of bolus insulin as they did before the trial.

No adjustments of NovoRapid® should be performed by the Investigator unless for safety reasons in the run-in period.

### 3.4 Titration of faster-acting insulin aspart or NovoRapid® from randomisation (Visit 10)

Titration of bolus insulin (faster-acting insulin aspart or NovoRapid®) should be performed from randomisation (Visit 10) and onwards while the adjustments of basal insulin dose(s) may be performed according to the Investigators' discretion.

Subjects will be instructed to perform 4-point profiles every day during the conduct of the trial for titration purposes.

Faster-acting insulin aspart or NovoRapid® should be adjusted according to Section [3.4.1](#) if the subject follows bolus dosing algorithms or according to Section [3.4.2](#) if the subject follows the principles of flexible insulin therapy.

#### 3.4.1 Bolus dosing algorithms

Faster-acting insulin aspart or NovoRapid® should be titrated twice weekly:

- 1) At the scheduled visit/phone contact, adjustment of faster-acting insulin aspart or NovoRapid® doses should be based on pre-prandial and/or bedtime SMPG values which are measured during last 3 days before each scheduled visit/phone contact.
- 2) In between the scheduled visit/phone contacts the subject should be instructed by the Investigator to use the same titration algorithm to self-titrate faster-acting insulin aspart or

NovoRapid® doses based on SMPG values measured on the last 3 days before the day of self-titration.

The adjustments should be according to [Table 3](#).

- Breakfast faster-acting insulin aspart or NovoRapid® will be titrated according to pre-lunch SMPG values measured on previous days
- Lunch faster-acting insulin aspart or NovoRapid® will be titrated according to pre-dinner SMPG values measured on previous days
- Dinner faster-acting insulin aspart or NovoRapid® will be titrated according to bedtime SMPG values measured on previous days

**Table 3 Faster-acting insulin aspart or NovoRapid® dose adjustment based on bolus dosing algorithm**

Mean of Pre-prandial or bedtime SMPG Values		Dose adjustment	Rules for dose adjustment
mmol/L	mg/dL	U	
< 4.0	< 71	- 1	≥ 1 SMPG below target
<b>4.0 – 6.0</b>	<b>71 -108</b>	<b>0</b>	<b>0-1 SMPG above target No SMPGs below target</b>
> 6.0	> 108	+ 1	≥ 2 SMPGs above target No SMPGs below target

Additional bolus dosing is allowed at the investigator's recommendation. The dose will be entered in the eDiary.

### 3.4.2 Carbohydrate counting - subjects following principles of flexible bolus insulin therapy

Faster-acting insulin aspart and NovoRapid® should be dosed in accordance with principles of flexible dosing whereby the meal carbohydrate content and pre-prandial plasma glucose value are used to determine bolus insulin dose.

Using this method, bolus insulin dose adjustment is conducted several times daily in accordance with the Insulin:Carbohydrate (I:Carb) ratio and the plasma glucose correction factor (sensitivity factor). Bolus insulin dose consists of meal bolus to cover for carbohydrates consumed in the meal and, if required, a correction dose (to supplement or reduce the dose based on the difference between the SMPG and the target). This method is applicable to subjects with prior hands-on experience using this method of determining bolus insulin doses. It is the responsibility of the investigator to ensure that the subject is adequately educated and comfortable with this method. If more training is needed then this should be carried out according to local practice.

The I:Carb ratio expresses the amount of carbohydrate (in grams) for which 1U of bolus insulin would effectively minimise postprandial plasma glucose excursions. The plasma glucose correction factor (sensitivity factor) expresses the expected reduction in plasma glucose, when 1U of bolus insulin is administered. The I:Carb ratio and the correction factor (sensitivity factor) per type of meal should be recorded at trial start and should, if needed, be adjusted at the discretion of the investigator during the weekly contacts based on the reviewed SMPGs.

In this trial the target pre-prandial plasma glucose range is 4.0–6.0 mmol/L (71–108 mg/dL). In the following, an example on how to cover a subject's prandial insulin dose will be provided. In case of hypoglycaemic episodes, the dose will be reduced at the investigator's discretion.

### **Example 1 – Carbohydrate coverage of a meal and plasma glucose correction dose (sensitivity factor):**

A subject has pre-prandial plasma glucose of 10.0 mmol/L (180 mg/dL) and intends to eat a meal containing 60 g of carbohydrates. The I:Carb ratio has been estimated to 1U:10g.

The meal coverage dose is calculated as follows:

Total carbohydrate in meal \* I:Carb ratio = 60 g \* (1U/10g) = 6U.

The plasma glucose correction factor (sensitivity factor) has been estimated to be 2.0 mmol/L (36 mg/dL) per 1U. The pre-prandial plasma glucose target range is 4.0-6.0 mmol/L (71-108 mg/dL). The subject was advised to correct to the target plasma glucose of 6.0 mmol/L (108 mg/dL) at this meal.

The correction dose can be calculated as follows:

$$(\text{Pre-prandial plasma glucose} - \text{target plasma glucose}) \div \text{plasma glucose correction factor} = (10 \text{ mmol/L} - 6.0 \text{ mmol/L}) \div 2 \text{ mmol/L} = (180 \text{ mg/dL} - 108 \text{ mg/dL}) \div 36 \text{ mg/dL} = 2\text{U}$$

Thus this subject needs 8U of bolus insulin to cover for the meal and correct for hyperglycaemia before the meal.

### **3.5 Deviations from the recommended insulin dose**

It is recommended that the titration guideline is followed. However, it is also important that the decision to adjust the insulin degludec, faster-acting insulin aspart and NovoRapid® doses are based on all available information, such as symptoms of hypo- and/or hyperglycaemia, previous responses to dose adjustments as well as SMPG measurements other than those required as per protocol. A reason for deviating from the recommended insulin dose should be entered into the eDiary by the subject or in the web portal by the Investigator as applicable.

## 4 Data collection

The titration data should be entered into the eDiary within 24 hours (for details referring to Protocol).

If titration data on a subject is missing then the Investigator will be asked for the reason.

## 5 Review procedure

Surveillance of titration data will be performed centrally by Novo Nordisk in an unbiased manner. The data will be reviewed and significant changes from the titration algorithm will be followed up.

It is important that data regarding dose titration is entered into the eDiary. If delays occur, action cannot be taken in due time before the subject's next site visit/phone contact. The aim is to reduce the time periods in which a subject may receive suboptimal treatment.

The titration data should be reviewed by Novo Nordisk within 24 hours (on weekdays). The reviewer may contact the investigator to get clarification regarding the reason for deviation.

When the investigator receives an inquiry, a response should be received at Novo Nordisk within 24 hours (on weekdays).

During the trial HbA<sub>1c</sub> will be monitored by Novo Nordisk for additional surveillance of the glycaemic control. Novo Nordisk may 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<sub>1c</sub>. This will be done in an unbiased and whenever possible in a blinded manner.



## 6 References

- 1 Rosenstock J, Davies M, Home PD, Larsen J, Koenen C, Schernthaner G. A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naïve people with type 2 diabetes. *Diabetologia* 2008; 51(3):408-416.
- 2 Hermansen K, Davies M, Derezinski T, Martinez RG, Clauson P, Home P. A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naïve people with type 2 diabetes. *Diabetes Care* 2006; 29(6):1269-1274.
- 3 Philis-Tsimikas A, Charpentier G, Clauson P, Ravn GM, Roberts VL, Thorsteinsson B. Comparison of once-daily insulin detemir with NPH insulin added to a regimen of oral antidiabetic drugs in poorly controlled type 2 diabetes. *Clin Ther* 2006; 28(10):1569-1581.
- 4 Riddle MC, Rosenstock J, Gerich J. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care* 2003; 26(11):3080-3086.
- 5 Garber AJ, King AB, Del PS, Sreenan S, Balci MK, Munoz-Torres M et al. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 2 diabetes (BEGIN Basal-Bolus Type 2): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. *Lancet* 2012; 379(9825):1498-1507.
- 6 Heller S, Buse J, Fisher M, Garg S, Marre M, Merker L et al. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 1 diabetes (BEGIN Basal-Bolus Type 1): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. *Lancet* 2012; 379(9825):1489-1497.

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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

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1 of 4

**Novo Nordisk**

**Protocol Amendment**  
**No. 1**  
**to Protocol, final version 1**  
**dated 10 July 2015**

**Trial ID: NN1218-4131**

**Efficacy and Safety of Faster-acting Insulin Aspart compared to  
NovoRapid® both in combination with Insulin Degludec in Adults with  
Type 1 Diabetes  
onset<sup>®8</sup>**

**Trial phase: 3b**

**Applicable to Austria, Germany and Italy**

Amendment originator:

[REDACTED], [REDACTED]

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## 1 Introduction including rationale for the protocol amendment

This local protocol amendment is made to accommodate requests from the European regulatory authorities (Voluntary Harmonised Procedure) received during the approval process.

In this protocol amendment:

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

## 2 Changes

### 6.3 Exclusion criteria

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 Austria, Germany and Italy only: Adequate contraceptive measures are defined as those which result in a less than 1% failure rate per year when used consistently and correctly such as implants, injectables, combined oral contraceptives, hormonal intrauterine devices, sexual abstinence or vasectomised partner.*

For Japan only: Adequate contraceptive measures are abstinence (not having sex), diaphragm, condom (by the partner), intrauterine device, sponge, spermicide or oral contraceptives.

*19. For Austria, Germany and Italy only: Known hypoglycaemic unawareness as judged by the Investigator*

*20. For Austria, Germany and Italy only: Subjects with gastroparesis as judged by the Investigator*

**Protocol Amendment**  
**no 2**  
**to Protocol, final version 1.0**  
**dated 10 July 2015**

**Trial ID: NN1218-4131**

**Efficacy and Safety of Faster-acting Insulin Aspart compared to  
NovoRapid<sup>®</sup> both in combination with Insulin Degludec in Adults with  
Type 1 Diabetes**

**onset<sup>®</sup> 8**

**Trial phase: 3b**

**Applicable to all countries**

Amendment originator:

[REDACTED], [REDACTED]

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## 1 Introduction including rationale for the protocol amendment

This amendment was prepared based on feedback received from the U.S. Food and Drug Administration: The feedback included a request for introducing estimands into the protocols with an emphasis of using the ITT estimand as the primary.

As a result of this we have introduced a differentiation between trial drug and trial discontinuation. This has been incorporated by adding a premature discontinuation visit (visit 36A) and by adding the sections 6.4 and 6.6 that describe the criteria for run-in failure and the criteria for premature discontinuation of trial product. In addition to this the sections 8.1.13 (Premature discontinuation from trial product) and 8.1.14 (Withdrawal from Trial) has been added to section 8 of the protocol to describe how subjects that discontinue trial product prematurely should be followed and how a subject can withdraw from the trial.

The statistical analysis described in section 17 has been changed significantly to describe the estimands and the associated primary and sensitivity analyses. The wording of the endpoints was changed accordingly. Also a section that describes the choice of non-inferiority margin was included in section 5.

