Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT03268005
Sponsor trial ID:	NN1218-4113
Official title of study:	Efficacy and Safety of Fast-acting Insulin Aspart Compared to NovoRapid® both in Combination with Insulin Degludec with or without Metformin in Adults with Type 2 Diabetes (onset® 9)
Document date:	20 June 2019

16.1.1 Protocol and protocol amendments

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Redacted protocol
Includes redaction of personal identifiable information only.

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Protocol

Trial ID:NN1218-4113

Efficacy and Safety of Fast-acting Insulin Aspart Compared to NovoRapid® both in Combination with Insulin Degludec with or without Metformin in Adults with Type 2 Diabetes (onset® 9)

Trial phase: 3b

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List of abbreviations

ADA	American Diabetes Association
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BG	Blood glucose
CRF	case report form
DUN	dispensing unit number
ECG	electrocardiogram
eCRF	electronic case report form
eDiary	electronic diary
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FPG	fasting plasma glucose
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide-1
HbA_{1c}	glycosylated haemoglobin
IB	Investigator's Brochure
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	independent ethics committee

IMP	investigational medicinal product
IRB	institutional review board
IWRS	interactive voice/web response system
LPLV	last patient last visit
NIMP	non-investigational medicinal product
OAD	oral antidiabetic drug
PG	plasma glucose
PPG	postprandial glucose
PP	per protocol
SAE	serious adverse event
SmPC	summary of product characteristics
SMPG	self-measured plasma glucose
SUSAR	suspected unexpected serious adverse reaction
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TEAE	Treatment Emergent Adverse Event
TMM	Trial Materials Manual
UTN	Universal Trial Number

1 Summary

Objective(s) and endpoint(s):

Primary objective

To confirm the effect in terms of glycaemic control of treatment with fast-acting insulin aspart compared to NovoRapid® both in combination with insulin degludec with or without metformin in adults with type 2 diabetes mellitus treated with a basal-bolus regimen, using a non-inferiority approach.

Secondary objectives

To confirm superiority of fast-acting insulin aspart compared to NovoRapid® both in combination with insulin degludec with or without metformin in adults with type 2 diabetes mellitus treated with a basal-bolus regimen in terms of:

- Postprandial glucose regulation
- Overall glycaemic control
- Postprandial glucose excursions

To compare the safety of fast-acting insulin aspart to NovoRapid® both in combination with insulin degludec with or without metformin in adults with type 2 diabetes mellitus treated with a basal-bolus regimen.

Primary endpoint

Change from baseline in HbA_{1c} 16 weeks after randomisation

Key secondary endpoints

Confirmatory secondary endpoints:

- Change from baseline in 1-hour postprandial glucose increment 16 weeks after randomisation (meal test)
- Change from baseline in 1,5-anhydroglucitol 16 weeks after randomisation

Trial design:

This is a phase 3b, 16-week, multicentre, multinational, 1:1 randomised, double-blind, active controlled, treat-to-target, parallel group trial with a 12-week run-in period comparing the effect and safety of fast-acting insulin aspart to NovoRapid® both in combination with insulin degludec with or without metformin in subjects with type 2 diabetes mellitus treated with a basal-bolus regimen.

The trial includes two blinded dosing arms - mealtime fast-acting insulin aspart and mealtime NovoRapid®.

Trial population:

A total of 1803 subjects with Type 2 diabetes mellitus are planned to be screened and 1072 are planned to be randomised.

Key inclusion criteria:

- Male or female, age ≥ 18 years at the time of signing informed consent.
- Diagnosed with type 2 diabetes mellitus≥ 10 years prior to screening (Visit 1).
- Treated with a basal-bolus insulin regimen ≥ 1 year prior to the day of screening (Visit 1). A basal-bolus insulin regimen is defined as basal insulin once or twice daily and bolus insulin analogue taken with meals at least 3 times daily. Treatment with premixed insulin or soluble insulin combination is not considered a basal-bolus regimen.
- Treated with or without oral antidiabetic drugs including extended release formulations. HbA_{1c} 7.0-10.0% (both inclusive) as assessed by central laboratory at screening (Visit 1).

Key exclusion criteria:

- Any of the following: myocardial infarction, stroke, hospitalization for unstable angina or transient ischaemic attack within the past 180 days prior to the day of screening (Visit 1).
- Subjects presently classified as being in New York Heart Association (NYHA) Class IV.
- Planned coronary, carotid or peripheral artery revascularisation known on the day of screening (Visit 1).
- Treatment with injectable GLP-1 receptor agonists in a period of 90 days prior to screening (Visit 1).
- Anticipated initiation or change in concomitant medications (for more than 14 consecutive days) known to affect weight or glucose metabolism (e.g. treatment with orlistat, thyroid hormones, or corticosteroids).

Randomisation criterion:

- $HbA_{1c} \leq 9.0\%$ measured by the central laboratory at Visit 13 (week -1).

Key Assessments:

- HbA_{1c}
- Postprandial glucose increment (meal test)
- 1,5-anhydroglucitol
- Hypoglycaemic episodes
- Adverse events

Trial product(s):

Investigational medicinal products:

- Test products:
  - Fast-acting insulin aspart, 100 U/mL solution for subcutaneous injection, 3 mL PDS290 pen injector (blinded)
  - Insulin degludec, 100U/mL solution for subcutaneous injection, 3 mL PDS290 pen injector

- Reference therapy:
  - Insulin aspart (NovoRapid®), 100 U/mL solution for subcutaneous injection, 3 mL PDS290 pen injector (blinded)

Other medicinal products:

- Rapid acting insulin analogues (NovoRapid® or marketed formulations of insulin lispro or insulin glulisine) during run-in period
- Metformin, tablets for oral use

2 Flow chart

NN1218-4113	Protocol section	Screening	12-week run-in period							Randomisation	16- week treatment period Blinded trial product									End of treatment	Premature discontinuation	Follow-up 1	Follow-up 2
Visit (V) Phone contact (P)		V1	V2	P3 P4	V5	P6 P7 P8	V9	P10 P11 P12	V13	V14	P15	V16	P17	V18	P19 P20 P21	V22	P23 P24 P25	V26	P27 P28 P29	V30	V30A	V31	P32
Time of visit (weeks)		-14	-12	-11 -10	-9	-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		+7 days	+30 days
Visit window (days)		+10	±3	±3	±3	±3	±3	±3	±3	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		+10	+5
SUBJECT RELATED INFO/ASSESSMENTS																							
Informed consent	18.2	X																					
In/exclusion criteria	6.2 6.3	X	X																				
Run-in period exclusion criteria	6.4			X	X	X	X	X	X	X													
Randomisation criterion	6.5									X													
Randomisation	8.1.3									X													
Criteria for premature discontinuation of trial products	6.6										X	X	X	X	X	X	X	X	X				
Demography	8.2.1	X																					
Tobacco use	8.2.8	X																					
Diabetes history and diabetes complications	8.2.2, 8.2.6	X																					
Hypoglycaemia unawareness	8.2.3	X																					
Concomitant illness and medical history	8.2.4	X																					
Concomitant medication	8.2.5 8.2.6	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Child-bearing potential	8.2.7	X																					
EFFICACY																							
Meal test	8.3.1									X										X	X		
4-point profile (SMPG)	8.3.2		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
7-9-7-point profile (SMPG)	8.3.2									X						X				X	X		
1,5-anhydroglucitol	8.5.1									X				X		X		X		X	X		
Fasting plasma glucose	8.5.1									X						X				X	X		

NN1218-4113	Protocol section	Screening	12-week run-in period							Randomisation	16- week treatment period Blinded trial product									End of treatment	Premature discontinuation	Follow-up 1	Follow-up 2
Visit (V) Phone contact (P)		V1	V2	P3 P4	V5	P6 P7 P8	V9	P10 P11 P12	V13	V14	P15	V16	P17	V18	P19 P20 P21	V22	P23 P24 P25	V26	P27 P28 P29	V30	V30A	V31	P32
Time of visit (weeks)		-14	-12	-11 -10	-9	-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		+7 days	+30 days
Visit window (days)		+10	±3	±3	±3	±3	±3	±3	±3	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		+10	+5
HbA_{1c}	8.5.1	X			X		X		X	X				X		X		X		X	X		
Fasting C-peptide	8.5.1									X													
Lipids	8.5.1	X								X						X				X	X		
SAFETY																							
Adverse events	8.4.1, 12	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Injection site reactions	8.4.1.2		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hypoglycaemic episodes	8.4.2		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Technical complaints	12.1.6		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Body weight	8.4.5									X										X	X		
Height	8.4.5									X													
Physical examination	8.4.6	X								X										X	X		
Vital signs	8.4.7	X								X										X	X		
Eye examination	8.4.3	X								X										X	X		
ECG	8.4.4	X								X										X	X		
Biochemistry	8.5.2	X								X						X				X	X		
Haematology	8.5.2	X								X						X				X	X		
Pregnancy test	8.5.2	X								X										X	X		
TRIAL MATERIAL																							
Dispensing visit	9.4		X		X		X		X	X		X		X		X		X					
New (prescribed) dose of trial insulin	8.3.3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Dosing (Start/stop date of trial insulin)	8.3.3			X						X	X									X	X		
Insulin dose of basal and bolus insulin each day	8.3.3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Drug accountability	9.4		X		X		X		X	X		X		X		X		X		X	X		

NN1218-4113	Protocol section	Screening	12-week run-in period							Randomisation	16- week treatment period Blinded trial product									End of treatment	Premature discontinuation	Follow-up 1	Follow-up 2
Visit (V) **Phone contact (P)**		V1	V2	P3 P4	V5	P6 P7 P8	V9	P10 P11 P12	V13	V14	P15	V16	P17	V18	P19 P20 P21	V22	P23 P24 P25	V26	P27 P28 P29	V30	V30A	V31	P32
Time of visit (weeks)		-14	-12	-11 -10	-9	-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		+7 days	+30 days
Visit window (days)		+10	±3	±3	±3	±3	±3	±3	±3	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		+10	+5
IWRS call	10	X	X		X		X		X	X		X		X		X		X		X	X		
REMINDERS																							
Handout ID card	8.1.1	X																					
Confirmation of unchanged metformin	8.2.5		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Attend visit fasting	8.1.5									X						X				X	X		
Training in carbohydrate counting	8.6.1		X		X		X			X													
Handout direction for use	9.2		X																				
Training in trial product and pen handling	8.6.2		X		X		X			X				X		X							
Handout pen differentiation guide	9.2									X													
Training in pen differentiation	8.6.2									X				X		X							
Handout and instruct in eDiary	8.6.3		X																				
Handout and instruct in BG meter use	8.3.2		X																				
Handout and instruct in subject mealtime insulin dose adjustment guide	8.3.3									X													
eDiary collection	8.6.3																					X	
End of treatment	8.1.7																			X	X		
End of trial																							X

3 Background information and rationale for the trial

The trial will be conducted in compliance with this protocol, ICH GCP[1] and applicable regulatory requirements, and in accordance with the Declaration of Helsinki.[2]

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

Improvement in long-term glucose control, as obtained with intensified insulin therapy, may reduce the incidence of complications and delay the progression of existing complications in people with Type 1 Diabetes Mellitus (T1DM) and Type 2 Diabetes Mellitus (T2DM).[3, 4] Postprandial hyperglycaemia contributes significantly to the glycosylated haemoglobin (HbA_{1c}) level and its control is thus essential for achieving the HbA_{1c} target level.[5] Postprandial hyperglycaemia is associated with increased risk of micro- and macro-vascular complications.[6] Lowering of postprandial hyperglycaemia may reduce the progression of atherosclerosis and cardiovascular events in patients with T2DM.[7]

Basal-bolus insulin therapy aims at mimicking the physiological insulin response in the healthy state to the largest possible extent. For that purpose, rapid-acting insulin analogues were developed to more effectively control the postprandial glucose (PPG) excursions than subcutaneously injected human regular insulin, primarily through offering a faster onset and shorter duration of action.[8] However, unmet needs exist within prandial insulin therapy for people with diabetes. The current insulin analogues are not able to match the speed of the normal physiological postmeal insulin secretion, leading to suboptimal control of blood glucose (BG), and exogenous insulin with a faster glucose lowering effect is needed for tighter PPG control. In addition, a faster glucose lowering effect is also likely to offer greater flexibility in the time of dosing around meals thus increasing convenience for the patients and may allow the patients to better match the insulin taken to the meal.[9]

For an assessment of benefits and risks of the trial, see Section 18.1

3.1.1 Therapeutic Area

Due to the progressive nature of T2DM, many patients are likely to be candidates for intensified insulin therapy. Prandial insulin supplementation is recommended by European Association for the Study of Diabetes (EASD)/American Diabetes Association (ADA) guidelines[10] for treatment intensification in patients with T2DM who do not reach HbA_{1c} target below 7.0% on oral antidiabetic drugs (OADs) and basal insulin alone. The recommendation is a stepwise addition of bolus insulin when significant PPG excursions occur. A trial investigating step-wise addition of bolus insulin (basal-plus regimen) showed that around 75% of patients enrolled in the trial needed

three boluses after 36 weeks of treatment.[11] Results from the PREFER trial indicated that one-third of the total prandial insulin dose is delivered with each meal in the majority of patients achieving HbA1c ≤7.0%.[12] When used as part of a basal-bolus regimen in patients with T2DM who had previously received other insulin and/or OAD regimens, insulin aspart in combination with insulin degludec was a safe, well tolerated and effective treatment associated with clinically relevant reductions in hyperglycaemia.[13]

3.1.2 NovoRapid® (Insulin aspart)

Insulin aspart is currently marketed worldwide as NovoRapid® (in US it is NovoLog®) and is a rapid-acting insulin analogue indicated for the treatment of diabetes. In the remainder of this protocol the name NovoRapid® will be applied for the marketed formulation of 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 thereby is related to faster absorption as compared with regular human insulin. Compared with human insulin, NovoRapid® has a faster onset and a shorter duration of action, resulting in superior postmeal glucose control by means of lowering total glucose excursion following a meal, both in subjects with T1DM[3, 14, 15] and in subjects with T2DM.[16-18] This also allows NovoRapid® 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[19](SmPC) and the U.S. NovoLog® Label Information[20].

3.1.3 Fast-acting insulin aspart

Fast-acting insulin aspart (faster aspart) (markedet as Fiasp®) is insulin aspart in a new formulation. Faster aspart is being developed with the objective of achieving an increased early absorption of insulin aspart compared to NovoRapid® thereby providing a faster insulin action. Faster 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®. Results from clinical pharmacology trials in adults comparing pharmacokinetic and pharmacodynamic properties of faster aspart and NovoRapid® have shown that faster aspart resulted in an earlier onset of appearance and a greater early exposure to insulin aspart than NovoRapid® in subjects with T1DM, with the largest difference found within the first 15 minutes after injection. Faster aspart also resulted in a greater early glucose-lowering effect than NovoRapid®, but no statistically significant difference between faster aspart and NovoRapid® in total glucose-lowering effect.

In a therapeutic confirmatory basal-bolus trial in adult subjects with T1DM, faster aspart taken with the meal in combination with Levemir® effectively improved glycaemic control and the reduction in HbA_{1c} was statistically significantly larger than with NovoRapid®. Mealtime faster aspart provided superior PPG control compared to NovoRapid® 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 aspart. No statistically significant difference was seen in overall rate of severe or BG confirmed hypoglycaemic episodes between mealtime faster aspart and NovoRapid®. 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 aspart compared to NovoRapid®. The overall safety profile for faster aspart and NovoRapid® was similar and as expected for insulin aspart.

In a therapeutic confirmatory basal-bolus trial in adult subjects with T2DM, adding and titrating mealtime faster aspart in combination with insulin glargine also effectively improved glycaemic control and non-inferiority to NovoRapid® regarding HbA_{1c} change from baseline was confirmed. A statistically significant benefit in 2-hour PPG increment (meal test) could not be confirmed for faster aspart compared to NovoRapid®. A statistically significant difference was demonstrated for 1-hour PPG increment (meal test) in favour of faster aspart compared to NovoRapid®. No statistically significant difference was seen in overall rate of severe or BG confirmed hypoglycaemic episodes between faster aspart and NovoRapid®. The rate during the first two hours after start of a meal, constituting a small fraction of all severe or BG confirmed hypoglycaemic episodes, was statistically significantly higher for faster aspart compared to NovoRapid®. The overall safety profile for faster aspart and NovoRapid® was similar and as expected for insulin aspart.

The safety profile of faster aspart is expected to be similar to that of NovoRapid®. The insulin aspart molecule has a well-known safety profile based on more than 15 years of clinical experience. Compared to NovoRapid® faster aspart contains excipients which results in a faster initial absorption of insulin aspart following subcutaneous injection. The added excipients are included in the U.S. Food and Drug Administration's (FDA) list for approved drug products for injections, and no toxicological concerns have been predicted from subcutaneous use in humans at the proposed concentrations. For further details, please refer to the current version of the Fiasp® SmPC[21]. If not approved in the country of interest detailed information for faster aspart is available in the current edition of the Investigator's Brochure (IB)[22] and any updates hereof.

At the time of this protocol issuance, faster aspart is approved in EU and Canada among others.

3.1.4 Insulin degludec

Insulin degludec (marketed as Tresiba®) is a basal insulin with an ultra-long duration of action for once-daily subcutaneous administration at any time of the day, preferably at the same time every

day. After subcutaneous injection, soluble and stable multi-hexamers are formed creating a depot of insulin in the subcutaneous 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[23]. 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[24].

At the time of this protocol issuance, insulin degludec is approved in more than 70 countries including US, EU and Japan.

3.2 Rationale for the trial

The purpose of this trial is to confirm the effect and compare safety of faster aspart compared to NovoRapid® both in combination with insulin degludec with or without metformin in subjects with T2DM treated with a basal-bolus regimen. This trial will provide new information in subjects with T2DM already treated with a basal-bolus regimen as this was not studied in the phase 3a programme.

In the European Medicines Agency (EMA) and FDA note for guidance on clinical investigation of medicinal products for the treatment of diabetes, HbA_{1c} is considered the most widely accepted measure of overall, long-term glucose control. Consequently, HbA_{1c} will be included as the primary endpoint.[25, 26]

The trial is intended to confirm that administration of faster aspart gives overall glycaemic control non-inferior to NovoRapid® and to confirm that faster aspart, with its faster onset of action, is capable of demonstrating superior control of postprandial glucose regulation and excursions as well as a greater reduction in HbA_{1c} in subjects with T2DM.

4 Objectives and endpoints

4.1 Objectives

Primary objective

To confirm the effect in terms of glycaemic control of treatment with faster aspart compared to NovoRapid® both in combination with insulin degludec with or without metformin in adults with T2DM treated with a basal-bolus regimen, using a non-inferiority approach.

Secondary objectives

To confirm superiority of faster aspart compared to NovoRapid® both in combination with insulin degludec with or without metformin in adults with T2DM treated with a basal-bolus regimen in terms of:

- Postprandial glucose regulation
- Overall glycaemic control
- Postprandial glucose excursions

To compare the safety of faster aspart to NovoRapid® both in combination with insulin degludec with or without metformin in adults with T2DM treated with a basal-bolus regimen.

4.2 Endpoints

Baseline is defined as randomisation (Visit 14)

4.2.1 Primary endpoint

Change from baseline in HbA_{1c} 16 weeks after randomisation

4.2.2 Secondary endpoints

4.2.2.1 Confirmatory secondary endpoints

- Change from baseline in 1-hour PPG increment 16 weeks after randomisation (meal test)
- Change from baseline in 1,5-anhydroglucitol 16 weeks after randomisation

4.2.2.2 Supportive secondary endpoints

Supportive secondary efficacy endpoints

- Change from baseline in fasting plasma glucose (FPG) 16 weeks after randomisation
- If a subject achieves HbA_{1c} targets 16 weeks after randomisation:
    - HbA1c < 7.0%
    - HbA1c < 7.0% without severe hypoglycaemia
- Change from baseline in 30- minutes, 1- hour, 2- hour, 3- hour and 4- hour PPG and 30-minutes, 2- hour, 3- hour and 4- hour PPG increment 16 weeks after randomisation (meal test)
- Change from baseline in endpoints derived from the 7-9-7-point self-measured plasma glucose (SMPG) profile 16 weeks after randomisation:
    - Mean of the 7-9-7-point profile
    - Postprandial glucose and PPG increment (mean, breakfast, lunch, main evening meal)
    - Fluctuation in 7-9-7-point profile
    - Change in the nocturnal SMPG measurements
- If a subject achieves PPG target (overall mean of daily PPG measurements in 7-9-7-point SMPG profile) 16 weeks after randomisation:
    - Overall PPG (1 hour) ≤7.8 mmol/L [140 mg/dL]
    - Overall PPG (1 hour) ≤7.8 mmol/L [140 mg/dL] without severe hypoglycaemia
- Insulin dose (Units/day and Units/kg/day; total basal, total bolus and individual meal insulin dose) 16 weeks after randomisation
- Change from baseline in lipids-lipoproteins profile 16 weeks after randomisation (total cholesterol, high density lipoproteins (HDL) cholesterol, low density lipoproteins (LDL) cholesterol)

Supportive secondary safety endpoints

- Number of treatment emergent adverse events (AEs) during 16 weeks after randomisation
- Number of treatment emergent injection site reactions during 16 weeks after randomisation
- Number of treatment emergent hypoglycaemic episodes classified both according to the ADA definition and Novo Nordisk definition during 16 weeks after randomisation
    - Overall
    - Daytime hypoglycaemic episodes
    - 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 in clinical evaluations 16 weeks after randomisation:
    - Physical examination
    - Vital signs (diastolic blood pressure, systolic blood pressure and pulse)
    - Electrocardiogram
    - Fundoscopy/fundus photography
- Change from baseline in central laboratory assessments 16 weeks after randomisation:
    - Haematology (erythrocytes, haematocrit, haemoglobin, leucocytes, thrombocytes)
    - Biochemistry (alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, alkaline phosphatase, creatinine, potassium, sodium, total bilirubin)
- Change from baseline in body weight and body mass index 16 weeks after randomisation

5 Trial design

5.1 Type of trial

This is a phase 3b, 16-week, multicentre, multinational, 1:1 randomised, double-blind, active controlled, treat-to-target, parallel group trial with a 12-week run-in period comparing the effect and safety of faster aspart to NovoRapid® both in combination with insulin degludec with or without metformin in subjects with T2DM treated with a basal-bolus regimen.

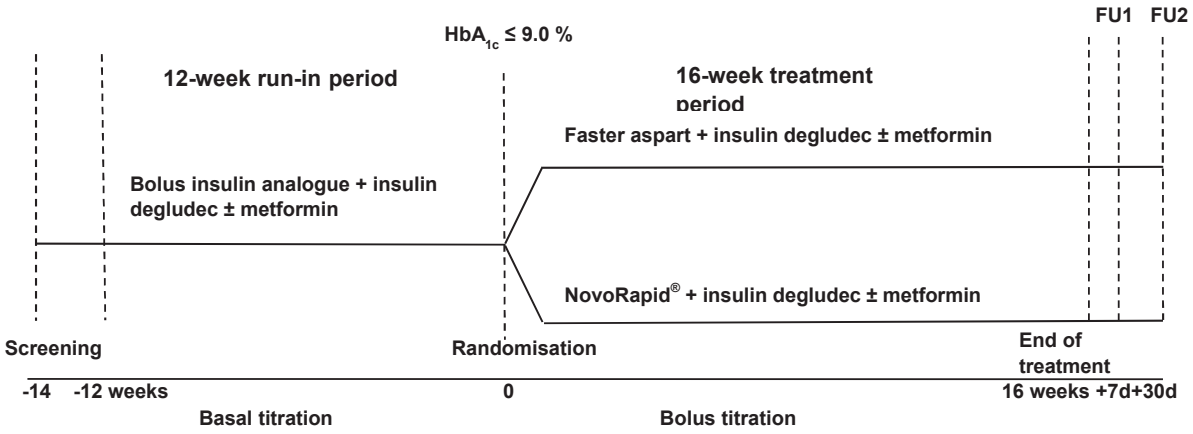


Figure 5–1 Trial Design.

The trial design is summarised in Figure 5–1. The total duration of the trial is approximately 34 weeks divided into the following periods:

- An approximately 2-week screening period
- A 12-week run-in period primarily for optimisation of the basal insulin and subject training
- A 16-week treatment period
- A 30-day follow-up period: FU1; 7 days after end of treatment and FU2; 30 days after end of treatment

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 a 12-week run-in period. After the run-in period, subjects eligible for randomisation ($HbA_{1c} \leq 9.0\%$ measured at Visit 13) will be randomised (1:1) to receive double blinded treatment with either faster aspart or NovoRapid® both in combination with once daily insulin degludec with or without metformin.

All subjects will have a standardised meal test at baseline (Visit 14 before randomisation) and at end of treatment (Visit 30). The meal test will be described in more details in section 8.3.1.

After the 16-week treatment period, each subject will have a 30-day safety follow-up period.

5.2 Rationale for trial design

The 12-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 16-week treatment period is needed to obtain valid and adequate efficacy and safety data.

The rational for the simple carbohydrate counting (carbohydrate awareness) is to ensure that subjects are able to better control the carbohydrate amount of their meals aiming at a similar carbohydrate intake between days as a supplement to the algorithm based titration.

The rationale for the meal test is to evaluate PPG regulation after a standardised meal when injecting faster 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 aspart and NovoRapid®.

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

5.2.1 Rational for choice of non-inferiority margin

In a recently finalised faster aspart trial (NN1218-4049, data on file) with 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 effect in change from baseline HbA_{1c} was - 0.94% [-1.17; -0.72]. In this trial the addition of 3 times daily faster aspart led to a reduction in HbA_{1c} of 1.16% after 18 weeks of treatment. In a similar phase 4 trial[27] investigating the stepwise addition of NovoRapid® to a full basal-bolus regimen in bolus naïve T2DM adults the observed reduction in HbA_{1c} after 21 weeks of treatment was 1.15% (data ANA-3786, data on file) with 3 times daily NovoRapid® added to basal insulin. This gives some indication that the effect of NovoRapid® versus placebo would be close to the 0.94% observed in trial NN1218-4049. Thus using a non-inferiority margin of 0.4%, one of the suggested margins in the FDA guidance[26], an improvement of approximately 0.54% would have been preserved using the 0.4% non-inferiority margin.

5.3 Treatment of subjects

At Visit 2, all eligible subjects will be enrolled in a run-in period where all subjects will be transferred from their pre-trial basal insulin treatment to insulin degludec once daily. They must

continue their pre-trial bolus insulin analogue with or without metformin. All OADs, except for metformin must be stopped at Visit 2. For subjects treated with metformin prior to the trial, they should continue with their pre-trial dose of metformin. The dose and dosing frequency of metformin should not be changed at any time during the trial, unless due to safety concerns. Initiation of any other diabetes treatment is not allowed during the screening, run-in or treatment period and must be reported (see section 8.2.6). This includes metformin for subjects not treated with metformin prior to the trial. During the run-in period, the investigator will focus on optimising the basal insulin treatment using a treat-to-target approach following the titration guideline (Appendix A). The bolus insulin 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 dietary training regarding simple carbohydrate counting (carbohydrate awareness) in the run-in period.

All subjects should consume 3 main meals (breakfast, lunch and dinner) daily throughout the trial.

In the treatment period, eligible subjects must discontinue their pre-trial bolus insulin analogue and will receive double blinded treatment with either faster aspart or NovoRapid® both in combination with once daily insulin degludec with or without metformin. The investigator should focus on optimising the bolus insulin treatment following the bolus dosing algorithm as described in the titration guideline (Appendix A). Surveillance of insulin titration will be performed by Novo Nordisk.

The maximum duration of treatment will be 28 weeks. No maximum dose is specified. Doses are adjusted according to SMPG values (Appendix A).

Use of flash glucose monitoring or a real time continuous glucose monitoring system is not allowed throughout the trial.

5.4 Treatment after discontinuation of trial products

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 BG measurements, considering the stable effect and long half-life of insulin degludec.

5.5 Rationale for treatment

Based on the currently available pharmacokinetic data on faster aspart, it is anticipated that treatment with faster 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 aspart SmPC[21] or IB.[22]

NovoRapid® will be used as a comparator to faster aspart in order to compare the effect and safety of faster aspart to the currently marketed insulin aspart formulation. As this is a double-blind trial, NovoRapid® and faster 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 effect and safety has been confirmed in adult subjects. The flat and stable glucose-lowering effect of insulin degludec makes it optimal when assessing the properties of bolus insulin (faster aspart compared to NovoRapid®).

Combination of insulin treatment with metformin is associated with better glycaemic control, fewer hypoglycaemic events, and less weight gain than treatment with insulin alone, therefore metformin should be continued when type 2 patients are on insulin therapy.

6 Trial population

6.1 Number of subjects

Number of subjects planned to be screened: 1803

Number of subjects planned to be included in the run-in period: 1262

Number of subjects planned to be randomised: 1072

A screening failure rate of approximately 30% and a run-in failure rate of approximately 15% 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 ≥ 18 years at the time of signing informed consent.

3. Diagnosed with type 2 diabetes mellitus ≥ 10 years prior to screening (Visit 1).

4. Treated with a basal-bolus insulin regimen ≥ 1 year prior to the day of screening (Visit 1). A basal-bolus insulin regimen is defined as basal insulin once or twice daily and bolus insulin analogue taken with meals at least 3 times daily. Treatment with premixed insulin or soluble insulin combination is not considered a basal-bolus regimen.

5. Treated with or without oral antidiabetic drugs including extended release formulations.

6. HbA_{1c} 7.0-10.0% (both inclusive) as assessed by central laboratory at screening (Visit 1).

7. Able and willing to adhere to the protocol including performance of SMPG profiles and meal test.

8. Able and willing to consume 3 main meals (breakfast, lunch and dinner) daily throughout 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 an adequate contraceptive method (adequate contraceptive measure as required by local regulation or practice).

   For Bulgaria, Czech Republic, Germany, Greece, Italy, Poland, Romania and Spain: The following contraceptive measures are considered adequate:

   - combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, transdermal or intravaginal)
   - progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable)
   - intrauterine device
   - intrauterine hormone-releasing system
   - sexual abstinence
   - vasectomised partner
   - double barrier method (a combination of male condom with either cap, diaphragm or sponge with spermicide)

4. Participation in any clinical trial of an approved or non-approved investigational medicinal product within 30 days before screening (Visit 1). Clinical trials do not include non-interventional studies.

5. Any disorder, except for conditions associated with type 2 diabetes mellitus, which in the investigator's opinion might jeopardise subject's safety or compliance with the protocol.

6. Any of the following: myocardial infarction, stroke, hospitalization for unstable angina or transient ischaemic attack within the past 180 days prior to the day of screening (Visit 1).

7. Subjects presently classified as being in New York Heart Association (NYHA) Class IV.

8. Planned coronary, carotid or peripheral artery revascularisation known on the day of screening (Visit 1).

9. Inadequately treated blood pressure defined as Grade 3 hypertension or higher (Systolic ≥180 mmHg or diastolic ≥110 mmHg) at screening (Visit 1).

10. Treatment with injectable GLP-1 receptor agonists in a period of 90 days prior to screening (Visit 1).

11. Anticipated initiation or change in concomitant medications (for more than 14 consecutive days) known to affect weight or glucose metabolism (e.g. treatment with orlistat, thyroid hormones, or corticosteroids).

12. Proliferative retinopathy or maculopathy requiring acute treatment. Verified by fundus photography or pharmacologically dilated fundoscopy performed within the past 90 days prior to Visit 2.

13. Presence or history of malignant neoplasms within the past 5 years prior to the day of screening (Visit 1). Basal and squamous cell skin cancer and any carcinoma *in-situ* is allowed.

14. For subjects treated with metformin: Any contraindications or restrictions to use of metformin (according to local labelling) at investigator's discretion.

6.4 Run-in period exclusion criteria

The subject must be withdrawn from the trial during the run-in period if the following applies after screening (Visit 1), and before or at randomisation (Visit 14):

1. Included in the trial in violation of the inclusion and/or exclusion criteria.

2. Pregnancy

3. Intention of becoming pregnant

4. Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product.

5. Any of the following: myocardial infarction, stroke, hospitalization for unstable angina or transient ischaemic attack.

6. Planned coronary, carotid or peripheral artery revascularisation.

7. Any disorder which in the investigator's opinion might jeopardise subject's safety.

8. Inability or lack of willingness to adhere to the protocol, based on the investigator's judgement.

6.5 Randomisation criterion

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

1. $HbA_{1c} \leq 9.0\%$ measured by the central laboratory at Visit 13 (week -1).

6.6 Criteria for premature discontinuation of trial products

Efforts must be made so that subjects attend and complete all scheduled visit procedures. Subjects should stay in the trial irrespective of lack of adherence to randomised treatment, lack of adherence to visit schedule or missing assessments. Only subjects who decline any further contact with the site in relation to the trial will be considered as withdrawn from the trial (see Section 6.7).

The subject may be prematurely discontinued from trial products at the discretion of the investigator due to a safety concern.

The subject must be prematurely discontinued from trial products if the following applies after randomisation:

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. Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product.

See Section 8.1.9 for procedures to be performed for subjects discontinuing trial products prematurely.

6.7 Withdrawal from trial

The subject may withdraw consent at will at any time.

A subject is considered withdrawn from trial if the following applies before Visit 30:

- Subject is lost to follow up (see Section 8.1.10))
- Subject withdraws consent
- Death

Subjects withdrawing from trial before randomisation are considered screening or run-in failures.

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 products but to stay in the trial, procedures described in section 8.1.9 must be followed.

See Section 8.1.10 for procedures to be performed for subjects withdrawing consent after randomisation.

6.8 Subject replacement

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

6.9 Rationale for trial population

The trial population consists of adult subjects with T2DM who have been treated with a basal-bolus insulin regimen for at least 365 days, but are not optimally controlled as demonstrated by an HbA_{1c} ≥ 7.0%, and may benefit from intensified insulin titration using a treat-to-target approach. The subjects need to have had T2DM for at least 10 years to ensure more progressed disease requiring a full basal bolus insulin supplementation. The subjects need to be on a basal-bolus insulin regimen for at least 365 days 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.

Subjects with an HbA_{1c} > 10% are not included in this trial. This is because the trial protocol requires strict adherence and good subject compliance and a likely cause of elevated HbA_{1c} > 10% 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 12-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. Subjects with an HbA_{1c} > 9% 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, a likely cause of HbA_{1c} > 9% after 12-week basal insulin titration period is poor compliance with treatment regimens or an atypical course of the disease.

7 Milestones

Planned duration of recruitment period: 36 weeks

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

Recruitment:
The screening and randomisation rate will be followed closely via the interactive voice/web response system (IWRS) 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 IWRS will be closed for further screening. All subjects screened during the recruitment period and found eligible for randomisation can be randomised within the timelines specified in the flow chart (see Section 2).

Trial registration:

Information of the trial will be disclosed at clinicaltrials.gov and novonordisk-trials.com. According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure[28], it will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE)[29], the FDA Amendment Act (FDAAA)[30], European Commission Requirements[31, 32] 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.

Primary Completion Date is the last assessment of the primary endpoint, and is for this protocol last subject first visit + 30 weeks corresponding to Visit 30. If the last subject is withdrawn/dropout early the Primary Completion Date is the date when the last subject would have completed Visit 30. The Primary Completion Date determines the deadline for results disclosure at clinicaltrials.gov according to FDAAA.

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 (Visit 1)

Informed consent must be obtained before any trial related activity, see Section 18.2.

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. Only subjects who have signed the informed consent form should be included on the logs. The subject screening log and subject enrolment log may be combined in one log.

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 IWRS.

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 AEs (SAEs) from screening failures must be transcribed by the investigator into the eCRF. Follow-up on SAEs must be carried out according to Section 12.

A screening failure session must be made in the IWRS. When data has been monitored and queries have been resolved the case book must be signed.

Re-screening is NOT allowed if the subject has failed one of the inclusion, exclusion or randomisation criteria, this includes re-sampling if the subject has failed one of the inclusion, exclusion or randomisation criteria related to laboratory parameters.

8.1.2 Run-in

If the subject is found eligible to continue in the trial the subject will enter a run-in period. 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.

In- or exclusion criteria must not be ticked "Yes" or "No" in the eCRF before source data is available. In case source data is not available "Result pending" must be chosen. This is particularly relevant for lab samples and in some cases the ECG (electrocardiogram) and eye examination result. 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 the basal insulin trial product (Insulin degludec). The subjects must be trained in how to handle the insulin pen injectors (see section 8.6.2). Training may be repeated during the trial if necessary. First date of trial product (basal insulin) must be recorded in the eCRF.

A run-in dispensing session must be performed in the IWRS. A drug accountability session confirming dispensing of allocated trial product should also be performed when dispensing trial product.

The BG meter and electronic diary (eDiary) should be provided to the subjects at Visit 2. Subjects must be trained in the BG meter and eDiary and complete a practise eDiary training, before the eDiary can be used.

Run-in failures

If the subject is not eligible to be randomised (i.e. has met one of the run-in period exclusion criteria, has not met the randomisation criterion or withdraw from trial before randomisation) then the subject will be considered a run-in failure. Consequently, a run-in failure session must be made in the IWRS system and a run-in failure form must be completed in the eCRF together with the reason for not continuing in the trial. The last date of trial product must be captured in the eCRF. No follow-up visit should take place and no additional assessments are needed.

The eDiary must be returned to the site.

For Argentina, Russia, Serbia and Ukraine: The BG meter should also be collected by the investigator.

SAEs and non-serious AEs from run-in failures must be recorded by the investigator in the eCRF. 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.

8.1.3 Randomisation

If the subject meets the randomisation criterion as measured at Visit 13, then the subject will at Visit 14 be randomised into one of the two treatment arms using an IWRS randomisation session. A drug accountability session confirming dispensing of allocated trial products should also be performed when dispensing trial products.

First date of the randomised trial product (bolus insulin) must be recorded in the eCRF.

The subject must attend randomisation visit fasting. For definition of fasting, please see section 8.1.5.

Investigator must hand out the subject mealtime insulin dose adjustment guide and instruct subjects how to self-titrate (section 8.3.3 and Appendix A).

8.1.4 Phone contacts

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. A phone contact may be converted to a site visit if needed.

8.1.5 Fasting visits

The subjects must attend the visits specified in the flowchart (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 and at Visit 14 before randomisation to trial product.

8.1.6 Rescheduled visits

The date of the rescheduled assessment in the eCRF should reflect the actual date of the rescheduled assessment (i.e. the actual visit date will differ from the assessment date under the same visit).

8.1.7 End of treatment

At end of treatment trial products must be discontinued and a completion IWRS session must be performed. Last date on the basal and bolus trial insulin must be recorded in eCRF.

The subject must be switched to a suitable marketed product at the discretion of the investigator and this product must be recorded on the concomitant medication (diabetes) form in eCRF, as described in section 8.2.6.

8.1.8 Follow-up period

The follow-up visit 1 (FU1) is a site visit and must take place 7-17 days after the end of treatment visit. Follow-up contact 2 (FU2) is a phone contact and must take place 30-35 days after the end of treatment visit.

Follow-up visit 1

The following data will be collected:

- AEs
- Concomitant medication
- Current diabetes medication
- Hypoglycaemic episodes
- Additional information on injection site reactions

Follow-up contact 2

The following data will be collected:

- AEs
- Concomitant medication
- Current diabetes medication
- Hypoglycaemic episodes

8.1.9 Premature discontinuation of trial products

If a subject prematurely discontinues trial products after randomisation (Visit 14), the investigator must undertake procedures similar to those for Visit 30 as soon as possible, also called Visit 30A (see flowchart section 2).

Premature discontinuation of trial products must be registered in the eDiary webportal. This must be performed at least 4 days prior to Visit 30A to ensure scheduling of the 7-9-7-point SMPG profile on the three days prior to Visit 30A. Subjects should perform this 7-9-7 point SMPG profile before discontinuing trial products.

At Visit 30A subjects must undergo the meal test before discontinuing trial products. The meal test should be performed with bolus trial insulin. If it is not feasible due to safety reasons including pregnancy as judged by the investigator the meal test should be performed with the marketed bolus product the subject is switched to.

The primary reason for premature discontinuation of trial products must be specified in the eCRF, and final drug accountability must be performed. A treatment discontinuation session must be made in the IWRS after the final meal test.

The subject should be switched to a suitable marketed product at the discretion of the investigator. The medication should be recorded on the concomitant medication (diabetes) form in the eCRF, as described in section 8.2.6 at each contact after trial product discontinuation.

The subject should also complete the follow-up visits (FU1 and FU2) 7 days and 30 days after discontinuation of trial product. Visit 31 (FU1) can be converted into a phone contact as the eDiary will not be collected at this visit for the subjects that discontinue trial products prematurely.

In addition, subjects prematurely discontinued from trial products should continue with the per protocol planned visits at 4 (Visit 18), 8 (Visit 22), 12 (Visit 26), 16 (Visit 30) weeks after randomisation depending on when the subject discontinues trial products. The meal test at Visit 30 should be done with the subjects' currently prescribed insulin treatment with the same bolus insulin dose as at baseline.

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

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

- If Visit 30A is within 2 weeks of one of the per protocol planned visits, only Visit 30A 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

It should be documented in the medical records if subject refuses to attend a visit from Visit 30A and onwards.

The eDiary must be returned to the site at the last site visit (Visit 30).

A subject that permanently discontinues trial product before the End of Treatment visit (V30), will be considered to be a treatment non-completer.

For Argentina, Russia, Serbia and Ukraine: The BG meter should be collected by the investigator at the last scheduled site visit (Visit 30).

eDiary records after premature discontinuation of trial products:

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 30A, Visit 22 and Visit 30 will be transferred to the eDiary, where each measurement should be assigned to the corresponding time point.

For hypoglycaemic episodes only a reduced amount of information should be recorded from one day after Visit 30A and to Visit 30 (see section 8.4.2):

8.1.10 Withdrawal from trial

If a subject withdraws consent, the investigator must aim to undertake procedures similar to those for Visit 30 including the meal test, as soon as possible, also called Visit 30A. The investigator must encourage the subjects to undergo the meal test at Visit 30A. The meal test must be performed with bolus trial insulin according to randomisation. If it is not feasible due to safety reasons including pregnancy as judged by the investigator the meal test should be performed with the marketed bolus product the subject is switched to.

If the subject agrees, the investigator must aim to perform the follow up visits (FU1 and FU2) 7 and 30 days after discontinuation of trial product.

In case a premature discontinuation of trial product subject chooses to withdraw consent from trial after completing Visit 30A, FU1 and FU2, the investigator must encourage the subjects to undergo procedures of Visit 30, as soon as possible, whereas FU1 and FU2 are not to be completed again.

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

Although a subject is not obliged to give his/her reason(s) for withdrawing consent, 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 withdrawing consent must be specified in the eCRF.

A subject that is withdrawn from trial before the End of Treatment Visit (V30), will be considered to be a treatment non-completer and a trial non-completer.

8.1.10.1 Lost to follow-up

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".

8.1.11 Review of results

Review of ECG results, eye examination report, laboratory reports, data entered in the eDiaries etc. must be documented either on the documents, printouts, in the eDiary webportal or in the subject's medical record.

If clarification of entries or discrepancies in the eDiary 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. Any discrepancies or missing data points available elsewhere related to a 7-9-7 point profile or hypoglycaemic episodes must be corrected or added.

8.2 Subject related information/assessments

8.2.1 Demography

Demography will be recorded at screening and consists of:

- Date of birth (according to local regulation)
- Sex
- Ethnicity (according to local regulation)
- Race (according to local regulation)

8.2.2 Diabetes history and diabetes complications

Diabetes history and diabetes complications will be recorded at screening and consists of:

- Date of diagnosis of T2DM
-
- Information regarding diabetes complications including date of onset
  - Diabetic retinopathy
  - Diabetic neuropathy
  - Diabetic nephropathy
  - Macroangiopathy (including peripheral vascular disease)

8.2.3 Hypoglycaemia unawareness

Information on hypoglycaemia unawareness will be recorded at screening according to Clarke's questionnaire, question 8.[33]
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 impaired awareness of hypoglycaemia.

8.2.4 Concomitant illness and medical history

- A **concomitant illness** is any illness 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 or other trial procedures performed before exposure to trial product.

T2DM and 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.

It must be possible to verify the subject's medical history in source documents such as subject's medical record. If a subject is not from the investigators own practice; the investigator must make

reasonable effort to obtain a copy of subject's medical record from relevant party e.g. primary physician. The investigator must document any attempt to obtain external medical information by noting the date(s) when information was requested and who has been contacted.

8.2.5 Concomitant medication

A **concomitant medication** is any medication, other than the trial product(s), which is taken during the trial, including the screening, run-in, treatment 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 Concomitant medication (diabetes)

Any diabetes medication other than the trial product(s) which is taken during the trial, including the screening, run-in, treatment and follow-up periods must be recorded in a separate concomitant medication (diabetes) form in the eCRF including the trade name or generic name, total daily dose, frequency, start date and stop date or continuation. For subjects treated with metformin it is the start date and dose of last stable metformin dose which should be reported.

At the run-in visit (Visit 2) basal insulin and all OADs except for metformin must be discontinued and a stop date recorded. For subjects treated with metformin, investigator should at each weekly contact (visit or phone contact), confirm with the subject that dose and frequency of metformin has been unchanged. This should be documented in the medical records.

At the randomisation visit (Visit 14) pre-trial bolus insulin must be discontinued and a stop date recorded.