Additional changes:

The order of the hierarchical testing was changed in the secondary objectives in section 4.1.

A few editorial changes were done in the flowchart in section 2.

Section 5.3.2 was updated to specify the bolus insulin will be titrated according to the pre-prandial and bedtime plasma glucose.

Inclusion criterion no. 10 in section 6.2 was updated to specify that flash glucose monitoring is not allowed during the trial.

Section 8.3.1 describing the meal test has been updated to specify that the subject will receive 78 g of carbohydrate in the standardised liquid meal that will be provided. This was changed as it will be more convenient for the subject to have 78 g of carbohydrate as this equals the amount in two bottles of the liquid meal that will be provided for this trial.

In section 8.4.1 the definition of childbearing potential was included as well as the period where it is required to use adequate contraceptive methods.

Changes related to the description of the electronic patient reported outcome (ePRO) database were introduced in section 8.6.4 and section 14.

Table 9.2 was updated to reflect the updated in-use storage conditions for insulin degludec and the US approval status of insulin degludec was updated. in section 3.5

Section 12: The period for safety reporting was updated to also accommodate correct collection period for the subjects that discontinue treatment prematurely. The SAE definition section was updated to report potential events of Hy's law using the seriousness criteria 'Important medical event' if no other seriousness criteria apply. It is a regulatory requirement in all clinical trials that events of suspected drug induced liver injury are reported to the regulatory authorities within expedited timelines.

Two new references were introduced in section 5.2.1 (Rationale for choice of non-inferiority margin) and the references to the SmPC for Insulin degludec will be updated to the current version in the updated protocol and the reference to the Investigators Brochure for insulin degludec will be changed to the current version of the Company Core Datasheet in section 12.2.

Appendix A was updated to reflect that it is not the mean pre-prandial blood glucose that is used for titration.

In this protocol amendment:

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

## 2 Changes

### 2.1 Section 1 Summary

#### Primary objective

To confirm ~~the effect~~ **efficacy** in terms of glycaemic control of treatment with mealtime faster-acting insulin aspart in combination with insulin degludec in adults with Type 1 Diabetes Mellitus.

#### Secondary objectives

To confirm ~~the effect~~ **efficacy** in terms of glycaemic control of treatment with postmeal faster-acting insulin aspart in combination with insulin degludec in adults with Type 1 Diabetes Mellitus.

To confirm superiority of mealtime faster-acting insulin aspart compared to mealtime NovoRapid® both in combination with insulin degludec in adults with Type 1 Diabetes Mellitus in terms of:

- Postprandial glucose regulation (meal test)
- ~~Postprandial glucose excursions (1,5-anhydroglucitol)~~ **Overall glycaemic control (HbA<sub>1c</sub>)**
- ~~Overall glycaemic control (HbA<sub>1c</sub>)~~ **Postprandial glucose excursions (1,5-anhydroglucitol)**

To compare other efficacy and safety endpoints across mealtime faster-acting insulin aspart, postmeal faster-acting insulin aspart and mealtime NovoRapid®, all in combination with insulin degludec in adults with Type 1 Diabetes Mellitus.

#### Primary endpoint

Change from baseline in HbA<sub>1c</sub> ~~after 26 weeks of treatment~~ **after randomisation**

#### Key secondary endpoints

Confirmatory secondary endpoints

- Change from baseline in 1-hour post prandial glucose increment ~~after 26 weeks of treatment~~ **after randomisation** (meal test)
- Change from baseline in 1,5-anhydroglucitol ~~after 26 weeks of treatment~~ **after randomisation**

Key exclusion criteria:

1. Within the past 180 days any of the following: myocardial infarction, stroke or hospitalization for unstable angina and/or transient ischemic attack
2. Subjects presently classified as being in New York Heart Association (NYHA) Class IV
3. Currently planned coronary, carotid or peripheral artery revascularisation

~~3.~~ 4. Diabetic ketoacidosis requiring hospitalisation within the last 180 days prior to screening (Visit 1)

~~4.~~ 5. Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria in a period of three months before screening (Visit 1)

[illegible]

Trial Periods	Protocol section	Screening	8 week run-in period						Randomisation	26 week treatment period																Follow-up 1	Follow-up 2	Premature Discontinuation
Visit (V) Phone contact (P)	8.1.7 8.1.8	V1	V2	P3 P4	V5	P6 P7 P8	V9	V10	V11	P12 P13	V14	P15 P16 P17	V18	P19 P20 P21	V22	P23 P24 P25	V26	P27 P28 P29	V30	P31 P32 P33	V34	P35	V36	V37	P38	V36A		
Timing of visit (weeks)		-10	-8	-7 -6	-5	-4 -3 -2	-1	0	1	2 3	4	5 6 7	8	9 10 11	12	13 14 15	16	17 18 19	20	21 22 23	24	25	26	7 days	30 days			
Visit window (days)		+10	±3	±3	±3	±3	±3	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+5	+5			
glucose																												
4-point profile	<a href="#">8.3.2.1</a>			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			x		
7-9-7-point profile	<a href="#">8.3.2.2</a>							x							x								x			x		
9-point profile	<a href="#">8.3.2.2</a>	-	-	-	-	-	-	⌘	-	-	-	-	-	-	⌘	-	-	-	-	-	-	-	⌘	-	-	⌘		
Glucose metabolism																												
1,5-anhydroglucitol	<a href="#">8.5.1.1</a>							x			x		x		x		x		x		x		x			x		
Fasting plasma glucose	<a href="#">8.5.1.2</a>							x							x						⌘		x			x		
HbA <sub>1c</sub>	<a href="#">8.5.1.3</a>	x			x		x	x			x		x		x		x		x		x		x			x		
Lipids	<a href="#">8.5.1.4</a>	x						x							x								x			x		
SAFETY																												
Adverse events	<a href="#">12</a>		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Hypoglycaemic episodes	<a href="#">8.4.1.1</a>		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x		
Injection site reaction	<a href="#">8.4.1.2</a>		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x		
Technical complaints	<a href="#">12.4</a>		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			x		
Body measurements																												
Height	<a href="#">8.4.4</a>	x																										
Weight	<a href="#">8.4.4</a>	x						x							x								x			x		
Physical examination	<a href="#">8.4.5</a>	x						x							x								x			x		
Vital signs	<a href="#">8.4.6</a>	x						x							x								x			x		
Eye examination	<a href="#">8.4.2</a>	x						x															x			x		
ECG	<a href="#">8.4.3</a>	x						x															x			x		

Trial Periods	Protocol section	Screening	8 week run-in period						Randomisation	26 week treatment period																Follow-up 1	Follow-up 2	Premature Discontinuation
Visit (V) Phone contact (P)	8.1.7 8.1.8	V1	V2	P3 P4	V5	P6 P7 P8	V9	V10	V11	P12 P13	V14	P15 P16 P17	V18	P19 P20 P21	V22	P23 P24 P25	V26	P27 P28 P29	V30	P31 P32 P33	V34	P35	V36	V37	P38	V364		
Timing of visit (weeks)		-10	-8	-7 -6	-5	-4 -3 -2	-1	0	1	2 3	4	5 6 7	8	9 10 11	12	13 14 15	16	17 18 19	20	21 22 23	24	25	26	7 days	30 days			
Visit window (days)		+10	±3	±3	±3	±3	±3	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+5	+5			
Biochemistry	8.5.2.1	x						x							x								x			x		
Haematology	8.5.2.2	x						x							x								x			x		
Antibodies	8.5.2.3							x							x								x			x		
Pregnancy test	8.5.2.4	x						x															x			x		
Urine sticks	8.5.2.4		(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)						
Urinalysis	8.5.2.5	x						x							x								x			x		
OTHER ASSESSMENTS																												
PRO questionnaires	8.6.1		x																									
TRIAL MATERIAL																												
IV/WRS call	10	x	x					x			x		x		x				x				x			x		
Administration of trial product																												
Dispensing visit	9		x					x			x		x		x				x									
New dose of trial insulin	8.3.3.1		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x						
Dose of trial insulin, day(s) before visit	8.3.3			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			x		
Start/stop date of trial insulin (dosing)	8.3.3.1			x					x														x			x		
Drug accountability	9.4							x			x		x		x				x				x			x		





## 2.3 Section 3.5 Insulin degludec

At the time of this protocol issuance, insulin degludec is approved in more than 60 countries including *US*, all EU countries and Japan.

## 2.4 Section 4 Objectives and endpoints

### 2.4.1 Section 4.1 Objectives

#### 2.4.1.1 Section 4.1.1 Primary objective

To confirm ~~the effect~~ efficacy in terms of glycaemic control of treatment with mealtime faster-acting insulin aspart in combination with insulin degludec in adults with Type 1 Diabetes Mellitus.

#### 2.4.1.2 Section 4.1.2 Secondary objectives

To confirm ~~the effect~~ efficacy in terms of glycaemic control of treatment with postmeal faster-acting insulin aspart in combination with insulin degludec in adults with Type 1 Diabetes Mellitus.

To confirm superiority of mealtime faster-acting insulin aspart compared to mealtime NovoRapid<sup>®</sup> both in combination with insulin degludec in adults with Type 1 Diabetes Mellitus in terms of:

- Postprandial glucose regulation (meal test)
- ~~Postprandial glucose excursions (1,5-anhydroglucitol)~~ Overall glycaemic control ( $HbA_{1c}$ )
- ~~Overall glycaemic control ( $HbA_{1c}$ )~~ Postprandial glucose excursions (1,5-anhydroglucitol)

To compare other efficacy and safety endpoints across mealtime faster-acting insulin aspart, postmeal faster-acting insulin aspart and mealtime NovoRapid<sup>®</sup>, all in combination with insulin degludec in adults with Type 1 Diabetes Mellitus.

### 2.4.2 Section 4.2 Endpoints

- Baseline is defined as randomisation (Visit 10).