It is important to ensure subjects adhere to treatment. Therefore, during the treatment period the investigator must also at each weekly contact (visit or phone contact), evaluate if the subject has taken any ancillary treatment since last contact. **Ancillary treatment** is defined as any diabetes medication - other than randomised treatment (trial products in the basal-bolus regimen with or without metformin) initiated in case of unsatisfactory glycaemic control. It should be registered as such on the concomitant medication (diabetes) form in the eCRF. For subjects not treated with metformin prior to the randomisation, initiation of long term use of metformin is considered as ancillary treatment. A medication error (Section 8.4.1.1) is as such not considered as ancillary treatment.

8.2.7 Childbearing potential

It must be recorded in the eCRF whether female subjects are of childbearing potential. Reason for not being of childbearing potential must be documented in the medical records.

Pregnancy testing must be performed on female subjects of childbearing potential as described in Section 8.5.2. Female subjects of childbearing potential must be instructed to use adequate contraceptive methods throughout the trial and until 1 week after end of treatment.

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

8.2.8 Tobacco use

Details of tobacco use must be recorded at Visit 1. Smoking is defined as smoking at least one cigarette or equivalent daily.
Smoking status:

- Never smoked
- Previous smoker
- Current smoker

8.3 Efficacy assessments

8.3.1 Meal test

The subject will undergo a standardised liquid meal test at two visits (see flowchart section 2) and will have their 30 minute and 1, 2, 3 and 4 hour PPG measured. The total duration of the meal test is expected to be up to 6 hours including preparations. During that time 6 blood samples will be drawn, as specified in the Table 8–1.

Before initiation of the meal test

The subject should be instructed to:

- Follow normal routine regarding eating and exercise habits on the day prior to the meal test
- Refrain from intake of alcohol and use of medications that affect motility (i.e. prokinetics, anticholinergics, tricyclic antidepressants) on the day prior to the meal test, unless the subject was on this medication at trial entry and does not change the product or product dose
- Remember to bring their current/trial bolus and basal insulin, eDiary and BG meter to the meal test visits
- Attend the meal test visits in a fasting condition. For definition of fasting, please refer to section 8.1.5. If subjects are normally dosing basal insulin in the morning, it is important they wait until after completion of the meal test
- Achieve an SMPG value within a range of 4.0-8.8 mmol/L [71-160 mg/dL] before beginning the meal test. The SMPG value should be verified at the site before starting the meal test.

The meal test should be re-scheduled within the visit window and at Visit 14 before randomisation to trial product in case:

- any hypoglycaemic episode occurs from midnight before the meal test
- the subject is not fasting or
- the SMPG value is outside the range.

At Visit 14 (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 14 meal test performed.

Bolus insulin dose and meal test carbohydrate calculation

The standardised liquid meal will be provided by Novo Nordisk. The volume of the liquid meal should be measured out by the investigator to be the equivalent to 78 grams of digestible carbohydrates.

At the baseline meal test, the bolus insulin dose should be calculated by the investigator by dividing the carbohydrate content of the standardised meal by a calculated insulin:carbohydrate ratio. The insulin:carbohydrate ratio in this trial is calculated by dividing 500 by the total daily dose (taken from the day before) of both basal and bolus insulin. The calculated dose should be rounded to the nearest whole unit.

Same bolus insulin dose will be used for the meal test at end of treatment. The insulin should be administered subcutaneously in the abdomen in accordance with Table 8–1.

Initiation of meal test

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

For the meal test at Visit 14 the subject must receive the bolus insulin that was also used in the run-in period.

For the meal test at Visit 30 the subject should receive the bolus trial insulin they were randomised to and have used throughout the treatment period. If subject has been prematurely discontinued they should perform a meal test both at Visit 30A and again at Visit 30; the meal test at Visit 30 should be performed with the marketed bolus product the subject was switched to.

The start of consumption of the liquid meal is defined as time point 0. The subject must consume the liquid meal as quickly as possible and within 12 minutes. The investigator should confirm that the subject consumed the required volume of the standardised liquid meal in the eCRF.

Table 8–1 Meal test schedule

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

Conduct of meal test

The subject should stay in the clinic to have the blood samples drawn after 30 minutes, 1, 2, 3 and 4 hours from the start of the standardised meal, as detailed in Table 8–1. The samples will be analysed by the central laboratory.

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 ≤3.9 mmol/L [70 mg/dL] are measured, then the hypoglycaemia should be treated with glucose rescue treatment according to local practice and the meal test should continue according to the investigator's discretion. The hypoglycaemic episode must be reported. Please see section 8.4.2.

After the end of the meal test, the investigator should make sure that the subject is safe to leave the site by performing an additional SMPG measurement.

Only after the meal test at Visit 14 is completed, the subject will be allowed to start treatment with randomised trial product.

Data collection

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
- Actual clock 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 consumed
- Actual clock time and dose of bolus insulin
- Actual clock time of blood samples
- Hypoglycaemic episodes, if relevant
    - SMPG value, time of intervention and amount of glucose rescue treatment and hypoglycaemic episode form

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 in order to keep the blinding of the subject and investigator.

8.3.2 Self-measured plasma glucose

At Visit 2, subjects will be provided with a BG meter including ancillaries as well as instructions for use, if needed. The subjects will be instructed in how to use the device.

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.

Only the BG meter provided by Novo Nordisk should be used for the measurements required in the protocol.

For Argentina, Russia, Serbia and Ukraine: The BG meter should be collected by the investigator at the last scheduled site visit FU1 (Visit 31).

Subjects must be instructed in how to transfer the results of the SMPG values daily into the eDiaries.

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 from Visit 2 to Visit 30 for titration purposes. The measurements should be performed at the following time points:

- Before breakfast
- Before lunch
- Before main evening meal (dinner)
- At bedtime

For SMPG measurements actual clock time, date and value should be transferred to the eDiary, where each measurement should be assigned to the corresponding time point.

SMPG values measured before breakfast, lunch, 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 main evening meal). 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.

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

The 7- and 9-point SMPG profiles will be used for titration purposes and evaluation of the effect 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 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)[a]
60 minutes after the start of breakfast	X	√	X
Before lunch	X	√	X
60 minutes after the start of lunch	X	√	X
Before main evening meal	X	√	X
60 minutes after the start of main evening meal	X	√	X
At bedtime	X	√	X
At 4 am		√	

[a]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, date and value should be transferred to the eDiary, where each measurement should be assigned to the corresponding time point.

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

The subject should be instructed to report the following concerning dosing of trial products in the eDiary:

- Date, actual clock time and dose of basal and bolus insulin on a daily basis from Visit 2 to Visit 30.
- Date, actual clock time, and dose for other (extra) bolus insulin administration as well as time and type of previous main meal and reason for the extra bolus from Visit 2 to Visit 30.

Dosing and dose adjustment (new dose)

The recommended insulin doses will be calculated in the eDiary webportal based on recommendations from the Insulin Titration Guideline (see Appendix A). At each visit/phone contact the investigator will titrate the subjects by making prescribed dose adjustments based on the recommendation from the eDiary webportal if applicable and provide the new prescribed dose to the subject.

Investigator must hand out the subject mealtime insulin dose adjustment guide at Visit 14 and should instruct subjects to perform self-titration of bolus (mealtime) trial insulin between the scheduled visits/phone contacts from Visit 14 to Visit 30.

The investigator should record the following in the eDiary webportal:

- Prescribed doses of trial products
- Reason for deviating in dose adjustments from the titration guideline, if applicable

The subject should report the following in the eDiary:

- Dose adjustment of bolus trial insulin

8.4 Safety assessments

In case of an abnormal and clinically significant finding, the investigator must record the finding on the concomitant illness form if it is present at screening. Any new finding fulfilling the definition stated in section 12 during the trial and any clinically significant worsening from baseline must be reported as an AE.

8.4.1 Adverse events

Adverse events (AEs) must be reported at each visit in accordance with the procedures outlined in Section 12.

8.4.1.1 Medication error

If a medication error is observed during the trial, the following information is required and a specific event form must be completed in the eCRF in addition to the AE form:

- Trial product(s) involved
- Classification of medication error
- Whether the subject experienced any hypoglycaemic episode and/or AEs as a result of the medication error
- Suspected primary reason for the medication error

For definition of medication errors, see Section 12.1.4.

8.4.1.2 Adverse events requiring additional data collection

For some AEs additional data collection is required and specific event forms must be completed in the eCRF in addition to the AE form.

In case any of these events fulfil the criteria for a SAE, please report accordingly, see Section 12.

Injection site reaction

If an event of injection site reaction is observed the following additional information must be obtained if available on the injection site reaction form:

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

The investigator has to evaluate whether further actions are needed (e.g. extra visits, supervised injection, premature discontinuation of trial products, dermatologist consultation).

If any injection site reactions occur after Visit 31 they should still be recorded as AEs, but the additional data collection on the specific event form in the eCRF is not required.

8.4.2 Hypoglycaemic episodes

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

All plasma glucose (PG) values:

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

should be reported in the eDiary by the subject from Visit 2 to Visit 31 (FU1) and in the eCRF by the investigator from FU1 to FU2 according to the instructions below . However, only a reduced amount of information will be collected for hypoglycaemic episode as marked with an asterisk* in this section in the following periods:

- During the run-in period from Visit 2 to Visit 14
- One day after Visit 30 to FU2
- For subjects discontinuing trial products prematurely: One day after Visit 30A to Visit 30

In case a subject is not able to fill in the eDiary e.g. in case of a fatal event, then investigator will be allowed to report the hypoglycaemic episode in the eCRF.

Upon onset of a hypoglycaemic episode the subject is recommended to measure PG every 15 minutes until the SMPG value is >3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved in accordance to current guidelines.[34]

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

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

The eDiary will automatically link multiple values within 60 minutes to the same hypoglycaemic episode following above principles.

The record should include the following information:

- Start date and time of the hypoglycaemic episode*
- The PG level before treating the episode (if available) and any follow up measurements.*

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

- 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 subject is therefore to be questioned whether there are changes to symptoms for each low SMPG value within the 60 minutes period or until the subject has confirmed that the hypoglycaemic episode is symptomatic.

- 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 subject is therefore to be questioned whether he/she is able to self-treat for each low SMPG value within the 60 minutes period or until the subject respond that he/she is not able to self-treat.

- Date, time and dose of last bolus insulin administration prior to the episode
- Date, time and dose of last basal administration prior to the episode
- Date and time of last main meal (not including snacks) prior to the episode
- Whether the episode occurred in relation to physical activity
- Change in any concomitant illness
- Any sign of fever and/or other acute disease
- 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 the subject able to treat him/herself?" must be answered "No" for an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of PG to normal is considered sufficient evidence that the event was induced by a low PG concentration.[34]

Oral carbohydrates must 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 another 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 change, medication error (i.e. overdose, mix-up between products, incorrect use of device), miscalculation of dose of antidiabetic medication, 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[35] (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 eDiary data for correct reporting of SMPGs and hypoglycaemic episodes. In case of incomplete or incorrect data in the eDiary, 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.

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 start date, SMPG value and whether the subject was able to self-treat due to decreased validity of such data.[36, 37]

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 (SIF) must also be filled in the eCRF, see Section 12. One AE-form and SIF can cover several hypoglycaemic episode forms if the subject has not recovered between the episodes.

8.4.3 Eye examination

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

The evaluation must follow the categories:

- Normal
- Abnormal
  - Was the result clinically significant? (Yes/No)

Abnormal and clinically significant findings must be recorded as described in Section 8.4.

If a fundus photography/pharmacologically dilated fundoscopy has been performed within 90 days before Visit 2 and if the results are available at Visit 2, then the procedure does not need to be repeated. If performed before the subject consents to participate in the trial, it must also be stated in the subject's medical records that this procedure was not performed in relation to the trial.

The eye examination must be performed prior to administration of bolus trial insulin at Visit 14 (the results do not need to be available for randomisation). An eye examination performed within 14 days prior to randomisation is acceptable.

Eye examination obtained within 21 days prior to Visit 30 is acceptable if the result is available at the visit.

For subjects prematurely discontinued trial products: eye examination performed 21 days in advance of Visit 30A are acceptable if the results are available at the scheduled visits. However eye examination performed at Visit 14 cannot be accepted for the Visit 30A.

8.4.4 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 or write the interpretation of the ECG in the subject's medical records.

The evaluation must follow the categories:

- Normal
- Abnormal
  - Was the result clinically significant? (Yes/No)

Abnormal and clinically significant findings must be recorded as described in Section 8.4

If an ECG-12 lead has already been performed within 21 days before screening (Visit 1), and if the results are available at the screening visit, the procedure does not need to be repeated. If performed before the subject consents to participate in the trial it must also be stated in the subject's medical records that this procedure was not performed in relation to the trial.

ECGs performed 21 days in advance of Visit 14 and Visit 30 are acceptable if the results are available at the scheduled visits.

For subjects prematurely discontinued trial products: ECGs performed 21 days in advance of Visit 30A are acceptable if the results are available at the scheduled visits. However ECGs performed at Visit 14 cannot be accepted for the Visit 30A.

8.4.5 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 must be measured prior to the start of the meal test at Visit 14 and Visit 30.

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.

8.4.6 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

The results must be transcribed to the eCRF as:

- Normal
- Abnormal
  - Was the result clinically significant? (Yes/No)

Abnormal and clinically significant findings must be recorded as described in Section 8.4

8.4.7 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.

Abnormal and clinically significant findings must be recorded as described in Section 8.4

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.

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.

Samples will be coded in order to keep subject's identity anonymous.

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.

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 Section 8.2.4 and Section 12. Review of laboratory reports must be documented either on the documents and/or in the subject's medical record.

Only laboratory samples specified in the protocol must be sent to the central laboratory for analysis; if additional laboratory sampling is needed, e.g. to follow up on AEs, this must be done at a local laboratory.

Laboratory samples will be destroyed on an ongoing basis and no later than at finalisation of the clinical trial report.

8.5.1 Laboratory assessments for efficacy

Glucose metabolism

Plasma glucose will be measured during the meal test. See section 8.3.1.

FPG is measured in order to evaluate metabolic control. The subject must attend these visits fasting. For definition of fasting, see Section 8.1.5.

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

The level of 1,5-anhydroglucitol (GlycoMark) is measured in order to evaluate post prandial glucose excursions.

Blood samples will be drawn to determine the HbA_{1c} level in order to evaluate metabolic control.

Fasting C-peptide is measured at randomisation in order to reflect endogenous insulin secretion.

Lipids

Blood samples for lipids will be analysed to determine:

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

8.5.2 Laboratory assessments for safety

Biochemistry

Blood samples for biochemistry will be analysed to determine:

- ALT
- AST
- albumin
- alkaline phosphatase
- creatinine
- potassium
- sodium
- total bilirubin
- total protein
- eGFR(estimated glomerular filtration rate) at screening

eGFR will be calculated by the central laboratory based on the creatinine value using the CKD-EPI equation in order to access exclusion criteria 15 according to local label.[33]

Haematology

Blood samples for haematology will be analysed to determine:

- erythrocytes
- haematocrit
- haemoglobin
- leucocytes
- thrombocytes

Pregnancy testing

For females of childbearing potential (see section 8.2.7), 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 pregnancy is suspected or if 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.

8.6 Other assessments

8.6.1 Dietary training in simple carbohydrate counting

During the run-in period all subjects should have dietary training regarding simple carbohydrate counting (e.g. sessions with a diabetes educator, dietician or qualified site staff) to improve subject's carbohydrate awareness and understanding of their eating habits effect on their diabetes. 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 [34]

A 3x24-hour meal record should be filled in by the subject prior to the visits indicated in the flowchart (Section 2) in order to evaluate the subject's ability to count the carbohydrate content of the meal. The meal records will not be collected by the sponsor.

8.6.2 Training in the pen injector

The subjects must be trained in how to handle the pen injector when handed out the first time. Training must be repeated according to flowchart (Section 2) in order to ensure correct use of the pen injector. The following should be emphasised:

- Always use a new needle for each injection as this will prevent contamination and blocked needles
- Remember to prime the pen to ensure product 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.
- Always check that the correct insulin pen is used (bolus or basal) e.g. by colour coding and label. Use the pen differentiation guide as a reference.
- In-use time and storage conditions of pen-injectors (Section 9.3).

8.6.3 eDiary

At the run-in visit (Visit 2) the subjects will be provided with an eDiary device. The investigator must carefully instruct the subject in how to use the eDiary. All data entered in the eDiary is considered source data, as described in sections 8.3.2, 8.3.3 and 8.4.2.

The investigator should record the following administrative information in the eDiary/webportal:

- Subject ID
- 7-9-7-point profile scheduling and confirmation
- Visit confirmation
- Hypoglycaemic episode confirmation
- Premature discontinuation of trial products, if applicable

All data entered by the subject in the eDiary will be transferred electronically to the ePRO database. Investigator must review data for the subjects belonging to the site through the eDiary webportal. The review of hypoglycaemic episode must be documented in the webportal or in the subject's medical record, while review of remaining data must be documented in the subject's medical record. The review of data must be performed before or during each visit/phone contact.

Selected titration data (e.g. certain SMPGs and dose data) will only be used during the trial for central titration surveillance, to ensure compliance with the titration guideline (Appendix A), and will not be reported in the CTR. All data will be stored by Novo Nordisk (Section 24).

The eDiary should be collected by the investigator at FU1 (Visit 31).The subject should be provided with a paper diary for collecting hypoglycaemic episodes in the remaining follow up period. The paper diary will not be returned to site by the subject since FU2 is a phone contact. Consequently, source data for FU2 (Phone Contact 32) 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. In addition, subject compliance will be assessed by monitoring of drug accountability at specified visits, please refer to the flow chart (Section 2). The unused amount of investigational medicinal product (IMP) will be assessed against the dispensed amount and, in case of discrepancies, the subject must be asked to clarify.

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.

The investigator will at each weekly contact (visit or phone contact) assess the subject's compliance by evaluating the glycaemic control, adherence to treatment and the visit schedule and completion of the subject's eDiary including the SMPG profiles, dose and hypoglycaemia reporting.

9 Trial supplies

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

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

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

9.1 Trial products

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

Table 9–1 Trial products

Trial product	Strength	Dosage form	Route of administration	Container/ delivery device
Faster aspart, (IMP), test product	100 U/ml	Solution for injection	Subcutaneously	3 ml prefilled pen
Insulin aspart (NovoRapid®) (IMP), reference therapy				
Insulin degludec (IMP), test product	100 U/ml	Solution for injection	Subcutaneously	3 ml prefilled pen

The following non-investigational medicinal products (NIMP) will not be provided by Novo Nordisk. However, they will be reimbursed if required according to local regulations.

- Rapid acting insulin analogues (NovoRapid® or marketed formulations of insulin lispro or insulin glulisine) in the run-in period
- Metformin, tablets for oral use

The comparator and active drug are visually identical.

9.2 Labelling

The trial products will be labelled in accordance with Annex 13[38], local regulations and trial requirements.

Each trial site will be supplied with sufficient trial products for the trial on an on-going basis controlled by the IWRS. Trial product will be distributed to the trial 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). Additionally, the pen differentiation guide must be provided to subjects at randomisation (Visit 14). Direction for use and pen differentiation guide can be provided as needed at the following dispensing visits.

9.3 Storage

Table 9–2 Storage conditions

Trial product	Storage conditions (not-in-use)	In-use conditions	In-use time[a]
Faster aspart Insulin aspart (NovoRapid®)	Store in refrigerator (2°C – 8°C) Do not freeze Protect from light	Store below 30°C Do not refrigerate Do not freeze Protect from light	Use within 4 weeks
Insulin degludec	Store in refrigerator (2°C – 8°C) Do not freeze Protect from light	Do not store above 30°C Protect from light Can be stored in refrigerator (2°C – 8°C) Do not freeze	Use within 8 weeks

[a] In-use time starts when first dose is taken

The investigator must ensure that trial product is kept under proper storage conditions and 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). Additional details regarding handling of temperature deviations can be found in the TMM.

Trial product that has been stored improperly must not be dispensed to any subject before it has been evaluated and approved for further use by Novo Nordisk. The investigator must take appropriate action to ensure correct storage.

9.4 Drug accountability and destruction

Drug accountability of all trial products received at site is the responsibility of the investigator.

Returned trial product (used/partly used and/or unused), expired or damaged trial product can be stored at room temperature and must be stored separately from non-allocated trial product.

Non-allocated trial products (expired, damaged and available) must be accounted as unused at the latest at closure of the trial site.

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

Destruction of trial products can be performed on an on-going basis and will be done according to local procedures after accountability is finalised and reconciled by the monitor in the IWRS. Destruction of products must be documented in the IWRS.

9.5 Auxiliary supplies

The following will be provided by Novo Nordisk:

- Direction for use for the prefilled pens
- Novo Nordisk needles
- Standardised liquid meal (for the meal test)
- MyGlucoHealth Wireless Meter (CE approved) and strips, lancets and control solution for BG meters
- eDiary

Only needles provided by Novo Nordisk must be used for administration of trial product.

The BG meter has not been approved in Argentina, Russia, Serbia and Ukraine and will be labelled for investigational use only. The BG meter has been selected in order to have automatic transfer of SMPG data to the eDiary and thereby increase the accuracy of SMPG values. It is expected that the better accuracy in SMPG data will facilitate an improvement in the insulin titration efforts during the trial.

Please refer to the TMM for further auxiliary details.

10 Interactive voice/web response system

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

IWRS is used for:

- Medication arrival
- Screening
- Screening failure
- Run-in dispensing
- Run-in failure
- Randomisation
- Dispensing
- Dispensing Verification (when barcode scanner is used)
- Treatment discontinuation
- Completion
- Code break
- Drug accountability
- Data change

IWRS user manuals will be provided to each trial site.

11 Randomisation procedure and breaking of blinded codes

At randomisation (Visit 14) the subject will be randomised to either faster aspart or NovoRapid®, both in combination with once daily insulin degludec with or without metformin.

The randomisation will be carried out in a 1:1 manner to the 2 different treatment possibilities described below using the IWRS:

- Faster aspart and insulin degludec with or without metformin
- NovoRapid® and insulin degludec with or without metformin

The investigator, subject and sponsor will be blinded to the bolus treatment.

11.1 Breaking of blinded codes

The IWRS 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 IWRS, 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 IWRS is not accessible at the time of code break the IWRS helpdesk should be contacted. Contact details are listed in Attachment I.

If the code has been broken by investigator, the subject must discontinue treatment with trial product and a treatment discontinuation session must be completed in IWRS.

12 Adverse events, technical complaints and pregnancies

12.1 Definitions

12.1.1 Adverse event

An adverse event (AE) is any untoward medical occurrence in a subject administered a medicinal product, and which does not necessarily have a causal relationship with this treatment.

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

An AE includes:

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

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

- Pre-existing conditions, including those found as a result of screening or other trial procedures performed before exposure to trial product (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 8.4.2.

The following three definitions are used when assessing an AE:

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

  Relationship between an AE and the relevant trial product(s):
  - **Probable** - Good reason and sufficient documentation to assume a causal relationship.
  - **Possible** - A causal relationship is conceivable and cannot be dismissed.
  - **Unlikely** - The event is most likely related to aetiology other than the trial product.