#### 2.4.2.1 Section 4.2.1 Primary endpoint

- Change from baseline in  $HbA_{1c}$  ~~after 26 weeks of treatment~~ after randomisation

#### 2.4.2.2 Section 4.2.2 Secondary endpoints

##### 2.4.2.3 Section 4.2.2.1 Confirmatory secondary endpoints

- Change from baseline in 1-hour post prandial glucose increment ~~after 26 weeks of treatment~~ after randomisation (meal test)
- Change from baseline in 1,5-anhydroglucitol ~~after 26 weeks of treatment~~ after randomisation

## 2.4.2.4 Section 4.2.2.2 supportive secondary endpoints

### Supportive secondary efficacy endpoints

*26 weeks after randomisation*

- Change from baseline in fasting plasma glucose ~~after 26 weeks of treatment~~
- Percentage of subjects reaching HbA<sub>1c</sub> targets  
~~HbA<sub>1c</sub> responder after 26 weeks of treatment:~~
  - HbA<sub>1c</sub> < 7.0%
  - HbA<sub>1c</sub> < 7.0% without severe hypoglycaemia
  - HbA<sub>1c</sub> < 7.0% without severe hypoglycaemia and minimal weight gain (<3.0%)
- Change from baseline in 30- min, 1- hour, 2- hour, 3- hour and 4- hour PPG and 30- min, 2- hour, 3- hour and 4- hour PPG increment ~~after 26 weeks of treatment~~ (meal test)
- Change from baseline in 7-9-7-point self-measured plasma glucose ~~assessed by~~ ~~after 26 weeks of treatment:~~
  - Mean of the 7-9-7-point profile
  - Post prandial glucose and post prandial glucose increment (mean, breakfast, lunch, main evening meal)
  - Fluctuation in 7- 9-7-point profile
  - Change in the nocturnal self-measured plasma glucose measurements
- *Percentage of subjects reaching Ppost prandial glucose target responders* (overall mean of daily post prandial glucose measurements in 7-9-7-point self-measured plasma glucose ) ~~after 26 weeks of treatment:~~
  - Overall post prandial glucose (1 hour) ≤7.8 mmol/L [140 mg/dL]
  - Overall post prandial glucose (1 hour) ≤7.8 mmol/L [140 mg/dL] without severe hypoglycaemia
  - Overall post prandial glucose (1 hour) ≤ 7.8 mmol/L [140 mg/dL] and HbA<sub>1c</sub> < 7.0% and minimal weight gain (<3.0%) without severe hypoglycaemia
- ~~Insulin dose (basal insulin dose, total and individual meal insulin dose) after 26 weeks of treatment.~~
- Change from baseline in lipids-lipoproteins profile ~~after 26 weeks of treatment~~ (total cholesterol, high density lipoproteins, low density lipoproteins)
- Insulin dose (basal insulin dose, total and individual meal insulin dose).

### Supportive secondary safety endpoints

- Number of *treatment emergent* adverse events *during the 26 weeks after randomisation* ~~during 26 weeks of treatment~~
- Number of *treatment emergent* injection site reactions *during the 26 weeks after randomisation* ~~during 26 weeks of treatment~~

- Number of hypoglycaemic episodes classified both according to the American Diabetes Association definition and Novo Nordisk definition *during the 26 weeks after randomisation* ~~during 26 weeks of treatment~~
  - 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
- Change from baseline *26 weeks after randomisation* ~~after 26 weeks of treatment~~ in clinical evaluations:
  - Physical examination
  - Vital signs
  - Electrocardiogram
  - Fundoscopy/fundus photography
- Change from baseline *26 weeks after randomisation* ~~after 26 weeks of treatment~~ in central laboratory assessments:
  - Haematology
  - Biochemistry
  - Urinalysis
- *Change from baseline in anti-insulin aspart (specific and cross-reacting with human insulin) antibody development*
- ~~Total insulin aspart antibodies (amount of antibodies specific for insulin aspart and cross-reacting with human insulin)~~
- Change from baseline ~~after 26 weeks of treatment~~ in weight and body mass index

## 2.5 Section 5.2.1 Rationale 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 NovoRapid<sup>®</sup> 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<sub>1c</sub> was - 0.94%-point [ -1.17; -0.72] (data on file). In this trial the addition of 3 times daily faster-acting insulin aspart lead to a reduction in HbA<sub>1c</sub> of 1.16%-point after 18 weeks of treatment. In a similar phase 4 trial (ref. 1) investigating the stepwise addition of NovoRapid<sup>®</sup> to a full basal bolus regimen in bolus naïve T2DM adults the observed reduction in HbA<sub>1c</sub> after 21 weeks of treatment was 1.15%-point (data on file) with 3 times daily NovoRapid<sup>®</sup> added to basal insulin. This gives some indication that the effect of NovoRapid<sup>®</sup> 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 guidance (Ref. 2), 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 endogenous insulin production and the true effect of NovoRapid<sup>®</sup> should be comparable to what is seen in a T2DM population.*

### 2.5.1 Section 5.3.2 Bolus insulin titration

In the 26 week treatment period, the Investigator should focus on optimising the bolus insulin. The bolus insulin will be titrated to the glycaemic target of ~~fasting and~~ pre-prandial *and bedtime* plasma glucose between 4.0-6.0 mmol/L [71 - 108 mg/dL] in a treat-to-target fashion.

## 2.6 Section 5.4 Treatment after discontinuation of trial product

When discontinuing trial products, the subject should be switched to a suitable marketed product at the discretion of the Investigator. *Doses of subsequent antidiabetic treatment should be carefully titrated based on blood glucose measurements, considering the stable effect and long half-life of insulin degludec.*

## 2.7 Section 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  $\geq 18$  years (for Japan and Taiwan: age  $\geq 20$  years) at the time of signing informed consent
3. Type 1 Diabetes Mellitus (based on clinical judgement and/or supported by laboratory analysis as per local guidelines)  $\geq 12$  months prior to screening
4. Currently treated with a basal-bolus insulin regimen for at least 12 months prior to screening (Visit 1)
5. Currently treated with a basal insulin analogue for at least 4 months prior to screening (Visit 1)
6. HbA<sub>1c</sub> 7.0-9.5% (53-80 mmol/mol) (both inclusive) as assessed by central laboratory
7. Body Mass Index  $\leq 35.0$  kg/m<sup>2</sup>
8. Ability and willingness to adhere to the protocol including performing of self-measured plasma glucose profiles and meal test
9. Ability and willingness to take at least three mealtime boluses a day every day during the trial
10. Not currently using *flash glucose monitoring* or real time continuous glucose monitoring system and/or willing not to use *flash glucose monitoring* or a real time continuous glucose monitoring system during the trial

## 2.8 Section 6.4 Run-in failure criteria

*The Subject must be withdrawn from the trial during the run-in period if the following applies:*

1. *Included in the trial in violation of the inclusion and/or exclusion criteria.*
2. *Pregnancy*
3. *Intention of becoming pregnant*
4. *Participation in another clinical trial anytime during the run-in period*

*Subjects fulfilling any of the above criteria or withdrawing consent prior to randomisation are considered as run-in failures and should be completed as described in section 8.1.5.*

## 2.9 Section 6.6 ~~Withdrawal criteria~~ Criteria for premature discontinuation of trial product

~~The subject may withdraw at will at any time.~~

The subject may be *discontinued from trial product* ~~withdrawn from the trial~~ at the discretion of the Investigator due to a safety concern.

The subject must be *discontinued from trial product* ~~withdrawn from the trial~~ if 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 another clinical trial ~~throughout~~ anytime during the trial

Subjects discontinued from trial product after randomisation will be followed as described in section 8.1.13.

## **2.10 Section 6.7 Withdrawal from Trial**

*The subject may withdraw consent at will at any time. The subject's request to withdraw from the trial must always be respected.*

*If the subject considers withdrawing 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 to stay in the trial, procedures described in section 8.1.13 must be followed.*

*If a subject decides to withdraw informed consent the subject should be encouraged to undergo procedures as described in section 8.1.14.*

*A subject will be considered lost to follow-up if he/she repeatedly fails to attend the scheduled visits and the Investigator is unable to establish contact with the subject.*

*The following actions must be taken in relation to a subject who fails to attend the site for a required visit:*

- *The site must attempt to contact the subject and 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 in which the subject is deemed lost to follow-up the investigator must make every effort to regain contact with the subject (e.g. telephone calls to friends or family members, e-mails or certified letter to the subject as applicable). These contact attempts must be documented in the subject's medical records. Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the trial with the primary reason being "lost to follow-up"*

## **2.11 Section ~~6.6~~ 6.8 Subject replacement**

Subjects who ~~are withdrawn~~ or discontinue trial product will not be replaced.

## **2.12 Section 8.1.6 Randomisation**

Randomisation (Visit 10) must occur after 8 weeks ( $\pm 3$  days) of run-in. If the subject meets the randomisation criterion at Visit 10, then the subject will be randomised into one of the three treatment arms by using IV/WRS; please see details in section 10. Stop date of NovoRapid<sup>®</sup> and start date of the randomised trial product must be recorded *in the eCRF*.

## **2.13 Section 8.1.7 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 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 product. Drug accountability should be performed at each dispensing visit from Visit 10 until end of treatment (~~Visit 36~~).

## **2.14 Section 8.1.11 ~~8.1.12~~ End of treatment**

At end of treatment (Visit 36) the randomised treatment with trial product must be discontinued and a completion IV/WRS session must be performed. ~~If the subject has completed treatment a completion session should be performed in IVRS.~~ The subject should be switched to a suitable marketed product at the discretion of the Investigator and this product must be recorded on the ~~Diabetes Treatment History~~ *concomitant diabetes medication* form in eCRF, as described in section 8.2.4. For procedures to be performed at end of treatment (Visit 36); please see flowchart in section 2. At end of treatment the ~~first treatment-related~~ part of the end of treatment/trial form must be completed.

## **2.15 Section 8.1.12 ~~8.1.13~~ Follow-up period**

The first follow-up visit (FU1) (Visit 37) is a site visit and must take place ~~no earlier than~~ 7-12 days after ~~the actual date of last day on trial product~~ the end of treatment visit (Visit 36). Follow-up Visit 2 (FU2) (Visit 38) is a phone contact and must take place ~~no earlier than~~ 30-35 days after the ~~last day on trial product~~ end of treatment visit.

## **2.16 Section 8.1.13 Premature discontinuation of trial product**

*If a subject is prematurely discontinued from trial product after randomisation (Visit 10), the Investigator must ensure every possible effort is made to undertake procedures for Visit 36A, as soon as possible.*



*Treatment discontinuation must be performed in the eDiary web portal. This must be performed at least 4 days prior to Visit 36A to ensure scheduling of the 7-9-7-point profile on the three days prior to Visit 36A.*

*At visit 36A subjects must undergo the meal test before discontinuing trial product. The meal test should be performed with trial drug according to randomisation unless this is not feasible due to safety reasons including pregnancy as judged by the investigator. This must be documented in the eCRF.*

*A "treatment discontinuation" session must be made in the IV/WRS after the meal test has been completed and primary reason for discontinuation of trial product must be specified in the first part of the end-of-treatment/trial form in the eCRF.*

*Final drug accountability must be performed. The subject should be switched to a suitable marketed product at the discretion of the Investigator. The medication should be recorded on the concomitant diabetes medication form in the eCRF, as described in section 8.2.4 at each contact after trial drug discontinuation.*

*The subject should also complete the follow-up visits (visit 37 and phone contact 38). Visit 37 can be converted into a phone contact as collection of the eDiary is not applicable at this visit for the subjects that discontinue trial product prematurely.*

*In addition, subjects prematurely discontinued from trial product should continue with the per protocol planned visits at 4 (Visit 14), 8 (Visit 18), 12 (Visit 22), 16 (Visit 26), 20 (Visit 30), 24 (Visit 34) and 26 (Visit 36) weeks after randomisation depending on when the subject discontinues trial product. The meal test at V36 should be done with the subjects' currently prescribed insulin treatment with a bolus insulin dose of 0.1 U/kg. The eDiary must be returned to the site at the end of visit 36.*

*The following assessments are not applicable for subjects that prematurely discontinue trial product: 4 point profiles, daily doses of trial insulin, time of injection, duration of meal, titration method, dose recommendation, reason for deviation and collection of technical complaints.*

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

- If V36A is within 2 weeks of one of the per protocol planned visits, only V36A should be performed*
- If any per protocol planned visit and the windows of a follow-up visit are overlapping according to visit schedule, only the per protocol planned visit should be performed*

### ***eDiary records after premature discontinuation of trial product:***

*Date, actual clock time and value of the SMPG measurements performed as part of the 7-9-7-point profiles on the three consecutive days prior Visit 36A, Visit 22 and Visit 36*

*For hypoglycaemic episodes only the following information should be recorded from visit 36A and onwards:*

- *Start date and time of hypoglycaemic episode*
- *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*

### **2.17    ~~Section 8.1.14~~ ~~8.1.11 Withdrawals~~ Withdrawal from trial**

If a subject is ~~withdrawn~~ *withdraws informed consent from the trial*, the Investigator must aim to undertake procedures similar to those for Visit 36 including the meal test, as soon as possible and the follow up visits (Visit 37 and 38). *The Investigator must encourage the subjects to undergo the meal test at Visit 36. The meal test must be performed with trial drug according to randomisation unless this is not feasible due to safety reasons including pregnancy as judged by the investigator.*

The end of treatment/trial form must be completed *in the eCRF* and final drug accountability must be performed even if the subject is not able to come to the trial site. A ~~withdrawal session~~ *“treatment discontinuation” session must be made in the IV/WRS. and the case book must be signed.*

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 *discontinuing trial product and not completing the trial* must be specified on the end of treatment/trial form in the eCRF *and the case book must be signed.*

*In case a premature discontinuation subject chooses to withdraw consent from trial after completing Visit 36A, FU1 and FU2, the Investigator must encourage the subjects to undergo procedures of Visit 36 whereas FU1 and FU2 visit are not to be completed again.*

### **2.18    Section 8.2.1 Demography**

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

- Date of birth (if not permitted according to local laws the year of birth will be collected)
- Ethnicity (if permitted according to local laws)

- Race (if permitted according to local laws)
- Sex

~~The Investigator must document whether females are of non-childbearing potential in the subject's medical record and in the eCRF.~~

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

*Female of non-childbearing potential is defined as:*

- *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 as described in Section 8.5.2.4.*

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

## **2.19 Section 8.3.1 Meal test**

Time point 0 is defined as the time when the subject starts the consumption of the liquid meal. The subject will have a carbohydrate-rich standardised liquid meal served. The standardised liquid meal must be consumed as quickly as possible and within 12 minutes. The Investigator should confirm that the subject consumed the required volume of the standardised meal in the eCRF and actual clock time of injection and ~~of~~ *actual clock time of the start of the* 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 ~~80~~ 78 gram of carbohydrate. The amount of mL of the standardised meal may differ from country to country.

## **2.20 Section 8.4.1.2 Injection site reactions**

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

Possible injection site reactions related both to the bolus and/or basal insulin must be recorded as an AE on an AE form and on a specific injection site reaction form in the eCRF. The following information should be obtained:

- Type of reaction – local or generalised
- Symptoms associated to the event

- Treatment given for the event
- Association with the trial product(s)
- Risk factors associated to the event

The Investigator has to evaluate whether further actions are needed (e.g. extra visits, supervised injection, ~~withdrawal~~ *premature discontinuation of trial product*, dermatologist consultation).

## 2.21 Section 8.5.4 eDiary

At the run-in visit (Visit 2) the subjects will be provided with an eDiary. ~~The eDiary should be returned by the subject at FU1 (Visit 37).~~ The Investigator must carefully instruct the subject in how to use the eDiary. The eDiary is considered as source data for all data entered in the eDiary as described in sections 8.3.2, 8.3.3, ~~and~~ 8.4.1.1 and 14.

The Investigator should record the following administrative information in the eDiary web portal:

~~Time and date of next site visit and/or phone contact~~

- Subject ID
- Bolus dosing ~~algorithm~~ *titration method* to be followed by subject
- Subject randomisation status (mealtime dosing or postmeal dosing)
- *7-9-7-point profile scheduling and confirmation*
- *Visit confirmation*
- *Hypoglycaemic episode confirmation*

All data ~~entered by the subject in~~ *from* the eDiary will be transferred electronically to ~~a the~~ *the electronic patient reported outcomes (ePRO) database* ~~trial database~~ from where the Investigator must review all the data for the subjects belonging to the site through the web portal. The review of data must be performed before each visit/phone contact.

The eDiary should be collected by the Investigator at FU1 (Visit 37) and the subject should not be provided with a paper diary for the remaining follow up period. Consequently, source data for FU2 (Phone Contact 38) is the notes written in subject's medical record.

## 2.22 Section 9.3 Storage

**Table 2–1 Table 9.2 Storage of trial products**

<b>Trial product</b>	<b>Storage conditions (not-in-use)</b>	<b>In-use conditions</b>	<b>In-use time<sup>a</sup></b>
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 <sup>®</sup> )	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 degludec	Store in refrigerator (2°C – 8°C)  Do not freeze  Protect from light	Do not store above 30°C  <del>Do not refrigerate</del>  Protect from light  <i>Can be stored in            refrigerator (2°C –            8°C)</i>  <i>Do not freeze</i>	Use within 8 weeks

<sup>a</sup> In-use time starts when first dose is taken.

## **2.23 Section 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:

- Medication arrival
- Screening
- Screening failure
- Run-in dispensing
- Run-in failure
- Randomisation
- Dispensing
- ~~Withdrawal~~ *Treatment discontinuation*
- Completion
- Code break
- Drug accountability
- Data change

As the trial is blinded with regards to faster-acting insulin aspart and NovoRapid® it is important that, at all times during the trial, only DUNs allocated by the IV/WRS are dispensed to the subject.

If a subject requires additional trial product between dispensing visits, the site must perform an additional dispensing session in IV/WRS.

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

## 2.24 Section 11.2 Breaking of blinded codes

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

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.

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 *discontinue treatment prematurely* ~~be withdrawn from the trial~~ and a “*treatment discontinuation*” ~~session withdrawal session~~ must be completed in IV/WRS.

## 2.25 Section 12 Adverse events, and technical complaints and pregnancies

### 2.25.1 Section 12.1 Definitions

#### Adverse event

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 adverse event (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 the first trial related activity after the subject has signed the informed consent.
- Non-serious hypoglycaemia is an AE, but is reported on a hypoglycaemic episode form *in the eDiary* instead of on an AE form, see section 8.4.1.1.

#### Serious adverse event

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

- Death.
- A life-threatening<sup>a</sup> experience.
- In-patient hospitalisation<sup>b</sup> or prolongation of existing hospitalisation.
- A persistent or significant disability or incapacity<sup>c</sup>.
- A congenital anomaly or birth defect.
- Important medical events that may not result in death, be life threatening<sup>a</sup> or require hospitalisation<sup>b</sup> 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<sup>d</sup>.



~~Suspicion of transmission of infectious agents via the trial product must always be considered an SAE.~~

- <sup>a</sup>. 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.
- <sup>b</sup>. The term "hospitalisation" is used when a subject:
- Is admitted to a hospital or in-patient, irrespective of the duration 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.

- <sup>c</sup>. 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).
- <sup>d</sup>. 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.

*The following events must always be reported as a SAE using the important medical event criteria if no other seriousness criteria are applicable:*

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

## **2.26 Section 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 informed consent until ~~the end of the last phone contact/site visit post-treatment follow-up period (Visit 38)~~. The events must be recorded in the applicable eCRF forms in a timely manner, see timelines below and 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, either 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: Faster-acting insulin aspart IB. Current version and any updates hereof<sup>9</sup>
- NovoRapid®: Company Core Data Sheet. Current version and any updates hereof<sup>33</sup>
- Insulin degludec: ~~Insulin degludec IB~~ *Company Core Data Sheet*. Current version and any updates hereof (Ref. 3)<sup>47</sup>

## 2.27 Section 14 Monitoring procedures

All data must be verifiable in source documentation other than the eCRF except for *data entered by the subject in the eDiary device and by the investigator through the eDiary web portal. This data will be recorded directly in the device/web portal. All data entered in the eDiary device will be automatically transferred to the ePRO database, where it is kept as a certified copy of the source data. Data entered in the device will upon confirmation of a successful back-up be deleted from the device. Hence the certified copy in the ePRO database is regarded as source data. All data entered through the web portal is entered directly into the ePRO database and hence the ePRO database is regarded as source data.*

Monitors must review the subject's medical records and other source data (eDiary data uploaded/entered into the ePRO trial database and PRO questionnaires) to ensure consistency and/or identify omissions ~~compared to the eCRF~~. If discrepancies are found, the Investigator must be questioned about these.

## 2.28 Section 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.

The eDiary software and hardware implementation are compliant with the requirements of FDA 21 ~~CFR~~ CFR Part 11 and ICH E6 (EU directive for personal data protection). After trial finalisation, each site will be supplied with long-life DVDs. These DVDs will contain site-specific subject records including the subject's eDiary data and audit trail as well as any data additions and corrections made on each form. The eDiary vendor will furthermore retain and securely store copies of all archived documents and data for 50 years or as required by local data retention laws for trial data.

## 2.29 Section 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 the randomisation visit (Visit 10). In case a measurement is not available at the randomisation visit, the most recent measurement prior to the randomisation visit 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 treatment discontinuation.*
- On-treatment: the observation period from date of first dose of NovoRapid<sup>®</sup>/faster-acting insulin aspart and no later than 7 days after the day of last dose of NovoRapid<sup>®</sup>/faster-acting insulin aspart. The on-treatment observation period includes data collected up to and including 7 days after treatment discontinuation.*

~~Analyses of efficacy endpoints will be based on the full analysis set (FAS).~~ *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 (SAS) 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 intervals 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 will only be summarised descriptively.*

### Estimands

The primary objective, confirming the ~~efficacy~~ effect of treatment with mealtime faster-acting insulin aspart compared to NovoRapid<sup>®</sup> both in combination with insulin degludec in adults with

type 1 diabetes, will be assessed ~~comparing~~ by the change from baseline HbA<sub>1c</sub> to NovoRapid<sup>®</sup> using a non-inferiority approach.