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

12.1.2 Serious adverse event

A serious adverse event (SAE) is an experience that at any dose results in any of the following:

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

a. The term "life threatening" in the definition of SAE refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe.

b. The term "hospitalisation" is used when a subject:

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

[c.] A substantial disruption of a subject's ability to conduct normal life functions (e.g. following the event or clinical investigation the subject has significant, persistent or permanent change, impairment, damage or disruption in his/her body function or structure, physical activity and/or quality of life).

[d.] For example intensive treatment in an emergency room or at home of allergic bronchospasm, blood dyscrasia or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

The following AEs must always be reported as an SAE using the important medical event criterion if no other seriousness criteria are applicable:

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

12.1.3 Non-serious adverse event

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

12.1.4 Medication errors

A medication error concerning trial products is defined as:

- Administration of wrong drug.

  Note: Use of wrong dispensing unit number (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), misuse or abuse of trial product.
- Accidental administration of a lower or higher dose than intended. The administered dose must deviate from the intended dose to an extent where clinical consequences for the trial subject were likely to happen as judged by the investigator, although they did not necessarily occur.

Medication errors must be reported on an AE form and a specific event form, see Section 8.4.1.1.

12.1.5 Adverse events requiring additional data collection

AEs requiring additional data collection are AEs where the additional data will benefit the evaluation of the safety of the trial product.

In this trial the following AEs require the completion of specific event forms in the eCRF

- Injection site reaction

For details, see Section 8.4.1.2.

12.1.6 Technical complaints

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)
- All packaging material including labelling
- 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 (FU2). For subjects discontinuing trial products prematurely this also includes events after the post-treatment follow-up period until the last contact (Visit 30). 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.

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.

For all non-serious AEs, the applicable forms should be signed when the event is resolved or at the end of the trial at the latest.

Timelines for initial reporting of AEs:

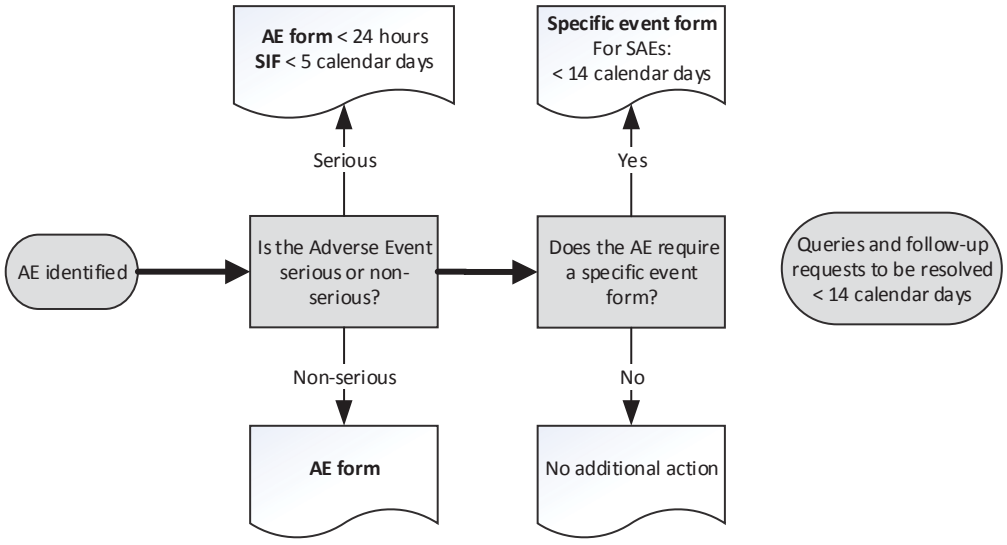
The investigator must complete the following forms in the eCRF within the specified timelines:

- **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.

  For SAEs requiring reporting on a specific event form: In addition to the above the specific event form within **14 calendar days** from the investigator's first knowledge of the AE.

If the eCRF is unavailable, the concerned AE information must be reported on a paper AE form 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 form into the eCRF.

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



Timelines are for the completion of forms from the time of investigator's awareness.
AEs requiring specific event forms are descibed in Section 12.1.4 and 12.1.5.

AE: Adverse Event SIF: Safety Information form

Figure 12–1 Reporting of AEs

Novo Nordisk assessment of AE expectedness:

Novo Nordisk assessment of expectedness is performed according to the following reference documents:

- Faster aspart IB[22] current version and any updates thereto.
- Insulin degludec Company Core Data Sheet current version and any updates thereto.
- NovoRapid®, Company Core Data Sheet current version and any updates thereto.

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.[1] 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 IRBs/IECs of trial product-related SUSARs in accordance with local requirement and ICH GCP[1], unless locally this is an obligation of the investigator.

Novo Nordisk and non-Novo Nordisk products used as concomitant medication or non-investigational medicinal product:

If an AE is considered to have a causal relationship with a non-Novo Nordisk and Novo Nordisk marketed product used as NIMP (NovoRapid® in run-in period) and metformin or concomitant medication in the trial, it is important that the suspected relationship is reported to Novo Nordisk, e.g. in the alternative aetiology section on the safety information form. Novo Nordisk may need to report this AE to relevant regulatory authorities.

12.3 Follow-up of adverse events

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

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

- **SAEs:** All SAEs must be followed until the outcome of the event is "recovered/resolved", "recovered/resolved with sequelae" or "fatal", and until all queries have been resolved. Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome "recovering/resolving" or "not recovered/not resolved". Cases can be closed with the outcome of "recovering/resolving" when the subject has completed the follow-up period and is expected by the investigator to recover.

  The SAE follow-up information should only include new (e.g. corrections or additional) information and must be reported **within 24 hours** of the investigator's first knowledge of the

information. This is also the case for previously non-serious AEs which subsequently become SAEs.

- **Non-serious AEs:** Non-serious AEs must be followed until the outcome of the event is "recovering/resolving", "recovered/resolved" or "recovered/resolved with sequelae" or until the end of the follow-up period stated in the protocol, whichever comes first, and until all queries related to these AEs have been resolved. Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome "recovering/resolving" or "not recovered/not resolved". Cases can be closed with the outcome of "recovering/resolving" when the subject has completed the follow-up period and is expected by the investigator to recover.

The investigator must ensure that the recording of 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.

SAEs after end of trial: If the investigator becomes aware of an SAE with a suspected causal relationship to the IMP occurring to a subject after the subject has ended the trial, the investigator should report this SAE within the same timelines as for SAEs during the trial.

12.4 Technical complaints and technical complaint samples

12.4.1 Reporting of technical complaints

For Novo Nordisk Products

All technical complaints on any of the following products:

- Faster aspart, 100 U/mL solution for subcutaneous injection, 3 mL PDS290 pen injector (blinded)
- NovoRapid®, 100 U/mL solution for subcutaneous injection, 3 mL PDS290 pen injector (blinded)
- Insulin degludec, 100U/mL solution for subcutaneous 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 and/or SAEs.

Technical complaints must be reported on a separate technical complaint form:

- One technical complaint form must be completed for each affected DUN
- If DUN is not available, a technical complaint form for each batch, code or lot number 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.

Only technical complaints related to AEs will be reported in the clinical trial report.

For BG meters, strips, lancets and control solution

All Technical Complaints on BG meter, strips, lancets and control solution should be reported directly to the supplier using the supplier reporting form within the following timelines:

- Technical complaint assessed as related or potential related to an SAE **within 24 hours**
- All other technical complaints **within 5 calendar days**

Contact details (e-mail and address) are provided in Attachment I to the protocol.

12.4.2 Collection, storage and shipment of technical complaint samples

For Novo Nordisk Products

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 copy of the technical complaint form must be included in the shipment of the sample. If several samples are returned in one shipment, the individual sample and the corresponding technical complaint form must be clearly separated.

The investigator must ensure that the technical complaint sample contains the batch, code or lot number and, if available, the DUN. All parts of the DUN should be returned.

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.

For BG meters strips, lancets and control solution

The investigator must collect the technical complaint sample and send it to the supplier using the contact details provided in Attachment I.

12.5 Pregnancies in female subjects

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:

- AE form[a] **within 14 calendar days** of the investigator's first knowledge of the initial or follow-up information to the non-serious AE.

SAEs:

- AE form[a] **within 24 hours** of the investigator's first knowledge of the SAE.
- 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.

[a] 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. If the AE occurred in the foetus or newborn infant, the AE can only be reported on paper AE and safety information form.

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 8.4.2). 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 aspart IB[22], Insulin degludec IB[24] and for NovoRapid®, please refer to the current versions of the SmPC[19] or U.S. Novolog® Label Information.[20]

12.7 Committees related to safety

12.7.1 Novo Nordisk safety committee

Novo Nordisk will constitute an internal faster aspart safety committee to perform ongoing safety surveillance. The faster 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 case report forms (CRFs):

- Pregnancy forms

The following will be provided as paper CRFs to be used when access to the eCRF is revoked or if the eCRF is unavailable:

- AE forms
- Safety information forms
- Technical complaint forms (also to be used to report complaints that are not subject related (e.g. discovered at trial site before allocation)

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.

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

14 Monitoring procedures

Monitoring will be conducted using a risk based approach including risk assessment, monitoring plans, centralised monitoring and visits to trial sites. 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 and to monitor drug accountability. The first monitoring visit will be performed as soon as possible after first patient first visit at the trial site and no later than 4 weeks after. The monitoring visit intervals will depend on the outcome of the centralised monitoring of the eCRFs (remote assessment of data by Novo Nordisk), the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP, but will not exceed 12 weeks until LPLV at the trial site.

The monitor must be given direct access to all 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. Data entered by the subject in the eDiary device will be recorded directly in the device. All data entered in the eDiary device will be automatically transferred to a 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 database is regarded as source data. For data entered by the investigator through the webportal the source documentation can be the medical records but if entered directly into the webportal, the database is regarded as 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.

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.
- Screen failure date and reason
- Date of visit
- Demography (date of birth, sex and race (according to local regulation))
- Eligibility criteria
- SAE

Monitors will review the subject's medical records and other source data to ensure consistency and/or identify omissions compared to the eCRF. If discrepancies are found, the investigator must be questioned about these.

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 (CRO).

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

Data from central laboratories will be transferred electronically. 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 may be written in addition to the protocol, including a more technical and detailed elaboration of the statistical analyses. The statistical analysis plan will be finalised before database lock.

General considerations

In general, for endpoints evaluated as a change from baseline and/or where a baseline adjustment is made, baseline is defined as information collected at randomisation (Visit 14). In case a measurement is not available at randomisation, the most recent measurement prior to randomisation will be used as baseline.

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

- In-trial: The observation period from date of randomisation and until last trial-related subject-site contact. The in-trial observation period includes data collected after treatment discontinuation.
- On-treatment: The observation period from date of first dose of randomised NovoRapid®/faster aspart and to 7 days after the first occurrence of:
    - The day of last dose of randomised NovoRapid®/faster aspart
    - The day before initiation of ancillary treatment

All efficacy endpoints will be summarised and analysed using the full analysis set (FAS), unless otherwise stated. Safety endpoints will be summarised using the safety analysis set and analysed using the FAS. The FAS is defined in section 17.2.

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

Data collected before randomisation (Visit 14) will only be summarised descriptively.

The primary objective of the trial is to confirm the effect of treatment with faster aspart compared to NovoRapid®, both in combination with insulin degludec with or without metformin in adults with T2DM in terms of glycaemic control, using a non-inferiority approach.

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

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

The steps in the hierarchical testing procedure are as follows:

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

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

Step 3: HbA_{1c} superiority of faster aspart versus NovoRapid®

Step 4: 1,5-anhydroglucitol superiority of faster aspart versus NovoRapid®

Estimands

Primary estimand

The primary estimand is defined as the treatment difference between subjects randomised to faster aspart and NovoRapid® both in combination with insulin degludec with or without metformin, in adults with T2DM not optimally controlled with a basal-bolus regimen assessed by change from baseline in HbA_{1c} 16 weeks after randomisation for all randomised subjects regardless of treatment discontinuation or use of ancillary treatment.

The primary estimand assesses the expected benefit a future population with T2DM can achieve if prescribed to faster aspart as compared to NovoRapid®. 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 treatment reflects clinical practice. Thereby the primary estimand provides a treatment difference for clinicians concerning the glycaemic effect of faster aspart compared to NovoRapid® in the day to day life in subjects with T2DM in an adult population.

Secondary estimand

A secondary estimand is defined as the treatment difference in change from baseline in HbA_{1c} 16 weeks after randomisation between treatment with faster aspart and treatment with NovoRapid® both in combination with insulin degludec with or without metformin in adult subjects with T2DM

not optimally controlled with a basal-bolus regimen if all subjects had adhered to randomised treatment and did not receive ancillary treatment.

The condition 'adhered to randomised treatment and did not receive ancillary treatment' should be interpreted as the exclusion of information collected after initiation of antidiabetic treatment that can mask or exaggerate the effect of the initially randomised treatment. Only data collected prior to discontinuation of trial product or initiation of ancillary treatment is used to draw inference. This avoids confounding effects of ancillary treatment.

The two estimands will be repeated for the confirmatory endpoints

- Change from baseline in 1-hour PPG increment (meal test) 16 weeks after randomisation
- Change from baseline in 1,5-anhydroglucitol 16 weeks after randomisation

17.1 Sample size calculation

The sample size is determined to ensure a sufficient power for step 1 and step 2 in the hierarchical testing procedure for the primary estimand presented in section 17. The power for step 3 and 4 in the hierarchical testing procedure will also be presented. The sample size is determined using a non-inferiority limit of 0.4% in step 1, which was chosen as described in section 5.2.1. The statistical evaluation will be done as described in section 17.3.

In previous confirmatory trials where faster aspart has been investigated, the completion rates have been high. Therefore it will be expected that treatment discontinuation might be as low as 10% where trial discontinuation constitutes half of these and with similar withdrawal reasons in the treatment arms.

Power for the non-inferiority step (Step 1) is based on a t-statistic under the assumption of a one-sided test of size 2.5% for the FAS. A mean treatment difference of -0.1% for the comparison between faster aspart and NovoRapid® in favour of faster aspart is expected. As trials in this population where data from treatment withdrawn subjects is retrieved is limited, a conservative estimate of the standard deviation (SD) in change from baseline in HbA_{1c} of 0.8% was chosen. The power for superiority in step 3 will be calculated using the same assumptions as for step 1 but without the non-inferiority margin.

For determination of power in step 2 in the hierarchical testing, where change from baseline in 1-hour PPG increment 16 weeks after randomisation is compared between faster aspart and NovoRapid® a t-statistic with a two-sided test of size 5% is used, where the treatment difference is expected to be at least 0.6 mmol/L [11 mg/dL]. The SD=3.5 mmol/L [63 mg/dL] in change from baseline in 1-hour PPG increments 16 weeks after randomisation based on laboratory analysed PG in a standardised meal test will be considered reasonable based on trials NN1218-3852 and NN1218-3853.

The power in step 4, where superiority of faster aspart over NovoRapid® in change from baseline in 1,5-anhydroglucitol 16 weeks after randomisation is tested a t-statistic with a two-sided test of size 5% is used. The mean treatment difference is expected to be at least 0.2 µg/mL and an SD of 3.5µg/mL will be used based on trials NN1218-3852 and NN1218-3853.

The power calculations are done using proc power in SAS 9.4. Please refer to Table 17–1 for assumptions for the sample size calculation.

Table 17–1 Specifications assumed for sample size calculations

	Statistical test	Significance level	Analysis population	Non-inferiority margin	SD	Mean difference	Randomisation scheme
Step 1	2-group t-test	One-sided 2.5 %	FAS	0.4 % (absolute)	0.8 %	-0.1 %	1:1
Step 2	2-group t-test	Two-sided 5.0%	FAS	NA	3.5 mmol/L	0.6 mmol/L	1:1
Step 3	2-group t-test	Two-sided 5.0%	FAS	NA	0.8 %	-0.1 %	1:1
Step 4	2-group t-test	Two-sided 5.0%	FAS	NA	3.5 µg/mL	0.2 µg/mL	1:1

In Table 17–2 the sensitivity of the sample size to the power shown for three different sizes of FAS. Three different choices of the mean difference are used to calculate the power in step 2.

Table 17–2 Sensitivity of sample size to power

N total	N per arm	Step 1			Step 2			Step 3			Step 4		
FAS	FAS	Mean diff (%)	SD (%)	Power (%)	Mean diff (mmol/L)	SD (mmol/L)	Power (%)	Mean diff (%)	SD (%)	Power (%)	Mean diff (µg/mL)	SD (µg/mL)	Power (%)
		-0.1	0.8	>99.9	0.5	3.5	58.1	-0.1	0.8	47.4	0.2	3.5	13.9
920	460	-0.1	0.8	>99.9	0.6	3.5	73.8	-0.1	0.8	47.4	0.2	3.5	13.9
		-0.1	0.8	>99.9	0.7	3.5	85.8	-0.1	0.8	47.4	0.2	3.5	13.9
		-0.1	0.8	>99.9	0.5	3.5	64.7	-0.1	0.8	53.4	0.2	3.5	15.5
1072	**536**	**-0.1**	**0.8**	**>99.9**	**0.6**	**3.5**	**80.1**	**-0.1**	**0.8**	**53.4**	**0.2**	**3.5**	**15.5**
		-0.1	0.8	>99.9	0.7	3.5	90.5	-0.1	0.8	53.4	0.2	3.5	15.5
		-0.1	0.8	>99.9	0.5	3.5	70.4	-0.1	0.8	58.9	0.2	3.5	17.0
1224	612	-0.1	0.8	>99.9	0.6	3.5	85.0	-0.1	0.8	58.9	0.2	3.5	17.0
		-0.1	0.8	>99.9	0.7	3.5	93.8	-0.1	0.8	58.9	0.2	3.5	17.0

In conclusion, 1072 subjects in the FAS (536 subjects per group) will ensure a marginal power of >99.9% to show non-inferiority in step 1, given that the actual treatment difference is -0.1%, and a marginal power of 80.1% to show superiority in step 2, given that the actual treatment difference is 0.6 mmol/L.

Assuming a screening failure rate of 30% and run-in failure rate of 15%, 1803 subjects should be screened for inclusion in the trial.

17.2 Definition of analysis sets

The following analysis sets are defined in accordance with the ICH-E9 guidance [39].

- Full Analysis Set (FAS) includes all randomised subjects. In exceptional cases, randomised subjects may be excluded from the FAS. In such cases, the reason for exclusion will be justified and documented. Subjects in the FAS will contribute to the evaluation "as randomised"
- Per Protocol (PP) Analysis Set includes all subjects in the FAS, 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"
- Safety Analysis Set includes all subjects receiving at least one dose of randomised treatment. Subjects in the safety analysis set will contribute to the evaluation "as treated".

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

Before data are released for statistical review, a blinded review of all data will take place to identify serious non-adherence to the protocol that may potentially affect the results. Furthermore, extreme values and outliers will be identified by the statistician during programming and data review, according to ICH-E9.[39] This will be performed by using a fake randomisation.

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

17.3 Primary endpoint

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

Primary analysis:

1) The primary estimand will be addressed by the below primary analysis on all subjects included in the FAS and using the in-trial observation period. Note that if subjects withdraw

consent to contribute additional information or are completely lost to follow-up, missing data will occur. The primary analysis will be implemented as a statistical model using multiple imputations where the subjects without any available HbA_{1c} measurements at scheduled visits will have their HbA_{1c} value imputed from the available information from the treatment group the subject has been randomised to. Note that this resembles in essence a mixed model of repeated measurements analysis. Subjects without any 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 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 metformin use at baseline (Yes/No) as factors and baseline HbA_{1c} as covariate is fitted to the change in HbA_{1c} from baseline to week 4 for each treatment group separately. The estimated parameters, and their variances, from these models are used to impute missing values at week 4 for subjects in each treatment group, based on region, metformin use at baseline (Yes/No) and baseline $HbA_{1c.}$

- In the third step, for each of the 100 copies of the dataset, missing values at week 8 are imputed in the same way as for week 4. The imputations are based on an analysis of variance model with region and metformin use at baseline (Yes/No) as factors and baseline HbA_{1c} and change from baseline in HbA_{1c} at week 4 as covariates.

- This stepwise procedure is then repeated sequentially for week 12 and 16.

- For each of the complete data sets, the change from baseline to week 16 is analysed using an analysis of variance model with treatment, region and metformin use at baseline (Yes/No) as factors, and baseline HbA_{1c} 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:

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

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

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

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

Non-inferiority of faster aspart 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

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

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

Note that as the anticipated number of subjects discontinuing treatment, but not trial is low, multiple imputations based on such subjects is not expected to be suitable.

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

Sensitivity analysis for the primary analysis addressing the primary estimand

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

2) First the primary analysis in 1) will be repeated, but excluding all factors except from treatment in the model. This analysis will explore the influence of the different factors.
3) The primary analysis approach chosen for this trial relies on the assumption that missing data is missing at random (MAR). This assumption implies that the HbA_{1c} for subjects leaving the trial, after their withdrawal, develops in a similar way as the HbA_{1c} for similar subjects that remain in the trial (not necessarily on treatment) and had similar development of HbA_{1c} before withdrawal. The MAR assumption may be questionable for subjects withdrawing at own will. Therefore the statistical models using multiple imputation will be repeated with the following alteration:

a) Imputations will be done from the treatment arm that the subject was randomised to and a value of 0.4% (non-inferiority margin) is added to the change from baseline in HbA_{1c} at week 16 for subjects randomised to faster aspart who withdrew from the trial.[40]

b) Imputations will be done from the comparator arm (NovoRapid®). This will serve as a supplementary sensitivity analysis for the superiority analysis. It does not rely on the MAR assumption, but assumes that all subjects who withdraw from the trial in the faster aspart arm shift to NovoRapid®. The imputation will be done conditional on observed information for subjects that withdraw from the faster aspart arm such that the treatment effect diminishes gradually after trial discontinuation (copy reference/conditional imputation). The analysis will use data from the in-trial observation period.

c) Imputation will be done from the comparator arm (NovoRapid®). This will serve as a supplementary sensitivity analysis for the superiority analysis. It does not rely on the MAR assumption, but it is assumed that all subjects who withdraw from the trial in the faster aspart arm respond at week 16 as if they have been treated with NovoRapid® for the entire trial. That is, all collected post-randomisation data for subjects who withdraw from the trial in the faster aspart arm will be set to missing. The analysis will use data from the in-trial observation period.

Analyses addressing the secondary estimand

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

4) The secondary estimand will be analysed using the same statistical model using multiple imputations as the primary analysis in 1) except using the on-treatment observation period.
5) A tipping point analysis based on a statistical model using multiple imputation model similar to 1), using the on-treatment observation period, will be made. In this analysis observations for subjects that discontinue randomised treatment are imputed based on the treatment arm they were randomised to and subjects discontinuing treatment in the faster aspart group are given a penalty. This is done to investigate the robustness of the conclusion in the primary analysis with respect to the MAR assumption and mimics a scenario where the HbA_{1c} of the subjects discontinuing treatment in the faster aspart groups evolve less favourably than predicted. As a first step imputations will be done without penalty assuming MAR in the treatment group. Second, the imputed values for week 16 in the faster aspart group will be added a penalty. This is done repeatedly, gradually increasing the penalty until the conclusion from the non-inferiority analysis no longer holds. This will serve as a sensitivity analysis for the non-inferiority analysis and the specific value of the penalty that changes the conclusion will be used to evaluate the robustness of the conclusion of the non-inferiority analysis.