*More specifically the upper limit of the 95% confidence interval should be compared to a non-inferiority margin of 0.4%. If it is below 0.4% non-inferiority will be considered confirmed and effect demonstrated.*

*The trial also aims to compare treatment arms 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 the null hypothesis only will be confirmed 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:*

**Step 1 (Primary analysis):** HbA<sub>1c</sub> non-inferiority of meal-time faster-acting insulin aspart versus meal-time NovoRapid<sup>®</sup>

**Step 2:** HbA<sub>1c</sub> non-inferiority of post-meal faster-acting insulin aspart versus meal-time NovoRapid<sup>®</sup>

**Step 3:** 1-hour PPG increments superiority of meal-time faster-acting insulin aspart versus meal-time NovoRapid<sup>®</sup>

**Step 4:** HbA<sub>1c</sub> superiority of meal-time faster-acting insulin aspart versus meal-time NovoRapid<sup>®</sup>

**Step 5:** 1,5-Anhydroglucitol superiority of meal-time faster-acting insulin aspart versus meal-time NovoRapid<sup>®</sup>

#### **Primary Estimand (de facto)**

*The primary estimand is defined as the treatment difference between subjects randomised to faster-acting insulin aspart and NovoRapid<sup>®</sup> both in combination with insulin degludec, in adults with type 1 diabetes assessed by change from baseline in HbA<sub>1c</sub> 26 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 glycaemic benefit a future population with type 1 diabetes can achieve if prescribed to faster-acting insulin aspart as compared to NovoRapid<sup>®</sup>. By not putting any restrictions on the 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 reflect clinical practice. Thereby the primary estimand provides a treatment difference for clinicians concerning the glycaemic effect of faster-acting insulin aspart compared to NovoRapid® in the day to day life in individual subjects with type 1 diabetes in an adult population.*

### **Secondary Estimand (de jure)**

*Unlike the the primary estimand, a second estimand is defined as the treatment difference in change from baseline in HbA<sub>1c</sub> 26 weeks after randomisation between faster-acting insulin aspart and NovoRapid® both in combination with insulin degludec in adult subjects with type 1 diabetes if subjects continue on-treatment until 26 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 intake of ancillary medication may equalize the treatment effect resulting in a difficult assessment if a difference is seen with respect to ancillary medication.*

*The two estimands will be repeated for the endpoints*

- *1-hour PPG increment (meal test)*
- *1,5-Anhydroglucitol*

~~All secondary efficacy endpoints will be summarised and analysed using the FAS. Safety endpoints will be summarised using the safety analysis set (SAS) and analysed using the FAS.~~

~~The impact of protocol deviations and outliers may be investigated further in sensitivity analyses if deemed relevant.~~

~~All continuous endpoints will be summarised descriptively at each visit by treatment. Endpoints that are analysed untransformed, and endpoints that are not formally analysed are summarised by the arithmetic mean, standard deviation (SD), median, and minimum and maximum value. Endpoints that are analysed log-transformed are summarised by the geometric mean, coefficient of variation (CV%), median, minimum and maximum value.~~

~~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 intervals 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 will only be summarised descriptively.~~

## 2.29.1 Section 17.1 Sample size calculation

The primary objective of this trial is to confirm ~~the effect~~ ~~efficacy~~ of treatment with mealtime faster-acting insulin aspart in combination with insulin degludec. This is done by showing that mealtime faster-acting insulin aspart is non-inferior to mealtime NovoRapid® both in combination with insulin degludec in terms of glucose lowering effect as assessed by mean change from baseline in HbA<sub>1c</sub> ~~after 26 weeks after randomisation of treatment~~ using a non-inferiority margin of 0.4% (absolute). The non-inferiority margin of 0.4% (absolute) was chosen ~~in accordance with the FDA guidance~~<sup>19</sup> *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 ~~efficacy~~ *the effect* of treatment with mealtime faster-acting insulin aspart and postmeal faster-acting insulin aspart, for a number of secondary confirmatory endpoints using the hierarchical testing procedure as described in section ~~2.29.3.1~~ *17.1*. The sample size is determined to ensure a sufficient power for the first step (the primary objective: HbA<sub>1c</sub> non-inferiority of mealtime faster-acting insulin aspart) and the second step (HbA<sub>1c</sub> non-inferiority of postmeal faster-acting insulin aspart) in the hierarchical testing procedure.

*In previous trials where faster aspart has been investigated in similar designs, the completion rates have been high. Therefore it will not be unexpected that treatment discontinuation might be as low as 8% where trial discontinuation constitutes half of these.*

Power for the non-inferiority steps are based on a t-statistic under the assumption of a one-sided test of size 2.5%. A zero mean treatment difference for the comparison between mealtime faster-acting insulin aspart and mealtime NovoRapid® is expected, and for the comparison of postmeal faster-acting insulin aspart and mealtime NovoRapid® a mean difference of 0.1% in favor of mealtime NovoRapid® is expected. ~~As trials in this population where subjects discontinuing treatment are followed up is limited, Based on experience from previous phase 3 trials in subjects with T1DM treated with NovoRapid®~~ a conservative estimate of the SD in change from baseline in HbA<sub>1c</sub> of 1.42% ~~would be anticipated~~ was chosen. The power calculation is done using proc power in SAS 9.34. Please refer to Table 17-1 ~~for~~ assumption of the sample size calculation.



Table 2–2 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%	<i>FASPP</i>	0.4% (absolute)	1.42	0.0	1:1
Step 2	2-group t-test	One-sided 2.5%	<i>FASPP</i>	0.4% (absolute)	1.42	0.1	1:1

~~As this is a non-inferiority trial, the power calculation is based on the anticipated number of subjects in the PP analysis set. It is assumed that 85% of the randomised subjects will be in the PP analysis set based on previous phase 3 trials in T1DM treated with insulin and sample size is scaled in the FAS to have integer sample size for each arm that adheres exactly to the arm allocation weights (1:1:1).~~

Table 2–3 Table 17.2 Sensitivity of sample size to power in each step

			Primary (Step 1)			Step 2			
N total FAS	N per arm FAS PP		Mean Diff	SD	Power (step 1) (%)	Mean Diff	SD	Power (step 2) (%)	Power (step 1 and 2) (%)
813	271	230	0	1.42	97.32	0.1	1.42	83.1	80.982.8
999	333	283	0	1.42	99.40	0.1	1.1	89.9	89.189.6
1176	392	333	0	1.42	99.7	0.1	1.42	94.0	93.793.8

From the Table 17-2 it can be seen that, based on the previously defined assumptions, a total of ~~283333~~ subjects per arm in the PP analysis set give 99.04% power to conclude HbA<sub>1c</sub> non-inferiority in the first step. This sample size gives 89.69% marginal power to conclude HbA<sub>1c</sub> non-inferiority in the second step. Under the assumption of independence between the hypothesis tests, this sample size results in a combined power for the 2 steps of 89.1%, which is considered sufficient.

Table 17.3 summarises the anticipated number of subjects in FAS and PP analysis set.

~~Table 2.4~~ ~~Table 17.3~~ Anticipared number of subjects in FAS and PP analysis set

	<b>Mealtime faster- acting insulin aspart</b>	<b>Postmeal faster- acting insulin aspart</b>	<b>Mealtime NovoRapid®</b>	<b>Total</b>
Number of subjects in the FAS	333	333	333	999
Number of subjects in the PP analysis set:	283	283	283	849

## 2.29.2 Section 17.2 Definition of analysis sets

The following analysis sets are defined in accordance with the ICH-E9 guideline<sup>34</sup>.

- 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”
- ~~PP analysis set includes all subjects in the full analysis set who fulfils the following criteria:~~
  - ~~have not violated any inclusion criteria~~
  - ~~have not fulfilled any exclusion criteria~~
  - ~~have a non-missing HbA<sub>1c</sub> measurement at screening and/or randomisation~~
  - ~~have at least 12 actual treatment weeks of exposure~~
  - ~~have at least one non-missing HbA<sub>1c</sub> measurement after 12 actual weeks of exposure~~
- 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 criteria*

Subjects in the PP analysis set will contribute to the evaluation “as treated”

- SAS includes all subjects receiving at least one dose of the investigational product or its comparator. Subjects in the SAS will contribute to the evaluation “as treated”.
- ~~Completer set: includes subjects who completed the trial and with a valid measurement of primary endpoint (i.e. HbA<sub>1c</sub>) at end of treatment. Subjects in the completer set will contribute to the evaluation “as randomised”~~

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

Before data are released for statistical analysis, a blinded review of all data will take place to identify protocol deviations 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-E9<sup>34</sup>.

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.

### 2.29.3 Section 17.3 Primary endpoint

The primary endpoint is change from baseline in HbA<sub>1c</sub> after 26 weeks of treatment after randomisation.

#### **Primary analysis:**

1) *The primary estimand will be addressed by the below primary analysis on all subjects included in 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 imputation where the Subjects without any available HbA<sub>1c</sub> measurements at scheduled visits will have their HbA<sub>1c</sub> 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 region and bolus adjusting method at randomisation (principles of flexible dosing based on the carbohydrate content of the meal or using bolus dosing algorithms) as factors, and baseline HbA<sub>1c</sub> as a covariate is fitted to the change in HbA<sub>1c</sub> 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 region, bolus adjusting method and baseline HbA<sub>1c</sub>.*
- 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 region and bolus adjusting method as factors and baseline HbA<sub>1c</sub> and change from baseline in HbA<sub>1c</sub> at week 4 as covariates.*

- This stepwise procedure is then repeated sequentially for week 12, 16, 20, 24 and 26
- For each of the complete data sets, the change from baseline to week 26 is analysed using an analysis of variance model with treatment, region and bolus adjusting method 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:

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

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 (see also the second step in the hierarchy).

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

$$H_0: D > 0.4\% \text{ against } H_A: D \leq 0.4\%$$

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

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

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

Furthermore similar sensitivity analyses can be made to further investigate the remaining confirmatory hypothesis.

### **Sensitivity analyses for the primary analysis addressing the primary estimand**

- 2) First the primary analysis in 1) will be repeated, but excluding all factors and covariates except from treatment in the model. This analysis will explore the influence of the different factors and covariates. The analysis will use the in-trial observation period.

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<sub>1c</sub> for subjects leaving the trial, after their withdrawal, develops in a similar way as the HbA<sub>1c</sub> for similar subjects that remain in the trial (not necessarily on treatment) and had similar development of HbA<sub>1c</sub> before withdrawal. The MAR assumption may be questionable for subjects withdrawing at own will. Therefore the statistical model using multiple imputation will be repeated with the following alterations:*

- a. Imputation will be done from the treatment arm that the subject was randomised to and a value of 0.4% (the non-inferiority limit) is added to the change in HbA<sub>1c</sub> at 26 weeks for Subjects, on either of the faster-acting insulin aspart arms, withdrawing from the trial<sup>35</sup>. The analysis will use the in-trial observation period.*
- b. Imputation will be done from the comparator arm (NovoRapid<sup>®</sup>). It does not rely on the MAR assumption, but assumes that all subjects that withdraw the trial in the faster-acting insulin aspart arms shift to NovoRapid<sup>®</sup>. Hence missing measurements after withdrawal from trial will be imputed from the comparator arm without further penalty (copy reference). The analysis will use the in-trial observation period.*
- c. Imputation will be done from the comparator arm (NovoRapid<sup>®</sup>), but assuming that all subjects that withdraw the trial in the faster-acting insulin aspart arms responded as if they had been on NovoRapid<sup>®</sup>. Hence all measurements for the withdrawn subjects will be imputed from the comparator arm without further penalty (jump to reference). The analysis will use the in-trial observation period.*