6) A tipping point analysis based on a statistical model using multiple imputation, similar to 5) but with the modification that subjects discontinuing treatment due to non-eligibility (Subjects discontinuing randomised treatment prematurely due to criteria 1, 2, 3, and 4, which are defined in section 6.6) in the faster aspart group will not have a penalty added. These analyses are motivated by the fact that data from subjects prematurely discontinuing randomised treatment due to non-eligibility can reasonably be assumed to be missing completely at random.
7) The same statistical model using multiple imputations as the analysis in 4), but using the PP analysis set and analysed using the on-treatment observation period. This analysis will investigate the situation that subjects might have deviated from the inclusion and exclusion criteria and will serve as sensitivity analysis for the non-inferiority analysis.

17.4 Secondary endpoints

17.4.1 Confirmatory secondary endpoints

If the effect of treatment with faster aspart can be confirmed in the primary analysis, the trial also aims to confirm effect of treatment with faster aspart for a number of secondary confirmatory endpoints using a hierarchical (fixed sequence) testing procedure as described in section 17 (General consideration). 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 aspart.

The confirmatory secondary endpoints are:

- Change from baseline in 1-hour PPG increment 16 weeks after randomisation (meal test)
- Change from baseline in 1,5-anhydroglucitol 16 weeks after randomisation

The steps in the hierarchical testing procedure are as follows:

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

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

Step 3: HbA_{1c} superiority of faster aspart versus NovoRapid®

Step 4: 1,5-anhydroglucitol superiority of faster aspart versus NovoRapid®

The primary estimand for the primary endpoint will be repeated for the confirmatory secondary endpoints, change from baseline in 1-hour PPG increment (meal test) and change from baseline in 1,5-anhydroglucitol 16 weeks after randomisation. The analyses related to these estimands are

defined below and will be used for the decisions to continue or not, throughout the hierarchical testing procedure. These analyses will be based on the FAS and use the in-trial observation period.

As sensitivity analysis the secondary analysis 4) will also be repeated for the confirmatory secondary endpoints. The analyses will be based on the FAS and using the on-treatment observation period.

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

As the second step of the hierarchical testing procedure changes from baseline in 1-hour PPG increment (meal test) 16 weeks after randomisation will be tested for superiority of faster aspart compared to NovoRapid®.

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

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

- An analysis of variance model with region and metformin use at baseline (Yes/No) as factors and baseline 1-hour PPG increment as covariate is fitted to the change from baseline in 1-hour PPG increment at week 16 for the NovoRapid® group only. The estimated parameters, and the variance, from this model are used to impute missing values using stochastic simulation at week 16 for subjects in both treatment groups in order to generate 100 complete datasets.
- For each of the complete data sets, the change from baseline to week 16 is analysed using an analysis of variance model with treatment, region and metformin use at baseline (Yes/No) as factors, and baseline 1-hour PPG increment as covariate.
- The estimates and standard deviations for the 100 data sets are pooled to one estimate and associated standard deviation using Rubins formula. From this, the pooled estimates and 95% confidence interval for the treatment difference is calculated.

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

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

Step 3 in the hierarchical testing procedure is to confirm superiority of change from baseline HbA_{1c} 16 weeks after randomisation of the effect of treatment with faster aspart compared to NovoRapid®. Superiority will be based on the same 95% CI that was used for addressing the primary analysis. Superiority will be confirmed if the upper boundary of the two-sided 95% confidence interval of the mean treatment difference (faster aspart minus NovoRapid®) is below 0%.

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

Step 4 in the hierarchical testing procedure is to confirm superiority of change from baseline 1,5-anhydroglucitol 16 weeks after randomisation of the effect of treatment with faster aspart compared to NovoRapid®. The endpoint will be analysed based on all planned post baseline measurements until or at 16 weeks after randomisation using a model similar to the primary analysis 1), but with baseline 1,5-anhydroglucitol as covariate. Superiority will be confirmed if the upper boundary of the two-sided 95% confidence interval of the mean treatment difference (faster aspart minus NovoRapid®) is below 0.

17.4.2 Supportive secondary endpoints

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 the safety analysis set and will therefore only use the on-treatment observation period.

Change from baseline in FPG 16 weeks after randomisation

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

If a subject achieves HbA_{1c} target 16 weeks after randomisation

HbA_{1c} < 7.0%

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

This responder endpoint will be analysed based on a logistic regression model using treatment, region and metformin use at baseline (Yes/No) as factors, and baseline HbA_{1c} as covariate. In analysis of the in-trial observation period subjects without an HbA_{1c} measurement at week 16 will be treated as non-responders. In the analysis using the on-treatment observation period both subjects who discontinue randomised treatment or withdraw from trial is included as non-responders.

HbA_{1c} < 7.0% without severe hypoglycaemia

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

This responder endpoint will be analysed based on a logistic regression model using treatment, region and metformin use at baseline (Yes/No) as factors and baseline HbA_{1c} as covariate. In the analysis of the in-trial observation period subjects without an HbA_{1c} measurement at week 16 will be treated as non-responders. In the analysis using the on-treatment observation period both subjects who discontinue randomised treatment or withdraw from trial will be included as non-responders.

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

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

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

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

In general, analyses will be based on the entire 7-9-7-point SMPG profile except for the analyses of nocturnal endpoints where information in the 9-point SMPG profile will be utilised.

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

Pre-prandial PG and PPG will be recorded by the subjects as part of the 7-9-7-point SMPG profile prior to three defined visits. Individual mean mealtime PPG (post-breakfast, post-lunch, post-main evening meal) will be derived from the three profiles. Overall mean PPG will be derived from the individual derived mealtime PPG values.

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

meal. Mean 1 hour PPG increments over all meals will be derived as the mean of all corresponding mean meal increments.

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

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

  Change from baseline in the mean of the 7-9-7-point SMPG profile 16 weeks after randomisation will be analysed based on all planned post baseline measurements until or at 16 weeks after randomisation using a model similar to 1) except with the corresponding baseline value as covariate.

- Change from baseline in PPG and PPG increment (mean, breakfast, lunch and main evening meal)

  Change from baseline in PPG and PPG increment endpoints 16 weeks after randomisation for mean over all three meals and the individual meals will be analysed separately based on all planned post baseline measurements until or at 16 weeks after randomisation using a model similar to 1) except with the corresponding baseline value as covariate.

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

  The fluctuation in the 7-9-7-point SMPG 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. It will be calculated using the linear trapezoidal technique.

  Fluctuation in the 7-9-7-point SMPG profile will be logarithmically transformed and analysed based on all planned post baseline measurements until or at 16 weeks after randomisation using a model similar to 1) except with the corresponding log-transformed baseline value as covariate. Estimated treatment means and the estimated treatment differences with corresponding 95% CI will be back-transformed to the original scale, resulting in estimated geometric means, a treatment ration and a 95% CI for the treatment ratio.

- Change from baseline in nocturnal SMPG measurements

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

Change from baseline in nocturnal SMPG measurements 16 weeks after randomisation will be analysed based on all planned post baseline measurements until or at 16 weeks after randomisation using a model similar to 1) except with the corresponding baseline values as covariate.

If a subject achieves PPG target (based on overall mean of daily PPG measurements in 7-9-7-point SMPG profile) 16 weeks after randomisation:

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

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

This responder endpoint will be analysed based on a logistic regression model using treatment, region and metformin use at baseline (Yes/No) as factors, and baseline overall 1-hour mean PPG as covariate. In analysis of the in-trial observation period subjects without an overall mean 1 hour PPG at week 16 will be treated as non-responder. In the on- treatment observation period analysis both subjects who discontinue randomised treatment or withdraw from trial will be included as non-responders.

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

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

This responder endpoint will be analysed based on a logistic regression model using treatment, region and metformin use at baseline (Yes/No) as factors, and baseline mean 1-hour PPG as covariate. In analysis of the in-trial observation period subjects without an overall mean 1 hour PPG at week 16 will be treated as non-responders. In the on- treatment observation period analysis both subjects who discontinue randomised treatment or withdraw from trial will be included as non-responders.

Insulin dose (Units/day and Units/kg/day; total basal, total bolus, total daily insulin dose and individual meal insulin dose) 16 weeks after randomisation

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

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

Change from baseline in lipid endpoints (total cholesterol, HDL cholesterol, LDL cholesterol) will be logarithmically transformed and analysed separately based on all planned post baseline measurements until or at 16 weeks after randomisation using a model similar to 1) except with the corresponding log-transformed baseline 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.

17.4.2.2 Safety endpoints

In terms of AEs, as a minimum, SAEs will be tabulated separately 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

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

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

TEAEs are summarised descriptively, whereas AEs 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 technical complaint, premature treatment discontinuation due to AEs, AEs leading to withdrawal from trial and outcome.

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

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

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

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

Number of treatment emergent injection site reactions

Treatment emergent injection site reactions occurring during the trial will be summarised and listed.

Classification of Hypoglycaemia

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

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

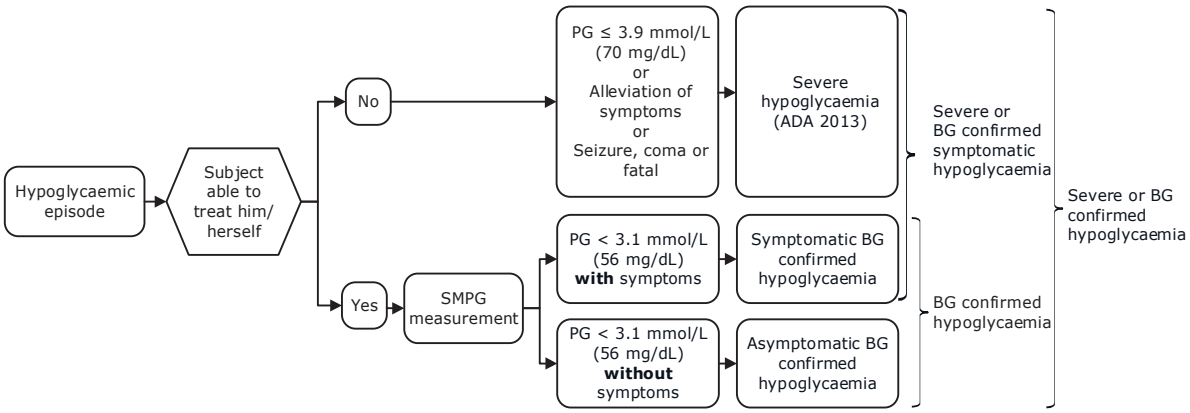
Hypoglycaemic episodes are classified according to the Novo Nordisk classification of hypoglycaemia (see Figure 17–1) and the ADA classification of hypoglycaemia (see Figure 17–2).

Novo Nordisk classification of hypoglycaemia

In normal physiology, symptoms of hypoglycaemia occur below a PG level of 3.1 mmol/L (56 mg/dL).[41] Therefore, Novo Nordisk has included hypoglycaemia with PG levels below this cut-off point in the definition of BG confirmed hypoglycaemia.

Novo Nordisk uses the following classification (see Figure 17–1) in addition to the ADA classification:

- Severe hypoglycaemia according to the ADA classification.[34]
- Severe or BG confirmed hypoglycaemia: An episode that is severe according to the ADA classification[34] or BG confirmed by a PG value <3.1 mmol/L (56 mg/dL) **with** or **without** symptoms consistent with hypoglycaemia.



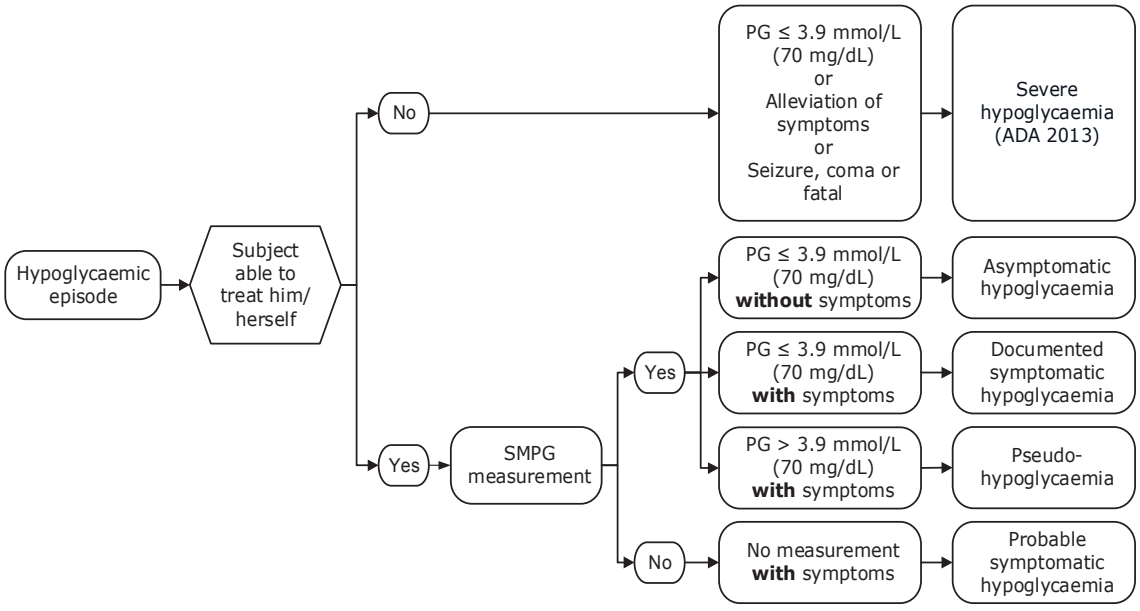
Note: Glucose measurements are performed with capillary blood calibrated to plasma equivalent glucose values

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

Figure 17–1 Novo Nordisk classification of hypoglycaemia

ADA classification[34] of hypoglycaemia

- 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 PG to normal is considered sufficient evidence that the event was induced by a low PG concentration.
- Asymptomatic hypoglycaemia: An episode not accompanied by typical symptoms of hypoglycaemia, but with a measured PG concentration ≤ 3.9 mmol/L (70 mg/dL).
- Documented symptomatic hypoglycaemia: An episode during which typical symptoms of hypoglycaemia are accompanied by a measured PG concentration ≤ 3.9 mmol/L (70 mg/dL).
- Pseudo-hypoglycaemia: An episode during which the person with diabetes reports any of the typical symptoms of hypoglycaemia with a measured PG concentration > 3.9 mmol/L (70 mg/dL) but approaching that level.
- Probable symptomatic hypoglycaemia: An episode during which symptoms of hypoglycaemia are not accompanied by a PG determination but that was presumably caused by a PG concentration ≤ 3.9 mmol/L (70 mg/dL).



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

PG: plasma glucose SMPG: Self-measured plasma glucose

Figure 17–2 ADA classification of hypoglycaemia

Treatment emergent hypoglycaemic episodes are presented in terms of the number of subjects with at least one event (N), the percentage of subjects with at least one event (%), the number of events (E) and the event rate per 100 years of exposure (R). Separate summaries are made by severity considering all episodes, nocturnal and daytime episodes using Novo Nordisk and ADA classified episodes. All episodes will also be summarised by category, including summaries in relation to time since start of meal, as occurring during1, 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 hours, 4 hours and from 2 hours (exclusive) to 4 hours (inclusive) after start of the meal) will be analysed based on the FAS using a negative binomial regression model with a log-link function and the logarithm of the time period in which a hypoglycaemic episode is considered treatment emergent as offset. The model will include treatment, region and metformin use at baseline (Yes/No) as factors. To the extent where data allow, separate analysis will be performed for severe hypoglycaemic episodes.

Change from baseline in clinical evaluations 16 weeks after randomisation:

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 using the on-treatment period. 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 the on-treatment period and both actual values as mean change and change from baseline.

Electrocardiogram

ECG findings will be summarised descriptively using the on-treatment period and 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

Fundoscopy/fundus photography findings will be summarised descriptively using the on-treatment period and 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.

Change from baseline in clinical laboratory assessments 16 weeks after randomisation

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

- Haematology (erythrocytes, haematocrit, haemoglobin, leucocytes, thrombocytes)
- Biochemistry (ALT, AST, albumin, alkaline phosphatase, creatinine, potassium, sodium, total bilirubin)

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

Change from baseline in body weight and body mass index 16 weeks after randomisation

The measurements will be summarised descriptively using the on-treatment period and the actual values as mean change.

Change from baseline in body weight will be analysed based on all planned post baseline measurements until or at 16 weeks after randomisation using a statistical model similar to 1) except with the corresponding baseline measurement as covariate.

18 Ethics

18.1 Benefit-risk assessment of the trial

All subjects included in the trial will be treated with basal-bolus regimen with insulin degludec as the basal insulin. Inclusion and exclusion criteria have been chosen to ensure that subjects enrolling in the trial have T2DM at a stage where basal-bolus treatment is needed (i.e. subjects must have been diagnosed with T2DM for 10 years or more and must have been on a basal-bolus treatment regimen at least 365 days prior to screening).

Subjects taking metformin at the enrolment in the trial should continue the metformin treatment unchanged. Metformin plus basal/bolus insulin is a recommended treatment for subjects with T2DM[9] and the combination of metformin and basal-bolus insulin therapy with faster aspart or NovoRapid® as the bolus insulin was included in the phase 3A faster aspart trials in T2DM.

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 in case of low BG measurement.

Trial products will be provided by Novo Nordisk free of charge during the trial. When treatment with trial products ends, the subject and investigator will decide on the best available treatment on the market. Novo Nordisk will not offer any free medications after the completion of the trial.

Summary of clinical pharmacology

The pharmacokinetic and pharmacodynamic profiles of faster aspart consistently demonstrated a left shift compared to that of NovoRapid® in subjects with T1DM and the profiles for faster aspart and NovoRapid® were similar in overall shape. Faster aspart produced a faster onset of exposure and increased initial absorption rate compared to NovoRapid® resulting in a faster onset of action and increased early glucose-lowering effect. Overall, the differences in the pharmacokinetic and pharmacodynamic properties for faster aspart compared to NovoRapid® were consistent across trials.[22] No safety concerns were raised during any of the trials.

Similar clinical pharmacology trials have not been performed in subjects with T2DM, however the phase 3A programme for faster aspart included trials in bolus naïve T2DM subjects. Non-inferiority to NovoRapid® with regard to HbA_{1c} change from baseline was demonstrated. In subjects with T2DM faster aspart statistically significantly improved control of the 1-hour PPG increment when compared to NovoRapid®.[22] No safety issues for faster aspart have been identified based on data from the clinical development programme, and the safety profile is similar to NovoRapid®.[22]

Clinical benefits and risk considerations for the trial

The purpose of this trial is to confirm the effect and compare safety of faster aspart compared to NovoRapid® both in combination with insulin degludec with or without metformin in subjects with T2DM treated with a basal-bolus regimen.

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, subjects 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 will provide the opportunity for optimising the titration of basal and bolus insulin based on SMPG values and thereby may contribute to obtaining improved HbA_{1c} results. All subjects will have reinforced dietary training including simple carbohydrate counting.

For the individual subjects, the anticipated risks include hypoglycaemia, hyperglycaemia, systemic allergic reactions, injection site reactions, lipodystrophy, 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. A phase 3A trial with faster aspart in T2DM showed a slight shift in distribution of the occurrence of hypoglycaemic episodes in relation to a meal when comparing to NovoRapid®. A statistical significant higher rate of hypoglycaemic episodes was seen during the first 2 hours after a meal for faster aspart. This is not unexpected and reflects the pharmacokinetic and pharmacodynamic properties of faster aspart.[22]

All treatments are contraindicated in case of hypersensitivity to the active substances or any of the excipients. The risk of hypersensitivity is partly mitigated by excluding subject with known hypersensitivity towards any trials products or related products.

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. Lipodystrophy (including lipohypertrophy, lipoatrophy) at the injection site can occur. Continuous rotation of the injection site within the particular injection area may help to reduce the risk of developing these reactions.

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

Subjects in this trial will be using bolus and basal insulin administered via two differently colour-coded prefilled 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. Subjects will be trained in distinguishing between the pens. 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.

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 aspart in non-clinical and clinical studies taken together with review of the additional excipients in the faster aspart formulation have not revealed any safety issues that would prohibit the administration of faster 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 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[1] and the requirements in the Declaration of Helsinki.[2]

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

- Data already collected and any data collected at the end-of-trial visit including follow-up visits will be retained by Novo Nordisk, entered into the database and used for the clinical 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 subjects 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 the 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

19.1 Protocol deviations

Deviations from the protocol should be avoided.

If deviations do occur, the investigator must inform the monitor and the implications of the deviation must be reviewed and discussed.

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

Documentation on protocol deviations must be kept in the investigator trial master file and sponsor trial master file.

19.2 Prevention of missing data

The importance of subject retention will be addressed by Novo Nordisk in the training and communication with the trial sites.

The subjects will be carefully informed about the trial procedures before signing informed consent, so that they know the implications of participating in the trial. The run-in period in this trial will reduce the likelihood of drop-outs as only those who adhere to the protocol requirements will undergo randomisation. Subjects will during the run-in period get an understanding of what is expected from them when taking part in the trial and thereby minimise discontinuation from trial product post randomisation. In addition, only absolutely necessary criteria for premature discontinuation of trial products primarily focusing on subjects safety are included and thereby reducing the number of discontinuations and limiting the amount of missing data.

Close surveillance of subject retention will be performed throughout the trial by Novo Nordisk with focus on reasons for premature discontinuation of trial products or withdrawal of consent to secure early mitigations in collaboration with the trial sites.

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[36, 37]; however a 7 days' timeline is applied for reporting of missing hypoglycaemic episode, The subject will be retrained in correct completion of the diary if missing data is identified.

The investigator will make every effort to ensure that all assessments are performed and data is collected. If missing data does occur the reason will be collected via the protocol deviation process, see section 19.1. Novo Nordisk will monitor protocol deviations on an on-going basis throughout the trial followed by appropriate actions (e.g. re-training of site staff).

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, written notification from Novo Nordisk must be received and 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
- 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 Investigational new drug (IND)
- All US investigators, as described above, will sign FDA Form 1572

For sites outside the US:

- Intended for participating sites outside of the US
- Not conducted under the Investigational new drug (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 agreement, each investigator agrees to comply fully with ICH GCP[1], applicable regulatory requirements and the Declaration of Helsinki.[2]

By signing the protocol agreement, each investigator also agrees to allow Novo Nordisk to make investigator's name and information about site name and address publically available if this is required by national or international regulations.