#### ***Analyses addressing the secondary estimand***

- 4) The secondary estimand will be addressed 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 imputations similar to 1), using the on-treatment observation period will be made. In this analysis Subjects that discontinued treatment are imputed based on the treatment arm they were randomised to and Subjects discontinuing treatment in the mealtime 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<sub>1c</sub> of the Subjects discontinuing treatment in the mealtime faster-acting insulin aspart group 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 26 in the mealtime faster-acting insulin aspart group will be added a penalty. This is done repeatedly gradually increasing the penalty until the conclusions of the primary analysis no longer holds. The*

*specific value of the penalty that changes the conclusion will be used to evaluate the robustness of the conclusion of the primary 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<sup>®</sup> prematurely due to criteria 1, 2, 3, and 4) in the mealtime faster-acting insulin aspart groups will not have a penalty added. These analyses are motivated by the fact that data from subjects prematurely discontinuing faster-acting insulin aspart/NovoRapid<sup>®</sup> due to non-eligibility can reasonably be assumed to be missing completely at random. The analysis will use the on-treatment observation period.*
- 7) *The same statistical model using multiple imputation 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 deviate from the ideal treatment during the on-treatment observation period and will serve as sensitivity analysis for the non-inferiority analysis.*

~~Change from baseline in HbA<sub>1c</sub> after 26 weeks of treatment will be analysed using a mixed effect model for repeated measurements (MMRM) where all calculated changes in HbA<sub>1c</sub> from baseline at planned post baseline visits until 26 weeks will be included in the analysis. This model will include treatment and region as fixed effects, HbA<sub>1c</sub> at baseline as a covariate and interactions between all fixed effects and visit, and between the covariate and visit. An unstructured covariance matrix will be used to describe the variability for the repeated measurements for a subject. From this model, contrasts will be set up to estimate the treatment difference after 26 weeks together with a 95% confidence interval.~~

~~Non-inferiority will be considered confirmed if the upper boundary of the two-sided 95% confidence interval is below or equal to 0.4% or equivalent if the p-value for the one-sided test of~~

$$H_0: D > 0.4\% \text{ against } H_A: D \leq 0.4\%$$

~~is less than or equal to 2.5%, where D is the mean treatment difference (mealtime faster-acting insulin aspart minus mealtime NovoRapid<sup>®</sup>).~~

~~The MMRM model is based on the assumption that the data are missing at random (MAR). For this trial the missing data are expected to be mainly due to subjects that are withdrawn from the trial. The possible withdrawal reasons and criteria are described in section 6.5. Data from subjects that are withdrawn due to withdrawal criteria 1, 2, 3 and 4 can reasonably be assumed to be missing completely at random (MCAR). Data from subjects withdrawn due ineffective therapy may be MAR because the withdrawal may in these cases be predictable from the HbA<sub>1c</sub> values measured before withdrawal. It is expected that a limited amount of the missing data will be due to this criterion.~~



The sensitivity analyses described below will be used to investigate whether the results from the MMRM model are robust towards deviations from the assumption of MAR.

### Sensitivity analyses

Sensitivity analyses will be performed for change from baseline in HbA<sub>1c</sub> after 26 weeks of treatment to investigate the sensitivity of the results associated with the different confirmatory hypothesis associated with the primary analysis with regard to the handling of missing data, and with regard to the choice of analysis set. The sensitivity analyses will include:

1. A MMRM model similar to the primary analysis but based on the PP analysis set.
2. A MMRM model similar to the primary analysis but based on the completer set.
3. An analysis of variance (ANOVA) based on imputation of missing data using the last observation carried forward (LOCF) principle. The ANOVA will have change from baseline in HbA<sub>1c</sub> after 26 weeks of treatment (using LOCF) as dependent variable, treatment and region as factors, and baseline HbA<sub>1c</sub> as a covariate. This analysis is based on the FAS.
4. A pattern mixture model approach mimicking an ITT scenario, where withdrawn subjects in the mealtime or postmeal faster acting insulin aspart groups are assumed to be switched to a treatment inferior to mealtime NovoRapid<sup>®</sup> after withdrawal. This analysis is based on the FAS. Multiple copies (100 copies) of the full dataset will be generated by imputing missing values based on estimated parameters for the mealtime NovoRapid<sup>®</sup> group. This will be done 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 treatment 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 ANOVA model with region as a factor, and baseline HbA<sub>1c</sub> as a covariate, is fitted to the change in HbA<sub>1c</sub> from baseline to visit 14 for the mealtime NovoRapid<sup>®</sup> group only. The estimated parameters, and their variances, from this model are used to impute missing values at visit 14 for subjects in all treatment groups, based on their region factor, and their HbA<sub>1c</sub> at baseline.
  - In the third step, for each of the 100 copies of the dataset, missing HbA<sub>1c</sub> values at visit 18 are imputed in the same way as for visit 14. Now the imputations are based on an ANOVA model with region as a factor, and the HbA<sub>1c</sub> values at baseline and visit 14 as covariates, fitted to the mealtime NovoRapid<sup>®</sup> group.
  - This stepwise procedure is then repeated sequentially for visits 22, 26, 30, 34 and 36.
  - For each withdrawn subject in the mealtime or postmeal faster acting insulin aspart group, a value of 0.4% (the non-inferiority limit) is added to the change in HbA<sub>1c</sub> at visit 36 (26 weeks). This step is included to mimic a scenario where withdrawn

~~subjects in the mealtime or postmeal faster acting insulin aspart group are switched to a treatment inferior to mealtime NovoRapid® after withdrawal.~~

- ~~○ For each of the complete data sets, the change from baseline to visit 36 is analysed using an ANOVA model with treatment and region as factors and the baseline HbA<sub>1c</sub> value as a covariate.~~
- ~~○ The estimates and standard deviations for the 100 data sets are pooled to one estimate and associated standard deviation using Rubin's formula:~~

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

~~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 intervals for the treatment differences are calculated.~~
- ~~5. The same analysis as in 4 above, but without adding the 0.4% to subjects withdrawing from the mealtime or postmeal faster acting insulin aspart treatment. This will mimic a scenario where subjects withdrawing from mealtime or postmeal faster acting insulin aspart treatment are switched to mealtime NovoRapid® after withdrawal. This analysis will in particular investigate the sensitivity of the superiority analysis (step 5 in the hierarchical testing procedure). This analysis is based on the FAS.~~
  - ~~6. The same analyses as in 4 and 5 above, with the modification that subjects withdrawn due to withdrawal criteria 1, 2, 3 and 4 in the mealtime or postmeal faster aspart group will have their imputations based on parameters estimated from the mealtime or postmeal faster aspart group (and not the mealtime NovoRapid® group). These analyses are motivated by the fact that withdrawals due to withdrawal criteria 1, 2, 3 and 4 can reasonable be assumed to be MCAR. This analysis is based on the FAS.~~

~~The results from the sensitivity analyses will be compared to the results of the MMRM method. Any marked difference concerning treatment differences between the missing value handling approaches above will be commented upon in the clinical trial report.~~

### 2.29.3.1 Section 17.4.1 Confirmatory secondary endpoints

~~If the efficacy effect of mealtime faster-acting insulin aspart can be confirmed in the primary analysis, the trial also aims to compare treatment arms 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 the null hypothesis only, will be confirmed for endpoints where all previous null hypotheses have been rejected in favour of faster-acting insulin aspart.~~

The steps in the hierarchical testing procedure are:

~~**Step 1 (Primary analysis):** Change from baseline in HbA<sub>1c</sub> after 26 weeks of treatment (non-inferiority of mealtime faster-acting insulin aspart versus mealtime NovoRapid<sup>®</sup>)~~

~~**Step 2:** Change from baseline in HbA<sub>1c</sub> after 26 weeks of treatment (non-inferiority of postmeal faster-acting insulin aspart versus mealtime NovoRapid<sup>®</sup>)~~

~~**Step 3:** Change from baseline in 1-hour PPG increments after 26 weeks of treatment (meal test) (superiority of mealtime faster-acting insulin aspart versus mealtime NovoRapid<sup>®</sup>)~~

~~**Step 4:** Change from baseline in 1,5-Anhydroglucitol after 26 weeks of treatment (superiority of mealtime faster-acting insulin aspart versus mealtime NovoRapid<sup>®</sup>)~~

~~**Step 5:** Change from baseline in HbA<sub>1c</sub> after 26 weeks of treatment (superiority of mealtime faster-acting insulin aspart versus mealtime NovoRapid<sup>®</sup>)~~

***Step 1 (Primary analysis):** HbA<sub>1c</sub> non-inferiority of meal-time faster-acting insulin aspart versus meal-time NovoRapid<sup>®</sup>*

***Step 2:** HbA<sub>1c</sub> non-inferiority of postmeal faster-acting insulin aspart versus meal-time NovoRapid<sup>®</sup>*

***Step 3:** 1-hour PPG increments superiority of meal-time faster-acting insulin aspart versus meal-time NovoRapid<sup>®</sup>*

***Step 4:** HbA<sub>1c</sub> superiority of meal-time faster-acting insulin aspart versus meal-time NovoRapid<sup>®</sup>*

***Step 5:** 1,5-Anhydroglucitol superiority of meal-time faster-acting insulin aspart versus meal-time NovoRapid<sup>®</sup>*

**Change from baseline in HbA<sub>1c</sub> after 26 weeks of treatment after randomisation (step 2)**

*If the primary objective is confirmed the effect of treatment with postmeal faster-acting insulin aspart in terms of glycaemic control is to be investigated by showing that postmeal faster-acting insulin aspart is non-inferior to NovoRapid<sup>®</sup> both in combination with insulin degludec in terms of glucose lowering effect as assessed by change from baseline in HbA<sub>1c</sub> 26 weeks after randomisation.*

*The non-inferiority will be evaluated based on a two-sided 95% confidence interval of mean treatment difference (postmeal faster-acting insulin aspart minus mealtime NovoRapid®) obtained from the primary statistical analysis in 1).*

~~Step 2 in the hierarchical testing procedure is to confirm efficacy of treatment with postmeal faster-acting insulin aspart in terms of glycaemic control by showing that postmeal faster-acting insulin aspart is non-inferior to NovoRapid® both in combination with insulin degludec in terms of glucose lowering effect as assessed by change from baseline in HbA1c after 26 weeks of treatment using a non-inferiority margin of 0.4%.~~

~~The non-inferiority will be evaluated as described in section 17.3 based on a two-sided 95% confidence interval of mean treatment difference (postmeal faster-acting insulin aspart minus mealtime NovoRapid®) obtained from the primary statistical analysis.~~

~~The sensitivity of the analysis will be addressed as described in section 17.3.~~

### **Change from baseline in 1-hour PPG increments after 26 weeks of treatment after randomisation (meal test) (step 3)**

As the third step of the hierarchical testing procedure changes from baseline in 1-hour PPG increments (meal test) after 26 weeks of treatment after randomisation will be tested for superiority of mealtime faster-acting insulin aspart compared to mealtime NovoRapid®.