22 Responsibilities

The investigator is accountable for the conduct of the trial at his/her site and must ensure adequate supervision of the conduct of the trial at the trial site. If any tasks are delegated, the investigator must maintain a log of appropriately qualified persons to whom he/she has delegated specified trial-related duties. The investigator must ensure that there is adequate and documented training for all staff participating in the conduct of the trial. It is the investigator's responsibility to supervise the conduct of the trial and to protect the rights, safety, and well-being of the subjects.

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

The investigator 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 must 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.

One investigator will be appointed by Novo Nordisk to review and sign the clinical trial report (signatory investigator) on behalf of all participating investigators. The signatory investigator will be appointed based upon the criteria defined by the International Committee of Medical Journal Editors for research publications.[42]

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.[28]

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.

Authorship

Authorship of publications should be in accordance with the Uniform Requirements of the International Committee of Medical Journal Editors[42] (sometimes referred to as the Vancouver Criteria).

Site-specific publication(s) by investigator(s)

For a multi-centre clinical trial, analyses based on single-site data usually have significant statistical limitations and frequently do not provide meaningful information for healthcare professionals or subjects, and therefore may not be supported by Novo Nordisk. It is a Novo Nordisk policy that such individual reports do not precede the primary manuscript and should always reference the primary manuscript of the trial.

Novo Nordisk reserves the right to prior review of such publications. Further to allow for the primary manuscript to be published as the first, Novo Nordisk asks for deferment of publication of individual site results until the primary manuscript is accepted for publication. As Novo Nordisk wants to live up to the industry publication policy, submission of a primary publication will take place no later than 18 months after trial completion.

23.2 Investigator access to data and review of results

As owner of the trial database, Novo Nordisk has the discretion to determine who will have access to the database.

Individual investigators will have their own research subjects' data, and will be provided with the randomisation code after results are available.

24 Retention of clinical trial documentation

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 and/or electronic devices supplied by Novo Nordisk. These data must be retained by the trial site. If the provided data (e.g. the CD-ROM) is not readable during the entire storage period, the investigator can request a new copy. A copy of all data will be stored by Novo Nordisk.

Novo Nordisk will maintain Novo Nordisk documentation pertaining to the trial for at least 20 years after discontinuation of the marketing authorisation, termination of the trial or cancellation of the research project whichever is longest.

The files from the trial site/institution must be retained for 15 years after end of trial as defined in Section 7, or longer if required by local regulations or Novo Nordisk. In any case trial files cannot be destroyed until the trial site/institution is notified by Novo Nordisk. The deletion process must ensure confidentiality of data and must be done in accordance with local regulatory requirements.

25 Institutional Review Boards/Independent Ethics Committees and regulatory authorities

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:

Poland: Novo Nordisk carries liability for the trial exclusively in the scope defined by the applicable laws and in particular by the Civil Code and the Pharmaceutical Law dated 6 September 2001 (uniform version Journal of Laws of 2008 No. 45 item 271 with amendments). In order to support potential claims for liability attributable to the trial, Novo Nordisk and the investigators are covered by the insurance policy issued according to applicable Polish law.

Russia: Federal law of 12 April 2010 No. 61-FZ ‘On Medicinal Drugs’ Circulation and Ministry of Healthcare of Russian Federation’ order of 01 April 2016 No. 200n “Approval of rules of good clinical practice.

27 References

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Protocol
Trial ID:NN1218-4113

Updated protocol including:
Protocol, final version 2.0 dated 28 March 2017
Global Amendment no. 1 version 1.0 dated 09 June 2017
Global Amendment no. 2 version 1.0 dated 23 February 2018

Efficacy and Safety of Fast-acting Insulin Aspart Compared to NovoRapid® both in Combination with Insulin Degludec with or without Metformin in Adults with Type 2 Diabetes (onset® 9)

Trial phase: 3b

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List of abbreviations

ADA	American Diabetes Association
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BG	Blood glucose
CRF	case report form
DUN	dispensing unit number
ECG	electrocardiogram
eCRF	electronic case report form
eDiary	electronic diary
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FPG	fasting plasma glucose
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide-1
HbA_{1c}	glycosylated haemoglobin
IB	Investigator's Brochure
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	independent ethics committee
IMP	investigational medicinal product

IRB	institutional review board
IWRS	interactive voice/web response system
LPLV	last patient last visit
NIMP	non-investigational medicinal product
OAD	oral antidiabetic drug
PG	plasma glucose
PPG	postprandial glucose
PP	per protocol
SAE	serious adverse event
SmPC	summary of product characteristics
SMPG	self-measured plasma glucose
SUSAR	suspected unexpected serious adverse reaction
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TEAE	Treatment Emergent Adverse Event
TMM	Trial Materials Manual
UTN	Universal Trial Number

1 Summary

Objective(s) and endpoint(s):

Primary objective

To confirm the effect in terms of glycaemic control of treatment with fast-acting insulin aspart compared to NovoRapid® both in combination with insulin degludec with or without metformin in adults with type 2 diabetes mellitus treated with a basal-bolus regimen, using a non-inferiority approach.

Secondary objectives

To confirm superiority of fast-acting insulin aspart compared to NovoRapid® both in combination with insulin degludec with or without metformin in adults with type 2 diabetes mellitus treated with a basal-bolus regimen in terms of:

- Postprandial glucose regulation
- Overall glycaemic control
- Postprandial glucose excursions

To compare the safety of fast-acting insulin aspart to NovoRapid® both in combination with insulin degludec with or without metformin in adults with type 2 diabetes mellitus treated with a basal-bolus regimen.

Primary endpoint

Change from baseline in HbA_{1c} 16 weeks after randomisation

Key secondary endpoints

Confirmatory secondary endpoints:

- Change from baseline in 1-hour postprandial glucose increment 16 weeks after randomisation (meal test)
- Change from baseline in 1,5-anhydroglucitol 16 weeks after randomisation

Trial design:

This is a phase 3b, 16-week, multicentre, multinational, 1:1 randomised, double-blind, active controlled, treat-to-target, parallel group trial with a 12-week run-in period comparing the effect and safety of fast-acting insulin aspart to NovoRapid® both in combination with insulin degludec with or without metformin in subjects with type 2 diabetes mellitus treated with a basal-bolus regimen.

The trial includes two blinded dosing arms - mealtime fast-acting insulin aspart and mealtime NovoRapid®.

Trial population:

A total of 1803 subjects with Type 2 diabetes mellitus are planned to be screened and 1072 are planned to be randomised.

Key inclusion criteria:

- Male or female, age ≥ 18 years at the time of signing informed consent.
- Diagnosed with type 2 diabetes mellitus≥ 10 years prior to screening (Visit 1).
- Treated with a basal-bolus insulin regimen ≥ 1 year prior to the day of screening (Visit 1). A basal-bolus insulin regimen is defined as basal insulin once or twice daily and bolus insulin analogue taken with meals at least 3 times daily. Treatment with premixed insulin or soluble insulin combination is not considered a basal-bolus regimen.
- Treated with or without oral antidiabetic drugs including extended release formulations.
- HbA_{1c} 7.0-10.0% (both inclusive) as assessed by central laboratory at screening (Visit 1).

Key exclusion criteria:

- Any of the following: myocardial infarction, stroke, hospitalization for unstable angina or transient ischaemic attack within the past 180 days prior to the day of screening (Visit 1).
- Subjects presently classified as being in New York Heart Association (NYHA) Class IV.
- Planned coronary, carotid or peripheral artery revascularisation known on the day of screening (Visit 1).
- Treatment with injectable GLP-1 receptor agonists in a period of 90 days prior to screening (Visit 1).
- Anticipated initiation or change in concomitant medications (for more than 14 consecutive days) known to affect weight or glucose metabolism (e.g. treatment with orlistat, thyroid hormones, or corticosteroids).

Randomisation criterion:

- $HbA_{1c} \leq 9.0\%$ measured by the central laboratory at Visit 13 (week -1).

Key Assessments:

- HbA_{1c}
- Postprandial glucose increment (meal test)
- 1,5-anhydroglucitol
- Hypoglycaemic episodes
- Adverse events

Trial product(s):

Investigational medicinal products:

- Test products:
  - Fast-acting insulin aspart, 100 U/mL solution for subcutaneous injection, 3 mL PDS290 pen injector (blinded)
  - Insulin degludec, 100U/mL solution for subcutaneous injection, 3 mL PDS290 pen injector

- Reference therapy:
  - Insulin aspart (NovoRapid®), 100 U/mL solution for subcutaneous injection, 3 mL PDS290 pen injector (blinded)

Other medicinal products:

- Rapid acting insulin analogues (NovoRapid® or marketed formulations of insulin lispro or insulin glulisine) during run-in period
- Metformin, tablets for oral use

2 Flow chart

NN1218-4113	Protocol section	Screening	12-week run-in period							Randomisation	16- week treatment period Blinded trial product									End of treatment	Premature discontinuation	Follow-up 1	Follow-up 2
Visit (V) Phone contact (P)		V1	V2	P3 P4	V5	P6 P7 P8	V9	P10 P11 P12	V13	V14	P15	V16	P17	V18	P19 P20 P21	V22	P23 P24 P25	V26	P27 P28 P29	V30	V30A	V31	P32
Time of visit (weeks)		-14	-12	-11 -10	-9	-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		+7 days	+30 days
Visit window (days)		+10	±3	±3	±3	±3	±3	±3	±3	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		+10	+5
SUBJECT RELATED INFO/ASSESSMENTS																							
Informed consent	18.2	X																					
In/exclusion criteria	6.2 6.3	X	X																				
Run-in period exclusion criteria	6.4			X	X	X	X	X	X	X													
Randomisation criterion	6.5									X													
Randomisation	8.1.3									X													
Criteria for premature discontinuation of trial products	6.6										X	X	X	X	X	X	X	X	X				
Demography	8.2.1	X																					
Tobacco use	8.2.8	X																					
Diabetes history and diabetes complications	8.2.2, 8.2.6	X																					
Hypoglycaemia unawareness	8.2.3	X																					
Concomitant illness and medical history	8.2.4	X																					
Concomitant medication	8.2.5 8.2.6	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Child-bearing potential	8.2.7	X																					
EFFICACY																							
Meal test	8.3.1									X										X	X		
4-point profile (SMPG)	8.3.3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
7-9-7-point profile (SMPG)	8.3.3									X						X				X	X		
1,5-anhydroglucitol	8.5.1									X				X		X		X		X	X		
Fasting plasma glucose	8.5.1									X						X				X	X		

NN1218-4113	Protocol section	Screening	12-week run-in period							Randomisation	16- week treatment period Blinded trial product									End of treatment	Premature discontinuation	Follow-up 1	Follow-up 2
Visit (V) Phone contact (P)		V1	V2	P3 P4	V5	P6 P7 P8	V9	P10 P11 P12	V13	V14	P15	V16	P17	V18	P19 P20 P21	V22	P23 P24 P25	V26	P27 P28 P29	V30	V30A	V31	P32
Time of visit (weeks)		-14	-12	-11 -10	-9	-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		+7 days	+30 days
Visit window (days)		+10	±3	±3	±3	±3	±3	±3	±3	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		+10	+5
HbA_{1c}	8.5.1	X			X		X		X	X				X		X		X		X	X		
Fasting C-peptide	8.5.1									X													
Lipids	8.5.1	X								X						X				X	X		
SAFETY																							
Adverse events	8.4.1, 12	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Injection site reactions	8.4.1.2		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hypoglycaemic episodes	8.4.2		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Technical complaints	12.1.6		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Body weight	8.4.5									X										X	X		
Height	8.4.5									X													
Physical examination	8.4.6	X								X										X	X		
Vital signs	8.4.7	X								X										X	X		
Eye examination	0	X								X										X	X		
ECG	8.4.4	X								X										X	X		
Biochemistry	8.5.2	X								X						X				X	X		
Haematology	8.5.2	X								X						X				X	X		
Pregnancy test	8.5.2	X								X										X	X		
TRIAL MATERIAL																							
Dispensing visit	9.4		X		X		X		X	X		X		X		X		X					
New (prescribed) dose of trial insulin	8.3.4		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Dosing (Start/stop date of trial insulin)	8.3.4			X						X	X									X	X		
Insulin dose of basal and bolus insulin each day	8.3.4		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Drug accountability	9.4		X		X		X		X	X		X		X		X		X		X	X		

NN1218-4113	Protocol section	Screening	12-week run-in period							Randomisation	16- week treatment period Blinded trial product									End of treatment	Premature discontinuation	Follow-up 1	Follow-up 2
Visit (V) Phone contact (P)		V1	V2	P3 P4	V5	P6 P7 P8	V9	P10 P11 P12	V13	V14	P15	V16	P17	V18	P19 P20 P21	V22	P23 P24 P25	V26	P27 P28 P29	V30	V30A	V31	P32
Time of visit (weeks)		-14	-12	-11 -10	-9	-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		+7 days	+30 days
Visit window (days)		+10	±3	±3	±3	±3	±3	±3	±3	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		+10	+5
IWRS call	10	X	X		X		X		X	X		X		X		X		X		X	X		
BG-meter start date[a]	8.3.2		(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
REMINDERS																							
Handout ID card	8.1.1	X																					
Confirmation of unchanged metformin	8.2.5		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Attend visit fasting	8.1.5									X						X				X	X		
Training in carbohydrate counting	8.6.1		X		X		X			X													
Handout direction for use	9.2		X																				
Training in trial product and pen handling	8.6.2		X		X		X			X				X		X							
Handout pen differentiation guide	9.2									X													
Training in pen differentiation	8.6.2									X				X		X							
Handout and instruct in diary	8.6.3		X		X		X		X	X		X		X		X		X		X	X	X	
Handout and instruct in BG meter use[a]	8.3.2, 8.3.3		X		(X)		(X)		(X)	(X)		(X)		(X)		(X)		(X)		(X)	(X)	(X)	
Handout and instruct in subject mealtime insulin dose adjustment guide	8.3.4									X													
Diary collection	8.6.3				X		X		X	X		X		X		X		X		X	X	X	
End of treatment	8.1.7																			X	X		
End of trial																							X

[a] (X) is only applicable for subjects who have used the glycaemic data collection system (the combination of the MyGlucoHealth Wireless BG-meter and an electronic diary) section 8.3.2.

3 Background information and rationale for the trial

The trial will be conducted in compliance with this protocol, ICH GCP[1] and applicable regulatory requirements, and in accordance with the Declaration of Helsinki.[2]

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

Improvement in long-term glucose control, as obtained with intensified insulin therapy, may reduce the incidence of complications and delay the progression of existing complications in people with Type 1 Diabetes Mellitus (T1DM) and Type 2 Diabetes Mellitus (T2DM).[3,4] Postprandial hyperglycaemia contributes significantly to the glycosylated haemoglobin (HbA_{1c}) level and its control is thus essential for achieving the HbA_{1c} target level.[5] Postprandial hyperglycaemia is associated with increased risk of micro- and macro-vascular complications.[6] Lowering of postprandial hyperglycaemia may reduce the progression of atherosclerosis and cardiovascular events in patients with T2DM.[7]

Basal-bolus insulin therapy aims at mimicking the physiological insulin response in the healthy state to the largest possible extent. For that purpose, rapid-acting insulin analogues were developed to more effectively control the postprandial glucose (PPG) excursions than subcutaneously injected human regular insulin, primarily through offering a faster onset and shorter duration of action.[8] However, unmet needs exist within prandial insulin therapy for people with diabetes. The current insulin analogues are not able to match the speed of the normal physiological postmeal insulin secretion, leading to suboptimal control of blood glucose (BG), and exogenous insulin with a faster glucose lowering effect is needed for tighter PPG control. In addition, a faster glucose lowering effect is also likely to offer greater flexibility in the time of dosing around meals thus increasing convenience for the patients and may allow the patients to better match the insulin taken to the meal.[9]

For an assessment of benefits and risks of the trial, see Section 18.1

3.1.1 Therapeutic Area

Due to the progressive nature of T2DM, many patients are likely to be candidates for intensified insulin therapy. Prandial insulin supplementation is recommended by European Association for the Study of Diabetes (EASD)/American Diabetes Association (ADA) guidelines[10] for treatment intensification in patients with T2DM who do not reach HbA_{1c} target below 7.0% on oral antidiabetic drugs (OADs) and basal insulin alone. The recommendation is a stepwise addition of bolus insulin when significant PPG excursions occur. A trial investigating step-wise addition of bolus insulin (basal-plus regimen) showed that around 75% of patients enrolled in the trial needed

three boluses after 36 weeks of treatment.[11] Results from the PREFER trial indicated that one-third of the total prandial insulin dose is delivered with each meal in the majority of patients achieving HbA1c ≤7.0%.[12] When used as part of a basal-bolus regimen in patients with T2DM who had previously received other insulin and/or OAD regimens, insulin aspart in combination with insulin degludec was a safe, well tolerated and effective treatment associated with clinically relevant reductions in hyperglycaemia.[13]

3.1.2 NovoRapid® (Insulin aspart)

Insulin aspart is currently marketed worldwide as NovoRapid® (in US it is NovoLog®) and is a rapid-acting insulin analogue indicated for the treatment of diabetes. In the remainder of this protocol the name NovoRapid® will be applied for the marketed formulation of 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 thereby is related to faster absorption as compared with regular human insulin. Compared with human insulin, NovoRapid® has a faster onset and a shorter duration of action, resulting in superior postmeal glucose control by means of lowering total glucose excursion following a meal, both in subjects with T1DM[3, 14, 15] and in subjects with T2DM.[16-18] This also allows NovoRapid® 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[19](SmPC) and the U.S. NovoLog® Label Information[20].

3.1.3 Fast-acting insulin aspart

Fast-acting insulin aspart (faster aspart) (markedet as Fiasp®) is insulin aspart in a new formulation. Faster aspart is being developed with the objective of achieving an increased early absorption of insulin aspart compared to NovoRapid® thereby providing a faster insulin action. Faster 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®. Results from clinical pharmacology trials in adults comparing pharmacokinetic and pharmacodynamic properties of faster aspart and NovoRapid® have shown that faster aspart resulted in an earlier onset of appearance and a greater early exposure to insulin aspart than NovoRapid® in subjects with T1DM, with the largest difference found within the first 15 minutes after injection. Faster aspart also resulted in a greater early glucose-lowering effect than NovoRapid®, but no statistically significant difference between faster aspart and NovoRapid® in total glucose-lowering effect.

In a therapeutic confirmatory basal-bolus trial in adult subjects with T1DM, faster aspart taken with the meal in combination with Levemir® effectively improved glycaemic control and the reduction in HbA_{1c} was statistically significantly larger than with NovoRapid®. Mealtime faster aspart provided superior PPG control compared to NovoRapid® 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 aspart. No statistically significant difference was seen in overall rate of severe or BG confirmed hypoglycaemic episodes between mealtime faster aspart and NovoRapid®. 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 aspart compared to NovoRapid®. The overall safety profile for faster aspart and NovoRapid® was similar and as expected for insulin aspart.

In a therapeutic confirmatory basal-bolus trial in adult subjects with T2DM, adding and titrating mealtime faster aspart in combination with insulin glargine also effectively improved glycaemic control and non-inferiority to NovoRapid® regarding HbA_{1c} change from baseline was confirmed. A statistically significant benefit in 2-hour PPG increment (meal test) could not be confirmed for faster aspart compared to NovoRapid®. A statistically significant difference was demonstrated for 1-hour PPG increment (meal test) in favour of faster aspart compared to NovoRapid®. No statistically significant difference was seen in overall rate of severe or BG confirmed hypoglycaemic episodes between faster aspart and NovoRapid®. The rate during the first two hours after start of a meal, constituting a small fraction of all severe or BG confirmed hypoglycaemic episodes, was statistically significantly higher for faster aspart compared to NovoRapid®. The overall safety profile for faster aspart and NovoRapid® was similar and as expected for insulin aspart.

The safety profile of faster aspart is expected to be similar to that of NovoRapid®. The insulin aspart molecule has a well-known safety profile based on more than 15 years of clinical experience. Compared to NovoRapid® faster aspart contains excipients which results in a faster initial absorption of insulin aspart following subcutaneous injection. The added excipients are included in the U.S. Food and Drug Administration's (FDA) list for approved drug products for injections, and no toxicological concerns have been predicted from subcutaneous use in humans at the proposed concentrations. For further details, please refer to the current version of the Fiasp® SmPC[21]. If not approved in the country of interest detailed information for faster aspart is available in the current edition of the Investigator's Brochure (IB)[22] and any updates hereof.

At the time of this protocol issuance, faster aspart is approved in EU, US and Canada among others.

3.1.4 Insulin degludec

Insulin degludec (marketed as Tresiba®) is a basal insulin with an ultra-long duration of action for once-daily subcutaneous administration at any time of the day, preferably at the same time every day. After subcutaneous injection, soluble and stable multi-hexamers are formed creating a depot of insulin in the subcutaneous 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[23]. 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[24].

At the time of this protocol issuance, insulin degludec is approved in more than 70 countries including US, EU, Canada and Japan.

3.2 Rationale for the trial

The purpose of this trial is to confirm the effect and compare safety of faster aspart compared to NovoRapid® both in combination with insulin degludec with or without metformin in subjects with T2DM treated with a basal-bolus regimen. This trial will provide new information in subjects with T2DM already treated with a basal-bolus regimen as this was not studied in the phase 3a programme.

In the European Medicines Agency (EMA) and FDA note for guidance on clinical investigation of medicinal products for the treatment of diabetes, HbA_{1c} is considered the most widely accepted measure of overall, long-term glucose control. Consequently, HbA_{1c} will be included as the primary endpoint.[25, 26]

The trial is intended to confirm that administration of faster aspart gives overall glycaemic control non-inferior to NovoRapid® and to confirm that faster aspart, with its faster onset of action, is capable of demonstrating superior control of postprandial glucose regulation and excursions as well as a greater reduction in HbA_{1c} in subjects with T2DM.

4 Objectives and endpoints

4.1 Objectives

Primary objective

To confirm the effect in terms of glycaemic control of treatment with faster aspart compared to NovoRapid® both in combination with insulin degludec with or without metformin in adults with T2DM treated with a basal-bolus regimen, using a non-inferiority approach.

Secondary objectives

To confirm superiority of faster aspart compared to NovoRapid® both in combination with insulin degludec with or without metformin in adults with T2DM treated with a basal-bolus regimen in terms of:

- Postprandial glucose regulation
- Overall glycaemic control
- Postprandial glucose excursions

To compare the safety of faster aspart to NovoRapid® both in combination with insulin degludec with or without metformin in adults with T2DM treated with a basal-bolus regimen.