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

*The 1-hour PPG increment primary estimand will be addressed using an analysis of variance model (ANOVA) including treatment region and bolus adjusting method as factors and 1-hour PPG increment at baseline as covariate. 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.*

~~The endpoint will be analysed using an ANOVA model including treatment and region as factors and 1-hour PPG increment at baseline as covariate. The superiority will be evaluated based on the comparison of mealtime faster-acting insulin aspart and mealtime NovoRapid®.~~

### ***Sensitivity analysis***

~~To investigate the sensitivity of the analysis with regard to the handling of missing data, a sensitivity analysis based on a pattern mixture model will be made, using the FAS. This analysis is motivated by the fact that withdrawals due to non-eligibility can reasonable be assumed to be MCAR. Multiple copies (100 copies) of the full dataset will be generated by imputing missing values based on estimated parameters as follows:~~

- ~~For each of the 100 copies of the dataset, an ANOVA model with treatment and region as factors and baseline 1-hour PPG increment as a covariate is fitted to the change in 1-hour PPG increment at week 26 for the mealtime NovoRapid<sup>®</sup> group only. The estimated parameters, and their variances, from this model are used to impute missing values at week 26 for subjects in all treatment groups. However, subjects withdrawn due to withdrawal criteria 1, 2, 3 and 4 in the mealtime faster aspart group will have their imputations based on parameters estimated from the mealtime faster aspart group.~~
- ~~For each of the complete data sets, the change from baseline to week 26 is analysed using an ANOVA model with treatment and region as factors, and baseline 1-hour PPG increment as a covariate.~~
- ~~The estimates and standard deviations for the 100 data sets are pooled to one estimate and associated standard deviation using Rubin's formula. From this, the pooled estimates and 95% confidence interval for the treatment difference is calculated.~~

#### ***Change from baseline in HbA<sub>1c</sub> 26 weeks after randomisation (step 4)***

*As the fourth step of the hierarchical testing procedure superiority of HbA<sub>1c</sub> 26 weeks after randomisation with mealtime faster-acting insulin aspart compared to NovoRapid<sup>®</sup> 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 (mealtime faster-acting insulin aspart minus mealtime NovoRapid<sup>®</sup>) is below 0%.*

#### ***Change from baseline in 1,5-Anhydroglucitol after 26 weeks of treatment after randomisation (step 5)***

*Step 5 in the hierarchical testing procedure is to confirm superiority of changes from baseline in 1,5-anhydroglucitol 26 weeks after randomisation with mealtime faster-acting insulin aspart compared to mealtime NovoRapid<sup>®</sup>.*

*The analysis for the primary 1,5-anhydroglucitol estimand will be done using all subjects included in FAS and using the in-trial observation period. The change from baseline in 1,5 anhydroglucitol will be analysed using a model similar to 1) except with the corresponding baseline value as covariates. Superiority will be confirmed if the upper boundary of the two-sided 95% confidence interval of the mean treatment difference (mealtime faster-acting insulin aspart minus mealtime NovoRapid<sup>®</sup>) is below 0%.*

~~Change from baseline in 1,5-anhydroglucitol after 26 weeks of treatment will be analysed based on all planned post-baseline measurements until or at 26 weeks using a MMRM for repeated measurements, similar to the model used for analysis of the primary endpoint except with baseline~~

~~1,5-anhydroglucitol as covariate. The superiority will be evaluated based on the comparison of mealtime faster acting insulin aspart and mealtime NovoRapid®.~~

~~The sensitivity of the analysis will be addressed using the pattern mixture models described in section 17.3. Only the sensitivity analyses 5) and 6) in section 17.3 will be applied excluding the analyses where the non-inferiority margin of 0.4% are added to subjects withdrawing in the faster-acting insulin aspart arm.~~

### **~~Change from baseline in HbA<sub>1c</sub> after 26 weeks of treatment (step 5)~~**

~~Step 5 in the hierarchical testing procedure is to confirm superiority of HbA<sub>1c</sub> after 26 weeks of treatment with mealtime faster acting insulin aspart compared to NovoRapid®.~~

~~The statistical analysis will be identical to the primary analysis. Superiority will be confirmed if the upper boundary of the two-sided 95% confidence interval of the mean treatment difference (mealtime faster acting insulin aspart minus mealtime NovoRapid®) is below 0%.~~

~~The sensitivity of the analysis will be addressed using the pattern mixture models as described in section 17.3. Only the sensitivity analyses 5) and 6) in section 17.3 will be applied excluding the analyses where the non-inferiority margin of 0.4% are added to subjects withdrawing in the faster-acting insulin aspart arm.~~

## **2.29.4 Section 17.4.2 Supportive secondary endpoints**

*For all supportive secondary endpoints, meal-time faster-acting insulin aspart will be compared to meal-time NovoRapid®, and post-meal faster-acting insulin aspart will be compared to meal-time NovoRapid®, unless otherwise stated.*

### **2.29.4.1 Section 17.4.2.1 Efficacy endpoints**

*All endpoints except insulin dose 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 will be presented using SAS and will therefore only use the on-treatment observation period.*

### **~~Change from baseline in FPG after 26 weeks of treatment~~after randomisation**

~~Change from baseline in FPG after 26 weeks of treatment~~after randomisation will be analysed based on all planned post-baseline measurements until or at 26 weeks using a model ~~an MMRM~~ similar to 1) the model used of the primary endpoint, except with baseline FPG as covariate.

### **HbA<sub>1c</sub> responder after 26 weeks of treatment after randomisation:**

#### **HbA<sub>1c</sub> < 7.0%**

A dichotomous (responder/non-responder) endpoint will be defined based on whether a subject has met the ADA HbA<sub>1c</sub> target (HbA<sub>1c</sub> <7.0%) after 26 weeks of treatment after randomisation.

This responder endpoint will be analysed based on a logistic regression model using treatment, region and *bolus adjusting method* as factors, and baseline HbA<sub>1c</sub> as covariate. *In analysis of the in-trial data subjects without an HbA<sub>1c</sub> measurement at week 26 will be treated as non-responders. In the on-treatment observation period analysis both subjects who discontinue faster-acting insulin aspart/NovoRapid<sup>®</sup> or withdraw from trial is included as non-responders. Predicted values from the model used for the primary analysis will be used for all subjects with no HbA<sub>1c</sub> at the last visit.*

#### **HbA<sub>1c</sub> < 7.0% without severe hypoglycaemia**

A dichotomous (responder/non-responder) endpoint will be defined based on whether a subject has met the ADA HbA<sub>1c</sub> target (HbA<sub>1c</sub> <7.0%) after 26 weeks after randomisation of treatment without treatment emergent severe hypoglycaemic episodes. ~~The withdrawals from their randomised treatment will be set to non-responders. This is based on the assumption that the subjects would experience a severe hypoglycaemia after the withdrawal. A predicted value from the model used for the primary analysis will be used if a treatment completer does not have HbA<sub>1c</sub> at the last visit.~~

This responder endpoint will be analysed based on a logistic regression model using treatment, region and *bolus adjusting method* as factors and baseline HbA<sub>1c</sub> as covariate. *In analysis of the in-trial data subjects without an HbA<sub>1c</sub> measurement at week 26 will be treated as non-responders. In the on-treatment observation period analysis both subjects who discontinue faster-acting insulin aspart/NovoRapid<sup>®</sup> or withdraw from trial is included as non-responders.*

#### **HbA<sub>1c</sub> < 7.0% without severe hypoglycaemia and minimal weight gain (<3.0%)**

A dichotomous (responder/non-responder) endpoints will be defined based on whether a subject has met the ADA HbA<sub>1c</sub> target (HbA<sub>1c</sub> <7.0%) after 26 weeks of treatment after randomisation without treatment emergent severe hypoglycaemic episodes, and *with* minimal weight gain from baseline to 26 weeks of treatment after randomisation (defined as less than a 3% increase).

*This responder endpoint will be analysed based on a logistic regression model using treatment, region and bolus adjusting method as factors and baseline HbA<sub>1c</sub> and baseline body weight as covariates. In analysis of the in-trial data subjects without an HbA<sub>1c</sub> measurement at week 26 will be treated as non-responders. In the on-treatment observation period analysis both subjects who discontinue faster-acting insulin aspart/NovoRapid<sup>®</sup> or withdraw from trial is included as non-responders. The withdrawals from their randomised treatment will be set to non-responders. This is*

~~based on the assumption that the subjects would experience a severe hypoglycaemia after the withdrawal. A predicted value from the MMRM model will be used if a treatment completer does not have HbA1c or body weight at the last visit.~~

~~This responder endpoint will be analysed based on a logistic regression model using treatment and region as factors and baseline HbA1c and baseline body weight as covariates.~~

**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 26 weeks of treatment after randomisation (meal test)**

Laboratory measured PG from the meal test will be analysed for 30, 60, 120, 180, and 240 minutes 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 endpoints 26 weeks after randomisation~~ ~~Change from baseline after 26 weeks of treatment in PPG and PPG increment endpoints~~ will be analysed separately using an ANOVA model including treatment, region and *bolus adjusting method* as factors, and the corresponding baseline value as covariate.

*Note as the meal test is only preformed once post baseline, subjects with no post baseline meal test will not contribute to the analysis.*

**Change from baseline in 7-9-7-point SMPG profile after 26 weeks of treatment after randomisation:**

In general, analyses will be based on the entire 7-9-7-point profile except for the analyses of nocturnal endpoints where information in the 9-point profile will be utilised. Duration of main meals and time of injection of bolus insulin, which will be collected in connection with 7-9-7 point profiles, will be summarised descriptively.

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

*PPG will be recorded by the subjects as part of two 7-point and one 9-point SMPG profile prior to the 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-point and 9-point 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 7-9-7-point profile~~**

The mean of the 7-9-7-point 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 7-9-7-point profile 26 weeks after randomisation will be analysed using a model similar to 1) except with the corresponding baseline value as covariate. ~~in mean of the 7-9-7-point profile will be analysed based on all planned post-baseline measurements until or at 26 weeks using a MMRM similar to the model used for analysis of the primary endpoint and the corresponding baseline value as covariate.~~*

### ***Change from baseline in mean PPG and PPG increment over all three meals***

*Change from baseline in mean PPG and PPG increment 26 weeks 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 and PPG increment***

*Change from baseline in PPG and PPG increment endpoints 26 weeks after randomisation for the individual meals (breakfast, lunch, main evening meal) will be analysed separately using a model similar to 1) except with the corresponding baseline value as covariate.*

### **~~PPG and PPG increment (mean, breakfast, lunch, main evening meal)~~**

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

~~PPG will be recorded by the patient as part of two 7-point and one 9-point SMPG profile prior to the 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-point and 9-point 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 PPG and PPG increment endpoints (mean and each separate meal) will be analysed based on all planned post baseline measurements until or at 26 weeks using a MMRM similar to the model used for analysis of the primary endpoint and the corresponding baseline value as covariate.~~

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

The fluctuation in the 7-9-7-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 7-9-7-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 values 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.*

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

### **Change in the nocturnal SMPG measurements**

~~Change from baseline~~ *Change in nocturnal PG values 26 weeks after randomisation 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 in the nocturnal SMPG measurements will be analysed in the same way as mean of the profile is analysed, *except with the corresponding baseline values as covariate.*



**PPG responders (overall mean of daily PPG measurements in SMPG) after 26 weeks of treatment after randomisation:**

**Overall PPG (1 hour)  $\leq 7.8$  mmol/L [140 mg/dL]**

A dichotomous endpoint will be defined based on whether a subject has reached an overall mean 1 hour PPG  $\leq 7.8$  mmol/L [140 mg/dL] after 26 weeks of treatment after randomisation, where PPG is derived from the 7- and 9-point profile.