4.2 Endpoints

Baseline is defined as randomisation (Visit 14)

4.2.1 Primary endpoint

Change from baseline in HbA_{1c} 16 weeks after randomisation

4.2.2 Secondary endpoints

4.2.2.1 Confirmatory secondary endpoints

- Change from baseline in 1-hour PPG increment 16 weeks after randomisation (meal test)
- Change from baseline in 1,5-anhydroglucitol 16 weeks after randomisation

4.2.2.2 Supportive secondary endpoints

Supportive secondary efficacy endpoints

- Change from baseline in fasting plasma glucose (FPG) 16 weeks after randomisation
- If a subject achieves HbA_{1c} targets 16 weeks after randomisation:
    - HbA1c < 7.0%
    - HbA1c < 7.0% without severe hypoglycaemia
- Change from baseline in 30- minutes, 1- hour, 2- hour, 3- hour and 4- hour PPG and 30-minutes, 2- hour, 3- hour and 4- hour PPG increment 16 weeks after randomisation (meal test)
- Change from baseline in endpoints derived from the 7-9-7-point self-measured plasma glucose (SMPG) profile 16 weeks after randomisation:
    - Mean of the 7-9-7-point profile
    - Postprandial glucose and PPG increment (mean, breakfast, lunch, main evening meal)
    - Fluctuation in 7-9-7-point profile
    - Change in the nocturnal SMPG measurements
- If a subject achieves PPG target (overall mean of daily PPG measurements in 7-9-7-point SMPG profile) 16 weeks after randomisation:
    - Overall PPG (1 hour) ≤7.8 mmol/L [140 mg/dL]
    - Overall PPG (1 hour) ≤7.8 mmol/L [140 mg/dL] without severe hypoglycaemia
- Insulin dose (Units/day and Units/kg/day; total basal, total bolus and individual meal insulin dose) 16 weeks after randomisation
- Change from baseline in lipids-lipoproteins profile 16 weeks after randomisation (total cholesterol, high density lipoproteins (HDL) cholesterol, low density lipoproteins (LDL) cholesterol)

Supportive secondary safety endpoints

- Number of treatment emergent adverse events (AEs) during 16 weeks after randomisation
- Number of treatment emergent injection site reactions during 16 weeks after randomisation
- Number of treatment emergent hypoglycaemic episodes classified both according to the ADA definition and Novo Nordisk definition during 16 weeks after randomisation
    - Overall
    - Daytime hypoglycaemic episodes
    - 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 in clinical evaluations 16 weeks after randomisation:
    - Physical examination
    - Vital signs (diastolic blood pressure, systolic blood pressure and pulse)
    - Electrocardiogram
    - Fundoscopy/fundus photography
- Change from baseline in central laboratory assessments 16 weeks after randomisation:
    - Haematology (erythrocytes, haematocrit, haemoglobin, leucocytes, thrombocytes)
    - Biochemistry (alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, alkaline phosphatase, creatinine, potassium, sodium, total bilirubin)
- Change from baseline in body weight and body mass index 16 weeks after randomisation

5 Trial design

5.1 Type of trial

This is a phase 3b, 16-week, multicentre, multinational, 1:1 randomised, double-blind, active controlled, treat-to-target, parallel group trial with a 12-week run-in period comparing the effect and safety of faster aspart to NovoRapid® both in combination with insulin degludec with or without metformin in subjects with T2DM treated with a basal-bolus regimen.

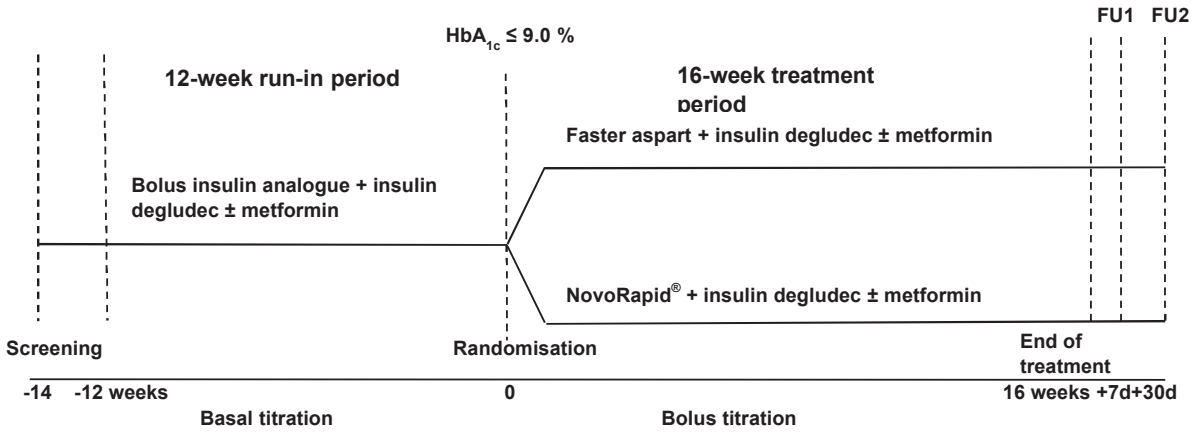


Figure 5–1 Trial Design.

The trial design is summarised in Figure 5–1. The total duration of the trial is approximately 34 weeks divided into the following periods:

- An approximately 2-week screening period
- A 12-week run-in period primarily for optimisation of the basal insulin and subject training
- A 16-week treatment period
- A 30-day follow-up period: FU1; 7 days after end of treatment and FU2; 30 days after end of treatment

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 a 12-week run-in period. After the run-in period, subjects eligible for randomisation ($HbA_{1c} \leq 9.0\%$ measured at Visit 13) will be randomised (1:1) to receive double blinded treatment with either faster aspart or NovoRapid® both in combination with once daily insulin degludec with or without metformin.

All subjects will have a standardised meal test at baseline (Visit 14 before randomisation) and at end of treatment (Visit 30). The meal test will be described in more details in section 8.3.1.

After the 16-week treatment period, each subject will have a 30-day safety follow-up period.

5.2 Rationale for trial design

The 12-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 16-week treatment period is needed to obtain valid and adequate efficacy and safety data.

The rational for the simple carbohydrate counting (carbohydrate awareness) is to ensure that subjects are able to better control the carbohydrate amount of their meals aiming at a similar carbohydrate intake between days as a supplement to the algorithm based titration.

The rationale for the meal test is to evaluate PPG regulation after a standardised meal when injecting faster 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 aspart and NovoRapid®.

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

5.2.1 Rational for choice of non-inferiority margin

In a recently finalised faster aspart trial (NN1218-4049, data on file) with 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 effect in change from baseline HbA_{1c} was - 0.94% [-1.17; -0.72]. In this trial the addition of 3 times daily faster aspart led to a reduction in HbA_{1c} of 1.16% after 18 weeks of treatment. In a similar phase 4 trial[27] investigating the stepwise addition of NovoRapid® to a full basal-bolus regimen in bolus naïve T2DM adults the observed reduction in HbA_{1c} after 21 weeks of treatment was 1.15% (data ANA-3786, data on file) with 3 times daily NovoRapid® added to basal insulin. This gives some indication that the effect of NovoRapid® versus placebo would be close to the 0.94% observed in trial NN1218-4049. Thus using a non-inferiority margin of 0.4%, one of the suggested margins in the FDA guidance[26], an improvement of approximately 0.54% would have been preserved using the 0.4% non-inferiority margin.

5.3 Treatment of subjects

At Visit 2, all eligible subjects will be enrolled in a run-in period where all subjects will be transferred from their pre-trial basal insulin treatment to insulin degludec once daily. They must

continue their pre-trial bolus insulin analogue with or without metformin. All OADs, except for metformin must be stopped at Visit 2. For subjects treated with metformin prior to the trial, they should continue with their pre-trial dose of metformin. The dose and dosing frequency of metformin should not be changed at any time during the trial, unless due to safety concerns. Initiation of any other diabetes treatment is not allowed during the screening, run-in or treatment period and must be reported (see section 8.2.6). This includes metformin for subjects not treated with metformin prior to the trial. During the run-in period, the investigator will focus on optimising the basal insulin treatment using a treat-to-target approach following the titration guideline (Appendix A). The bolus insulin 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 dietary training regarding simple carbohydrate counting (carbohydrate awareness) in the run-in period.

All subjects should consume 3 main meals (breakfast, lunch and dinner) daily throughout the trial.

In the treatment period, eligible subjects must discontinue their pre-trial bolus insulin analogue and will receive double blinded treatment with either faster aspart or NovoRapid® both in combination with once daily insulin degludec with or without metformin. The investigator should focus on optimising the bolus insulin treatment following the bolus dosing algorithm as described in the titration guideline (Appendix A). Surveillance of insulin titration will be performed by Novo Nordisk.

The maximum duration of treatment will be 28 weeks. No maximum dose is specified. Doses are adjusted according to SMPG values (Appendix A).

Use of flash glucose monitoring or a real time continuous glucose monitoring system is not allowed throughout the trial.

5.4 Treatment after discontinuation of trial products

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 BG measurements, considering the stable effect and long half-life of insulin degludec.

5.5 Rationale for treatment

Based on the currently available pharmacokinetic data on faster aspart, it is anticipated that treatment with faster 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 aspart SmPC[21] or IB.[22]

NovoRapid® will be used as a comparator to faster aspart in order to compare the effect and safety of faster aspart to the currently marketed insulin aspart formulation. As this is a double-blind trial, NovoRapid® and faster 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 effect and safety has been confirmed in adult subjects. The flat and stable glucose-lowering effect of insulin degludec makes it optimal when assessing the properties of bolus insulin (faster aspart compared to NovoRapid®).

Combination of insulin treatment with metformin is associated with better glycaemic control, fewer hypoglycaemic events, and less weight gain than treatment with insulin alone, therefore metformin should be continued when type 2 patients are on insulin therapy.

6 Trial population

6.1 Number of subjects

Number of subjects planned to be screened: 1803

Number of subjects planned to be included in the run-in period: 1262

Number of subjects planned to be randomised: 1072

A screening failure rate of approximately 30% and a run-in failure rate of approximately 15% 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 ≥ 18 years at the time of signing informed consent.

3. Diagnosed with type 2 diabetes mellitus ≥ 10 years prior to screening (Visit 1).

4. Treated with a basal-bolus insulin regimen ≥ 1 year prior to the day of screening (Visit 1). A basal-bolus insulin regimen is defined as basal insulin once or twice daily and bolus insulin analogue taken with meals at least 3 times daily. Treatment with premixed insulin or soluble insulin combination is not considered a basal-bolus regimen.

5. Treated with or without oral antidiabetic drugs including extended release formulations.

6. HbA_{1c} 7.0-10.0% (both inclusive) as assessed by central laboratory at screening (Visit 1).

7. Able and willing to adhere to the protocol including performance of SMPG profiles and meal test.

8. Able and willing to consume 3 main meals (breakfast, lunch and dinner) daily throughout 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 an adequate contraceptive method (adequate contraceptive measure as required by local regulation or practice).

   For Bulgaria, Czech Republic, Germany, Greece, Italy, Poland, Romania and Spain: The following contraceptive measures are considered adequate:

   - combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, transdermal or intravaginal)
   - progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable)
   - intrauterine device
   - intrauterine hormone-releasing system
   - sexual abstinence
   - vasectomised partner
   - double barrier method (a combination of male condom with either cap, diaphragm or sponge with spermicide)

4. Participation in any clinical trial of an approved or non-approved investigational medicinal product within 30 days before screening (Visit 1). Clinical trials do not include non-interventional studies.

5. Any disorder, except for conditions associated with type 2 diabetes mellitus, which in the investigator's opinion might jeopardise subject's safety or compliance with the protocol.

6. Any of the following: myocardial infarction, stroke, hospitalization for unstable angina or transient ischaemic attack within the past 180 days prior to the day of screening (Visit 1).

7. Subjects presently classified as being in New York Heart Association (NYHA) Class IV.

8. Planned coronary, carotid or peripheral artery revascularisation known on the day of screening (Visit 1).

9. Inadequately treated blood pressure defined as Grade 3 hypertension or higher (Systolic ≥180 mmHg or diastolic ≥110 mmHg) at screening (Visit 1).

10. Treatment with injectable GLP-1 receptor agonists in a period of 90 days prior to screening (Visit 1).

11. Anticipated initiation or change in concomitant medications (for more than 14 consecutive days) known to affect weight or glucose metabolism (e.g. treatment with orlistat, thyroid hormones, or corticosteroids).

12. Proliferative retinopathy or maculopathy requiring acute treatment. Verified by fundus photography or pharmacologically dilated fundoscopy performed within the past 90 days prior to Visit 2.

13. Presence or history of malignant neoplasms within the past 5 years prior to the day of screening (Visit 1). Basal and squamous cell skin cancer and any carcinoma *in-situ* is allowed.

14. For subjects treated with metformin: Any contraindications or restrictions to use of metformin (according to local labelling) at investigator's discretion.

6.4 Run-in period exclusion criteria

The subject must be withdrawn from the trial during the run-in period if the following applies after screening (Visit 1), and before or at randomisation (Visit 14):

1. Included in the trial in violation of the inclusion and/or exclusion criteria.

2. Pregnancy

3. Intention of becoming pregnant

4. Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product.

5. Any of the following: myocardial infarction, stroke, hospitalization for unstable angin a or transient ischaemic attack.

6. Planned coronary, carotid or peripheral artery revascu larisation.

7. Any disorder which in the investigator's opinion might jeopardise subject's safety.

8. Inability or lack of willingness to adhere to the protocol, based on the investigator's judgement.

6.5 Randomisation criterion

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

1. $HbA_{1c} \leq 9.0\%$ measured by the central laboratory at Visit 13 (week -1).

6.6 Criteria for premature discontinuation of trial products

Efforts must be made so that subjects attend and complete all scheduled visit procedures. Subjects should stay in the trial irrespective of lack of adherence to randomised treatment, lack of adherence to visit schedule or missing assessments. Only subjects who decline any further contact with the site in relation to the trial will be considered as withdrawn from the trial (see Section 6.7).

The subject may be prematurely discontinued from trial products at the discretion of the investigator due to a safety concern.

The subject must be prematurely discontinued from trial products if the following applies after randomisation:

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. Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product

5. Lack of efficacy defined as fulfilment of **all** 4 below criteria:
   - No reduction in HbA1c measured by central laboratory from screening (Visit 1) to visit 18, 22 or 26 **AND**
   - A daily average of 4-point SMPG readings (before breakfast, before lunch, before dinner and at bed time) on 3 consecutive days higher than 240 mg/dL (13.3 mmol/L) within the last two weeks period **AND**
   - A confirmatory FPG exceeding 240 mg/dL (13.3 mmol/L) or a confirmatory random PG exceeding 300 mg/dL (16.7 mmol/L) measured by central laboratory **AND**
   - No treatable intercurrent cause (e.g. non-compliance) for the hyperglycaemia at the investigator's judgment

6. Unacceptable adverse event (including toxicity) that cannot be solved by any medical intervention or considered as non-acceptable risk at the investigator's judgment.

See Section 8.1.9 for procedures to be performed for subjects discontinuing trial products prematurely.

6.7 Withdrawal from trial

The subject may withdraw consent at will at any time.

A subject is considered withdrawn from trial if the following applies before Visit 30:

- Subject is lost to follow up (see Section 8.1.10))
- Subject withdraws consent
- Death

Subjects withdrawing from trial before randomisation are considered screening or run-in failures.

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 products but to stay in the trial, procedures described in section 8.1.9 must be followed.

See Section 8.1.10 for procedures to be performed for subjects withdrawing consent after randomisation.

6.8 Subject replacement

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

6.9 Rationale for trial population

The trial population consists of adult subjects with T2DM who have been treated with a basal-bolus insulin regimen for at least 365 days, but are not optimally controlled as demonstrated by an HbA_{1c} $\geq$ 7.0%, and may benefit from intensified insulin titration using a treat-to-target approach. The subjects need to have had T2DM for at least 10 years to ensure more progressed disease requiring a full basal bolus insulin supplementation. The subjects need to be on a basal-bolus insulin regimen for at least 365 days 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.

Subjects with an HbA_{1c} > 10% are not included in this trial. This is because the trial protocol requires strict adherence and good subject compliance and a likely cause of elevated HbA_{1c} > 10% 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 12-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. Subjects with an HbA_{1c} > 9% 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, a likely cause of HbA_{1c} > 9% after 12-week basal insulin titration period is poor compliance with treatment regimens or an atypical course of the disease.

7 Milestones

Planned duration of recruitment period: 36 weeks

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

Recruitment:
The screening and randomisation rate will be followed closely via the interactive voice/web response system (IWRS) 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 IWRS will be closed for further screening. All subjects screened during the recruitment period and found eligible for randomisation can be randomised within the timelines specified in the flow chart (see Section 2).

Trial registration:

Information of the trial will be disclosed at clinicaltrials.gov and novonordisk-trials.com. According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure[28], it will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE)[29], the FDA Amendment Act (FDAAA)[30], European Commission Requirements[31, 32] 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.

Primary Completion Date is the last assessment of the primary endpoint, and is for this protocol last subject first visit + 30 weeks corresponding to Visit 30. If the last subject is withdrawn/dropout early the Primary Completion Date is the date when the last subject would have completed Visit 30. The Primary Completion Date determines the deadline for results disclosure at clinicaltrials.gov according to FDAAA.

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 (Visit 1)

Informed consent must be obtained before any trial related activity, see Section 18.2.

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. Only subjects who have signed the informed consent form should be included on the logs. The subject screening log and subject enrolment log may be combined in one log.

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 IWRS.

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 AEs (SAEs) from screening failures must be transcribed by the investigator into the eCRF. Follow-up on SAEs must be carried out according to Section 12.

A screening failure session must be made in the IWRS. When data has been monitored and queries have been resolved the case book must be signed.

Re-screening is NOT allowed if the subject has failed one of the inclusion, exclusion or randomisation criteria, this includes re-sampling if the subject has failed one of the inclusion, exclusion or randomisation criteria related to laboratory parameters.

8.1.2 Run-in

If the subject is found eligible to continue in the trial the subject will enter a run-in period. 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.

In- or exclusion criteria must not be ticked "Yes" or "No" in the eCRF before source data is available. In case source data is not available "Result pending" must be chosen. This is particularly relevant for lab samples and in some cases the ECG (electrocardiogram) and eye examination result. 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 the basal insulin trial product (Insulin degludec). The subjects must be trained in how to handle the insulin pen injectors (see section 8.6.2). Training may be repeated during the trial if necessary. First date of trial product (basal insulin) must be recorded in the eCRF.

A run-in dispensing session must be performed in the IWRS. A drug accountability session confirming dispensing of allocated trial product should also be performed when dispensing trial product.

The BG meter and diary should be provided to the subjects at Visit 2. Subjects must be trained in use of the BG meter and completion of the diary.

Run-in failures

If the subject is not eligible to be randomised (i.e. has met one of the run-in period exclusion criteria, has not met the randomisation criterion or withdraw from trial before randomisation) then the subject will be considered a run-in failure. Consequently, a run-in failure session must be made in the IWRS system and a run-in failure form must be completed in the eCRF together with the reason for not continuing in the trial. The last date of trial product must be captured in the eCRF. No follow-up visit should take place and no additional assessments are needed. The diary should be returned to the site.SAEs and non-serious AEs from run-in failures must be recorded by the investigator in the eCRF. 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.

8.1.3 Randomisation

If the subject meets the randomisation criterion as measured at Visit 13, then the subject will at Visit 14 be randomised into one of the two treatment arms using an IWRS randomisation session. A

drug accountability session confirming dispensing of allocated trial products should also be performed when dispensing trial products.

First date of the randomised trial product (bolus insulin) must be recorded in the eCRF.

The subject must attend randomisation visit fasting. For definition of fasting, please see section 8.1.5.

Investigator must hand out the subject mealtime insulin dose adjustment guide and instruct subjects how to self-titrate (section 8.3.4 and Appendix A).

8.1.4 Phone contacts

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. A phone contact may be converted to a site visit if needed.

8.1.5 Fasting visits

The subjects must attend the visits specified in the flowchart (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 and at Visit 14 before randomisation to trial product.

8.1.6 Rescheduled visits

The date of the rescheduled assessment in the eCRF should reflect the actual date of the rescheduled assessment (i.e. the actual visit date will differ from the assessment date under the same visit).

8.1.7 End of treatment

At end of treatment trial products must be discontinued and a completion IWRS session must be performed. Last date on the basal and bolus trial insulin must be recorded in eCRF.

The subject must be switched to a suitable marketed product at the discretion of the investigator and this product must be recorded on the concomitant medication (diabetes) form in eCRF, as described in section 8.2.6.

8.1.8 Follow-up period

The follow-up visit 1 (FU1) is a site visit and must take place 7-17 days after the end of treatment visit. Follow-up contact 2 (FU2) is a phone contact and must take place 30-35 days after the end of treatment visit.

Follow-up visit 1

The following data will be collected:

- AEs
- Concomitant medication
- Current diabetes medication
- Hypoglycaemic episodes
- Additional information on injection site reactions

Follow-up contact 2

The following data will be collected:

- AEs
- Concomitant medication
- Current diabetes medication
- Hypoglycaemic episodes

8.1.9 Premature discontinuation of trial products

If a subject prematurely discontinues trial products after randomisation (Visit 14), the investigator must undertake procedures similar to those for Visit 30 as soon as possible, also called Visit 30A (see flowchart section 2).

Premature discontinuation of trial products must be registered in IWRS . This must be performed at least 4 days prior to Visit 30A to ensure scheduling of the 7-9-7-point SMPG profile on the three days prior to Visit 30A. Subjects should perform this 7-9-7 point SMPG profile before discontinuing trial products.

At Visit 30A subjects must undergo the meal test before discontinuing trial products. The meal test should be performed with bolus trial insulin. If it is not feasible due to safety reasons including pregnancy as judged by the investigator the meal test should be performed with the marketed bolus product the subject is switched to.

The primary reason for premature discontinuation of trial products must be specified in the eCRF, and final drug accountability must be performed. A treatment discontinuation session must be made in the IWRS after the final meal test.

The subject should be switched to a suitable marketed product at the discretion of the investigator. The medication should be recorded on the concomitant medication (diabetes) form in the eCRF, as described in section 8.2.6 at each contact after trial product discontinuation.

The subject should also complete the follow-up visits (FU1 and FU2) 7 days and 30 days after discontinuation of trial product. Visit 31 (FU1) can be converted into a phone contact as the diary can be collected at the next site visit for the subjects that discontinue trial products prematurely.

In addition, subjects prematurely discontinued from trial products should continue with the per protocol planned visits at 4 (Visit 18), 8 (Visit 22), 12 (Visit 26), 16 (Visit 30) weeks after randomisation depending on when the subject discontinues trial products. The meal test at Visit 30 should be done with the subjects' currently prescribed insulin treatment with the same bolus insulin dose as at baseline.

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

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

- If Visit 30A is within 2 weeks of one of the per protocol planned visits, only Visit 30A 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

It should be documented in the medical records if subject refuses to attend a visit from Visit 30A and onwards. A subject that permanently discontinues trial product before the End of Treatment visit (V30), will be considered to be a treatment non-completer.

Diary records after premature discontinuation of trial products

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 30A, Visit 22 and Visit 30 must be transcribed to the eCRF. Additionally, hypoglycaemic episodes must be recorded in the diary and transcribed to the eCRF.

8.1.10 Withdrawal from trial

If a subject withdraws consent, the investigator must aim to undertake procedures similar to those for Visit 30 including the meal test, as soon as possible, also called Visit 30A. The investigator must encourage the subjects to undergo the meal test at Visit 30A. The meal test must be performed with bolus trial insulin according to randomisation. If it is not feasible due to safety reasons including

pregnancy as judged by the investigator the meal test should be performed with the marketed bolus product the subject is switched to.