This responder endpoint will be analysed based on a logistic regression model using treatment, region and *bolus adjusting method* as factors, and baseline overall mean 1 hour PPG as covariate. *In analysis of the in-trial data subjects without an overall mean 1 hour PPG at week 26 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.* Predicted values from the MMRM model for overall mean 1 hour PPG will be used for all subjects with no PPG at the last visit.

**Overall PPG (1 hour)  $\leq 7.8$  mmol/L [140 mg/dL] without severe hypoglycaemia**

A dichotomous endpoint will be defined based on whether a subject has reached an overall mean 1 hour PPG  $\leq 7.8$  mmol/L [140 mg/dL] after 26 weeks of treatment after randomisation without any treatment emergent severe hypoglycaemic episodes.

~~The withdrawals from their randomised treatment will be set to non-responders. This is based on the assumption that the subjects would experience a severe hypoglycaemia after the withdrawal. A predicted value from the MMRM model will be used if a treatment completer does not have overall mean 1 hour PPG at the last visit.~~

This responder endpoint will be analysed based on a logistic regression model using treatment, region and *bolus adjusting method* as factors, and baseline overall mean 1 hour PPG as covariate. *In analysis of the in-trial data subjects without an overall mean 1 hour PPG at week 26 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.*

**Overall PPG (1 hour)  $\leq 7.8$  mmol/L [140 mg/dL] and HbA<sub>1c</sub> < 7.0% and minimal weight gain (<3.0%) without severe hypoglycaemia**

A dichotomous endpoint will be defined based on whether a subject has reached an overall mean 1 hour PPG  $\leq 7.8$  mmol/L [140 mg/dL], have HbA<sub>1c</sub> < 7.0% and has had minimal weight gain (increase in body weight from baseline <3.0%) after 26 weeks of treatment after randomisation, and without any treatment emergent severe hypoglycaemic episodes.

*This responder endpoint will be analysed based on a logistic regression model using treatment, region and bolus adjusting method as factors, and baseline overall mean 1 hour PPG, baseline HbA<sub>1c</sub> and baseline body weight as covariates. In analysis of the in-trial observation period subjects without an overall mean 1 hour PPG or an HbA<sub>1c</sub> value or a body weight at week 26 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. The withdrawals from their randomised treatment will be set to non-responders. This is based on the assumption that the subjects would experience a severe hypoglycaemia after the withdrawal. A predicted value from the MMRM model will be used if a treatment completer does not have overall mean 1 hour PPG, HbA<sub>1c</sub> or body weight at the last visit.*

~~This responder endpoint will be analysed based on a logistic regression model using treatment and region as factors, and baseline overall mean 1 hour PPG, baseline HbA<sub>1c</sub> and baseline body weight as covariates.~~

#### **~~Insulin dose (basal insulin dose, total and individual meal insulin dose) after 26 weeks of treatment~~**

Basal and bolus insulin doses will be recorded *together with date and time point (for bolus doses) of administration throughout the trial*. The insulin doses will be summarised descriptively by treatment week according to regimen, both by ~~time point of administration~~ meal type and as total daily dose in units and units/kg (total daily and separately for each mealtime dose). *Insulin doses will be summarised using the on-treatment observation period and using the SAS.*

#### **~~Change from baseline in lipids-lipoproteins profile after 26 weeks of treatment after randomisation (total cholesterol, high density lipoproteins, low density lipoproteins)~~**

*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. Change from baseline in lipid endpoints (total cholesterol, HDL and LDL) after 26 weeks of treatment will be analysed based on all planned post-baseline measurements until or at 26 weeks using an MMRM similar to the model used for analysis of the primary endpoint, except with the corresponding baseline measurement as covariate.*

#### **2.29.4.2 Section 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 during 26 weeks of treatment~~**

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). ~~All AEs occurring during the 26 weeks of treatment~~ 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 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 (N), the percentage of subjects with at least one event(%), the number of events(E) and the event rate per 100 patient years of exposure(R). These summaries are done by seriousness, severity, relation to insulin treatment, relation to device, ~~withdrawal~~ *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 summarised and listed.

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

### **Number of treatment emergent injection site reactions**

Treatment emergent injection site reactions occurring during the trial will be summarised and listed. No formal statistical analysis will be made.

## Vital signs

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, ~~and the normal/abnormal not clinically significant/abnormal clinically significant categorisation in shift tables.~~

## Clinical laboratory assessments

Change from baseline *26 weeks after randomisation* ~~after 26 weeks of treatment~~ in central laboratory assessments:

- Haematology
- Biochemistry
- Urinalysis

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

***Change from baseline in anti-insulin aspart (specific and cross-reacting with human insulin) antibody development***~~Total insulin aspart antibodies (amount of antibodies specific for insulin aspart and cross-reacting with human insulin)~~

*The measurements and their change from baseline will be summarised descriptively. The correlation to other relevant variables such as bolus insulin dose and HbA<sub>1c</sub> are illustrated using graphs.*~~Change from baseline after 26 weeks of treatment in total insulin antibodies, antibodies specific for insulin aspart and antibodies cross-reacting with human insulin will be summarised descriptively.~~

**Change from baseline in body weight and BMI** ~~after 26 weeks of treatment~~*after randomisation*

The measurements will be summarised descriptively using both the actual values and change from baseline.

Change from baseline in body weight will be analysed *using a model similar to 1), except with the corresponding baseline measurement as covariate.*

~~based on all planned post-baseline measurements until or at 26 weeks using an MMRM similar to the model used for analysis of the primary endpoint, except with baseline body weight as covariate.~~

## 2.30 Section 18 Ethics

### 18.1 Benefit-risk assessment of the trial

#### Clinical benefits and risk considerations for the trial

The purpose of this trial is to confirm the ~~efficacy~~ *effect* and safety of faster-acting insulin aspart as mealtime insulin as well as postmeal injected insulin in combination with a basal insulin in subjects with T1DM.

#### Section 18.3 Data handling

If the subject ~~is withdrawn~~ *withdraws* from the trial or *is* lost to follow-up, then the subject's data will be handled as follows:

- Data already collected and data collected at the end of treatment visit and the follow-up visits 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.

## 2.31 Section 19 Protocol compliance

### Section 19.1 Missing data

Only absolutely necessary ~~withdrawal~~ criteria *for premature discontinuation of trial products* to ensure the safety of subjects are included and thereby reducing the number of *subjects that are discontinued from treatment prematurely* ~~withdrawals~~ and securing maximum number of data.

~~Surveillance of premature treatment discontinuation rates and withdrawal rate and withdrawal reasons will be performed throughout the trial by Novo Nordisk with focus on withdrawal reason (e.g. AEs, subject withdrawing consent or withdrawals due to any of the withdrawal criteria) to secure early mitigations in collaboration with the trial sites. Withdrawn subjects will be completed according to section 8.1.11.~~

*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 to secure early mitigations in collaboration with the trial sites.*

## 2.32 Appendix A section 3.4.1

**Table 2–4 Table 3 Faster-acting insulin aspart or NovoRapid® dose adjustment based on bolus dosing algorithm**

<del>Mean of</del> Pre-prandial or bedtime SMPG Values		Dose adjustment	Rules for dose adjustment
mmol/L	mg/dL	U	
< 4.0	< 71	- 1	≥ 1 SMPG below target
<b>4.0 – 6.0</b>	<b>71 -108</b>	<b>0</b>	<b>0-1 SMPG above target</b> <b>No SMPGs below target</b>
> 6.0	> 108	+ 1	≥ 2 SMPGs above target No SMPGs below target

### 3 References:

- 1) U.S.Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). Guidance for Industry, Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention. 1 Feb 2008.
- 2) Rodbard HW, Visco VE, Andersen H, Hiort LC, Shu DH. Treatment intensification with stepwise addition of prandial insulin aspart boluses compared with full basal-bolus therapy (FullSTEP Study): a randomised, treat-to-target clinical trial. Lancet Diabetes Endocrinol 2014; 2(1):30-37.
- 3) Novo Nordisk A/S. Company core data sheet (CCDS), Tresiba (Version 8). 2015.



**Protocol Amendment**  
**No. 3**  
**to Protocol, final version 1**  
**dated 10 July 2015**

**Trial ID: NN1218-4131**

**Efficacy and Safety of Faster-acting Insulin Aspart compared to  
NovoRapid® both in combination with Insulin Degludec in Adults with  
Type 1 Diabetes  
onset<sup>®8</sup>**

**Trial phase: 3b**

**Applicable to India**

Amendment originator: [REDACTED], [REDACTED]

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## 1 Introduction including rationale for the protocol amendment

This local protocol amendment is made to accommodate requests from the Central Drugs Standard Control Organization, India, received during the protocol review process.

In this protocol amendment:

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

## 2 Changes

### 6. Trial Population:

#### 6.2 Inclusion Criteria

3. Type 1 Diabetes Mellitus (based on clinical judgement and/or supported by laboratory analysis as per local guidelines)  $\geq 12$  months prior to screening.

*For India only: Please refer to protocol section 8.2.2 for local guidelines.*

#### 8.2.2 Diagnosis of Type 1 Diabetes Mellitus and diabetes complications

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.

*For India only:*

*Diagnosis of Type 1 Diabetes Mellitus will be based on clinical judgement and supported by laboratory analysis as per global guidelines (International Society for Paediatric and Adolescent Diabetes) which include testing for C-peptide levels ( $<0.5\text{ng/ml}$ ) or glutamic acid decarboxylase antibodies positive<sup>1</sup> (previously confirmed diagnosis supported by lab report available at the time of screening or test/s will be performed at local lab as a part of the screening procedure) or previous episode of documented diabetic ketoacidosis treated with insulin.*

#### Hypoglycaemia unawareness:

Information on hypoglycaemia unawareness must be recorded at screening according to Clarke's questionnaire, question 8<sup>25</sup>.

The investigator must ask the subject in the following way: "To what extent can you tell by your symptoms that your blood glucose is low?" The subject can answer never, rarely, sometimes, often or always.

Subjects answering 'never, rarely or sometimes' are considered as having reduced awareness of hypoglycaemia.

Protocol Amendment 3  
Trial ID: NN1218-4131  
UTN: U1111-1167-9495  
EudraCT No.: 2015-001047-36

~~CONFIDENTIAL~~

Date:	17 December 2015	<b>Novo Nordisk</b>
Version:	1.0	
Status:	Final	
Page:	5 of 5	

## 27 References

1. *Fischbach FT, Dunning MB III, eds. (2009). Manual of Laboratory and Diagnostic Tests, 8th ed. Philadelphia: Lippincott Williams and Wilkins.*