If the subject agrees, the investigator must aim to perform the follow up visits (FU1 and FU2) 7 and 30 days after discontinuation of trial product.

In case a premature discontinuation of trial product subject chooses to withdraw consent from trial after completing Visit 30A, FU1 and FU2, the investigator must encourage the subjects to undergo procedures of Visit 30, as soon as possible, whereas FU1 and FU2 are not to be completed again.

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

Although a subject is not obliged to give his/her reason(s) for withdrawing consent, 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 withdrawing consent must be specified in the eCRF.

A subject that is withdrawn from trial before the End of Treatment Visit (V30), will be considered to be a treatment non-completer and a trial non-completer.

8.1.10.1 Lost to follow-up

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".

8.1.11 Review of results

Review of ECG results, eye examination report, laboratory reports, data entered in the diaries etc. must be documented either on the documents, printouts or in the subject's medical record.

If clarification of entries or discrepancies in the diary 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. Any discrepancies or missing data points available elsewhere related to a 7-9-7 point profile or hypoglycaemic episodes must be corrected or added.

8.2 Subject related information/assessments

8.2.1 Demography

Demography will be recorded at screening and consists of:

- Date of birth (according to local regulation)
- Sex
- Ethnicity (according to local regulation)
- Race (according to local regulation)

8.2.2 Diabetes history and diabetes complications

Diabetes history and diabetes complications will be recorded at screening and consists of:

- Date of diagnosis of T2DM
- Information regarding diabetes complications including date of onset
  - Diabetic retinopathy
  - Diabetic neuropathy
  - Diabetic nephropathy
  - Macroangiopathy (including peripheral vascular disease)

8.2.3 Hypoglycaemia unawareness

Information on hypoglycaemia unawareness will be recorded at screening according to Clarke's questionnaire, question 8.[33]
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 impaired awareness of hypoglycaemia.

8.2.4 Concomitant illness and medical history

- A **concomitant illness** is any illness 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 or other trial procedures performed before exposure to trial product.

T2DM and 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.

It must be possible to verify the subject's medical history in source documents such as subject's medical record. If a subject is not from the investigators own practice; the investigator must make reasonable effort to obtain a copy of subject's medical record from relevant party e.g. primary physician. The investigator must document any attempt to obtain external medical information by noting the date(s) when information was requested and who has been contacted.

8.2.5 Concomitant medication

A **concomitant medication** is any medication, other than the trial product(s), which is taken during the trial, including the screening, run-in, treatment 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 Concomitant medication (diabetes)

Any diabetes medication other than the trial product(s) which is taken during the trial, including the screening, run-in, treatment and follow-up periods must be recorded in a separate concomitant medication (diabetes) form in the eCRF including the trade name or generic name, total daily dose, frequency, start date and stop date or continuation. For subjects treated with metformin it is the start date and dose of last stable metformin dose which should be reported.

At the run-in visit (Visit 2) basal insulin and all OADs except for metformin must be discontinued and a stop date recorded. For subjects treated with metformin, investigator should at each weekly

contact (visit or phone contact), confirm with the subject that dose and frequency of metformin has been unchanged. This should be documented in the medical records.

At the randomisation visit (Visit 14) pre-trial bolus insulin must be discontinued and a stop date recorded.

It is important to ensure subjects adhere to treatment. Therefore, during the treatment period (from randomisation to End of Treatment) the investigator must also at each weekly contact (visit or phone contact), evaluate if the subject has taken any ancillary treatment since last contact.
Ancillary treatment is defined as any diabetes medication - other than randomised treatment (trial products in the basal-bolus regimen with or without metformin) initiated in case of unsatisfactory glycaemic control. It should be registered as such on the concomitant medication (diabetes) form in the eCRF. For subjects not treated with metformin prior to the randomisation, initiation of long term use of metformin is considered as ancillary treatment. A medication error (Section 8.4.1.1) is as such not considered as ancillary treatment.

8.2.7 Childbearing potential

It must be recorded in the eCRF whether female subjects are of childbearing potential. Reason for not being of childbearing potential must be documented in the medical records.

Pregnancy testing must be performed on female subjects of childbearing potential as described in Section 8.5.2. Female subjects of childbearing potential must be instructed to use adequate contraceptive methods throughout the trial and until 1 week after end of treatment.

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

8.2.8 Tobacco use

Details of tobacco use must be recorded at Visit 1. Smoking is defined as smoking at least one cigarette or equivalent daily.
Smoking status:

- Never smoked
- Previous smoker
- Current smoker

8.3 Efficacy assessments

8.3.1 Meal test

The subject will undergo a standardised liquid meal test at two visits (see flowchart section 2) and will have their 30 minute and 1, 2, 3 and 4 hour PPG measured. The total duration of the meal test is expected to be up to 6 hours including preparations. During that time 6 blood samples will be drawn, as specified in the Table 8–1.

Before initiation of the meal test

The subject should be instructed to:

- Follow normal routine regarding eating and exercise habits on the day prior to the meal test
- Refrain from intake of alcohol and use of medications that affect motility (i.e. prokinetics, anticholinergics, tricyclic antidepressants) on the day prior to the meal test, unless the subject was on this medication at trial entry and does not change the product or product dose
- Remember to bring their current/trial bolus and basal insulin, diary and BG meter to the meal test visits
- Attend the meal test visits in a fasting condition. For definition of fasting, please refer to section 8.1.5. If subjects are normally dosing basal insulin in the morning, it is important they wait until after completion of the meal test
- Achieve an SMPG value within a range of 4.0-8.8 mmol/L [71-160 mg/dL] before beginning the meal test. The SMPG value should be verified at the site before starting the meal test.

The meal test should be re-scheduled within the visit window and at Visit 14 before randomisation to trial product in case:

- any hypoglycaemic episode occurs from midnight before the meal test
- the subject is not fasting or
- the SMPG value is outside the range.

At Visit 14 (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 14 meal test performed.

Bolus insulin dose and meal test carbohydrate calculation

The standardised liquid meal will be provided by Novo Nordisk. The volume of the liquid meal should be measured out by the investigator to be the equivalent to 78 grams of digestible carbohydrates (total carbohydrate content minus fibre).

At the baseline meal test, the bolus insulin dose should be calculated by the investigator by dividing the digestible carbohydrate content of the standardised meal by a calculated insulin:carbohydrate ratio. The insulin:carbohydrate ratio in this trial is calculated by dividing 500 by the total daily dose (taken from the day before) of both basal and bolus insulin. The calculated dose should be rounded to the nearest whole unit.

Same bolus insulin dose will be used for the meal test at end of treatment. The insulin should be administered subcutaneously in the abdomen in accordance with Table 8–1.

Initiation of meal test

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

For the meal test at Visit 14 the subject must receive the bolus insulin that was also used in the run-in period.

For the meal test at Visit 30 the subject should receive the bolus trial insulin they were randomised to and have used throughout the treatment period. If subject has been prematurely discontinued they should perform a meal test both at Visit 30A and again at Visit 30; the meal test at Visit 30 should be performed with the marketed bolus product the subject was switched to.

The start of consumption of the liquid meal is defined as time point 0. The subject must consume the liquid meal as quickly as possible and within 12 minutes. The investigator should confirm that the subject consumed the required volume of the standardised liquid meal in the eCRF.

Table 8–1 Meal test schedule

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

Conduct of meal test

The subject should stay in the clinic to have the blood samples drawn after 30 minutes, 1, 2, 3 and 4 hours from the start of the standardised meal, as detailed in Table 8–1. The samples will be analysed by the central laboratory.

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 ≤3.9 mmol/L [70 mg/dL] are measured, then the hypoglycaemia should be treated with glucose rescue treatment according to local practice and the meal test should continue according to the investigator's discretion. The hypoglycaemic episode must be reported. Please see section 8.4.2.

After the end of the meal test, the investigator should make sure that the subject is safe to leave the site by performing an additional SMPG measurement.

Only after the meal test at Visit 14 is completed, the subject will be allowed to start treatment with randomised trial product.

Data collection

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
- Actual clock 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 consumed
- Actual clock time and dose of bolus insulin
- Actual clock time of blood samples
- Hypoglycaemic episodes, if relevant
    - SMPG value, time of intervention and amount of glucose rescue treatment and hypoglycaemic episode form

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 in order to keep the blinding of the subject and investigator.

8.3.2 Discontinuation of MyGlucoHealth BG-meter and electronic diary

This section applies to subjects enrolled prior to implementation of Global Protocol Amendment no. 2.0. Subjects who have used the glycaemic data collection system (the combination of the MyGlucoHealth Wireless BG-meter and an electronic diary (eDiary)) have been instructed to discontinue this system and use an alternative BG-meter until a new trial BG-meter and paper diary is provided by Novo Nordisk.

The following must be recorded by the investigator in the eCRF:

- Start date of new trial BG-meter

8.3.3 Self-measured plasma glucose

At Visit 2, subjects will be provided with a BG meter including ancillaries as well as instructions for use, if needed. The subjects will be instructed in how to use the device.

The subjects should be instructed how to record the results of the SMPG values including a 7-9-7 point profile in the diaries. Data from the diary must be transcribed into the eCRF during or following the contact. If obtained via phone and a discrepancy is later detected, the values in the eCRF must be corrected.

Occasional review by the investigator of the values stored in the memory of the BG-meter and correct reporting of these in the diary is advised in order to ensure adequacy of the data reported in the trial database.

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.

Only the BG meter provided by Novo Nordisk should be used for the measurements required in the protocol.

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 from Visit 2 to Visit 30 for titration purposes. The measurements should be performed at the following time points:

- Before breakfast
- Before lunch
- Before main evening meal (dinner)
- At bedtime

For SMPG measurements actual clock time, time point (e.g. before breakfast), date and value should be recorded in the diary.

SMPG values measured before breakfast, lunch, 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 main evening meal). 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.

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

The 7- and 9-point SMPG profiles will be used for titration purposes and evaluation of the effect 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 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)[a]
60 minutes after the start of breakfast	X	√	X
Before lunch	X	√	X
60 minutes after the start of lunch	X	√	X
Before main evening meal	X	√	X
60 minutes after the start of main evening meal	X	√	X
At bedtime	X	√	X
At 4 am		√	

[a]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, time point (e.g. before breakfast), date and value should be recorded in the diary. SMPG values measured before breakfast, lunch and main evening meal and at bedtime should be performed before any insulin injection and just before the start of the meal (breakfast, lunch or main evening meal). SMPG values measured before breakfast should be performed in a fasting condition.

The measurements will be used to evaluate the glucose profile.

8.3.4 Insulin dose

The subject should be instructed to report the following concerning dosing of trial products in the diary:

- Date, actual clock time and dose of basal and bolus insulin on a daily basis from Visit 2 to Visit 30.
- Date, actual clock time, and dose for other (extra) bolus insulin administration as well as time and type of previous main meal and reason for the extra bolus from Visit 2 to Visit 30.

Data from the diary must be transcribed into the eCRF during or following the contact. If obtained via phone and a discrepancy is later detected, the values in the eCRF must be corrected.

Dosing and dose adjustment (new dose)

The recommended insulin doses will be calculated in the eCRF based on recommendations from the Insulin Titration Guideline (see Appendix A). At each visit/phone contact the investigator will titrate the subject's insulin doses by making prescribed dose adjustments based on the recommendation from the eCRF if applicable and provide the new prescribed dose to the subject.

Investigator must hand out the subject mealtime insulin dose adjustment guide at Visit 14 and should instruct subjects to perform self-titration of bolus (mealtime) trial insulin between the scheduled visits/phone contacts from Visit 14 to Visit 30.

The investigator should record the following in the eCRF:

- Prescribed doses of trial products
- Reason for deviating in dose adjustments from the titration guideline, if applicable

The subject should report the following in the diary:

- Dose adjustment of bolus trial insulin

8.4 Safety assessments

In case of an abnormal and clinically significant finding, the investigator must record the finding on the concomitant illness form if it is present at screening. Any new finding fulfilling the definition stated in section 12 during the trial and any clinically significant worsening from baseline must be reported as an AE.

8.4.1 Adverse events

Adverse events (AEs) must be reported at each visit in accordance with the procedures outlined in Section 12.

8.4.1.1 Medication error

If a medication error is observed during the trial, the following information is required and a specific event form must be completed in the eCRF in addition to the AE form:

- Trial product(s) involved
- Classification of medication error
- Whether the subject experienced any hypoglycaemic episode and/or AEs as a result of the medication error
- Suspected primary reason for the medication error

For definition of medication errors, see Section 12.1.4.

8.4.1.2 Adverse events requiring additional data collection

For some AEs additional data collection is required and specific event forms must be completed in the eCRF in addition to the AE form.

In case any of these events fulfil the criteria for a SAE, please report accordingly, see Section 12.

Injection site reaction

If an event of injection site reaction is observed the following additional information must be obtained if available on the injection site reaction form:

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

The investigator has to evaluate whether further actions are needed (e.g. extra visits, supervised injection, premature discontinuation of trial products, dermatologist consultation).

If any injection site reactions occur after Visit 31 they should still be recorded as AEs, but the additional data collection on the specific event form in the eCRF is not required.

8.4.2 Hypoglycaemic episodes

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

All plasma glucose (PG) values:

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

should be reported in the diary by the subject from Visit 2 to Visit 32 (FU2) and in the eCRF by the investigator according to the instructions below.

Upon onset of a hypoglycaemic episode the subject is recommended to measure PG every 15 minutes until the SMPG value is >3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved in accordance to current guidelines.[34]

A SMPG value ≤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, occurring within a period of 60 minutes after onset on a hypoglycaemic episode, will by default be considered as one hypoglycaemic episode until a succeeding SMPG value is >3.9

mmol/L (70 mg/dL) and/or symptoms have been resolved and should be reported on one hypoglycaemic episode form. SMPG measurements ≤3.9 mmol/L (70 mg/dL) or hypoglycaemic symptoms after the 60 minutes period shall trigger the reporting of a new hypoglycaemia episode and prompt the subject to fill out a new hypoglycaemic episode form until a succeeding measurement is >3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved.

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

The record should include the following information:

- Start date and time of the hypoglycaemic episode
- The PG level before treating the episode (if available) and any follow up measurements.
  The lowest value measured during the hypoglycaemic episode will be reported as the PG value for the episode, the remaining values will be kept as source data in the diary.
- 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.
- 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.Date, time and dose of last bolus insulin administration prior to the episode
- Date, time and dose of last basal administration prior to the episode
- Date and time of last main meal (not including snacks) prior to the episode
- Whether the episode occurred in relation to physical activity
- Change in any concomitant illness
- Any sign of fever and/or other acute disease
- 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 the subject able to treat him/herself?" must be answered "No" for an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of PG to normal is considered sufficient evidence that the event was induced by a low PG concentration.[34]

Oral carbohydrates must 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 another 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 change, medication error (i.e. overdose, mix-up between products, incorrect use of device), miscalculation of dose of antidiabetic medication, 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[35] (layman term used in the diary 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 for low SMPG values not reported as hypoglycaemic episodes. The subject must be questioned whether any of the low values were severe, i.e. whether the subject was able to self-treat or not. If the subject was not able to self-treat, it has to be reported as a severe hypoglycaemic episode.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 start date, SMPG value and whether the subject was able to self-treat due to decreased validity of such data.[36, 37]

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

If the hypoglycaemic episode fulfils the criteria for an SAE then an AE form and a safety information form (SIF) must also be filled in the eCRF, see Section 12. One AE-form and SIF can cover several hypoglycaemic episode forms if the subject has not recovered between the episodes.

8.4.3 Eye examination

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

The evaluation must follow the categories:

- Normal
- Abnormal
  - Was the result clinically significant? (Yes/No)

Abnormal and clinically significant findings must be recorded as described in Section 8.4.

If a fundus photography/pharmacologically dilated fundoscopy has been performed within 90 days before Visit 2 and if the results are available at Visit 2, then the procedure does not need to be repeated. If performed before the subject consents to participate in the trial, it must also be stated in the subject's medical records that this procedure was not performed in relation to the trial.

The eye examination must be performed prior to administration of bolus trial insulin at Visit 14 (the results do not need to be available for randomisation). An eye examination performed within 14 days prior to randomisation is acceptable.

Eye examination obtained within 21 days prior to Visit 30 is acceptable if the result is available at the visit.

For subjects prematurely discontinued trial products: eye examination performed 21 days in advance of Visit 30A are acceptable if the results are available at the scheduled visits. However eye examination performed at Visit 14 cannot be accepted for the Visit 30A.

8.4.4 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 or write the interpretation of the ECG in the subject's medical records.

The evaluation must follow the categories:

- Normal
- Abnormal
  - Was the result clinically significant? (Yes/No)

Abnormal and clinically significant findings must be recorded as described in Section 8.4

If an ECG-12 lead has already been performed within 21 days before screening (Visit 1), and if the results are available at the screening visit, the procedure does not need to be repeated. If performed before the subject consents to participate in the trial it must also be stated in the subject's medical records that this procedure was not performed in relation to the trial.

ECGs performed 21 days in advance of Visit 14 and Visit 30 are acceptable if the results are available at the scheduled visits.

For subjects prematurely discontinued trial products: ECGs performed 21 days in advance of Visit 30A are acceptable if the results are available at the scheduled visits. However ECGs performed at Visit 14 cannot be accepted for the Visit 30A.

8.4.5 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 must be measured prior to the start of the meal test at Visit 14 and Visit 30.

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.

8.4.6 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

The results must be transcribed to the eCRF as:

- Normal
- Abnormal
  - Was the result clinically significant? (Yes/No)

Abnormal and clinically significant findings must be recorded as described in Section 8.4

8.4.7 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.

Abnormal and clinically significant findings must be recorded as described in Section 8.4

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.

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.

Samples will be coded in order to keep subject's identity anonymous.

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.

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 Section 8.2.4 and Section 12. Review of laboratory reports must be documented either on the documents and/or in the subject's medical record.

Only laboratory samples specified in the protocol must be sent to the central laboratory for analysis; if additional laboratory sampling is needed, e.g. to follow up on AEs, this must be done at a local laboratory.

Laboratory samples will be destroyed on an ongoing basis and no later than at finalisation of the clinical trial report.

8.5.1 Laboratory assessments for efficacy

Glucose metabolism

Plasma glucose will be measured during the meal test. See section 8.3.1.

FPG is measured in order to evaluate metabolic control. The subject must attend these visits fasting. For definition of fasting, see Section 8.1.5.

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

The level of 1,5-anhydroglucitol (GlycoMark) is measured in order to evaluate post prandial glucose excursions.

Blood samples will be drawn to determine the HbA_{1c} level in order to evaluate metabolic control.

Fasting C-peptide is measured at randomisation in order to reflect endogenous insulin secretion.

Lipids

Blood samples for lipids will be analysed to determine:

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

8.5.2 Laboratory assessments for safety

Biochemistry

Blood samples for biochemistry will be analysed to determine:

- ALT
- AST
- albumin
- alkaline phosphatase
- creatinine
- potassium
- sodium
- total bilirubin
- total protein
- eGFR(estimated glomerular filtration rate) at screening

eGFR will be calculated by the central laboratory based on the creatinine value using the CKD-EPI equation which may help evaluate exclusion criteria 14 according to local label.[33]

Haematology

Blood samples for haematology will be analysed to determine:

- erythrocytes
- haematocrit
- haemoglobin
- leucocytes
- thrombocytes

Pregnancy testing

For females of childbearing potential (see section 8.2.7), 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 pregnancy is suspected or if 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.

8.6 Other assessments

8.6.1 Dietary training in simple carbohydrate counting

During the run-in period all subjects should have dietary training regarding simple carbohydrate counting (e.g. sessions with a diabetes educator, dietician or qualified site staff) to improve subject's carbohydrate awareness and understanding of their eating habits effect on their diabetes. 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 [34]

A 3x24-hour meal record should be filled in by the subject prior to the visits indicated in the flowchart (Section 2) in order to evaluate the subject's ability to count the carbohydrate content of the meal. The meal records will not be collected by the sponsor.

8.6.2 Training in the pen injector

The subjects must be trained in how to handle the pen injector when handed out the first time. Training must be repeated according to flowchart (Section 2) in order to ensure correct use of the pen injector. The following should be emphasised:

- Always use a new needle for each injection as this will prevent contamination and blocked needles
- Remember to prime the pen to ensure product 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.
- Always check that the correct insulin pen is used (bolus or basal) e.g. by colour coding and label. Use the pen differentiation guide as a reference.
- In-use time and storage conditions of pen-injectors (Section 9.3).

8.6.3 Diary

At the run-in visit (Visit 2) the subjects will be provided with a diary. The investigator must carefully instruct the subject in how to use the diary. At each following site visit the subject will be provided with a new diary. The diary must be collected at the next site visit and retained at the site as source data in accordance with Section 14.

At FU1 the subject should be provided with a diary for collecting hypoglycaemic episodes in the remaining follow up period. This diary will not be returned to site by the subject since FU2 is a phone contact. Consequently, source data for FU2 is the notes written in subject's medical record.

All data entered in the diary is considered source data, as described in sections 8.3.3, 8.3.4 and 8.4.2.

The subjects will be instructed in recording the following in the diary:

- Daily 4-point profiles
- Date, dose, clock time and time point of bolus insulin
- Date, dose and time of basal insulin
- 7-9-7- profiles (before visits 14, 22, 30 and 30A)
- Date of first basal dose of trial product (V2)
- Date of first bolus dose of trial product (V14)
- Date of last dose of trial product (V30)
- Hypoglycaemic episodes as described in section 8.4.2

The investigator is allowed to record the following in the diary:

- prescribed doses of trial insulin
- time and date of next visit and/or phone contact
- subject ID and site contact details

Diaries must be reviewed by the investigator to ensure that AEs, including any overall change in health and concomitant medication, are reported. The review must be documented on the front page of the diary and data must be transcribed into the eCRF.

Selected titration data (e.g. certain SMPGs and dose data) will only be used during the trial for central titration surveillance, to ensure compliance with the titration guideline (Appendix A), and will not be reported in the CTR. All data will be stored by Novo Nordisk (Section 24).

Diary records after premature discontinuation of trial product:
The Subject will be handed out premature discontinuation diaries at visit 30A to record the following:

- Hypoglycaemic episodes
- 7-9-7- profiles (visit 22 and 30)

8.7 Subject compliance

Throughout the trial, the investigator will remind the subjects to follow the trial procedures and requirements to ensure subject compliance. In addition, subject compliance will be assessed by monitoring of drug accountability at specified visits, please refer to the flow chart (Section 2). The

unused amount of investigational medicinal product (IMP) will be assessed against the dispensed amount and, in case of discrepancies, the subject must be asked to clarify.

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.

The investigator will at each weekly contact (visit or phone contact) assess the subject's compliance by evaluating the glycaemic control, adherence to treatment and the visit schedule and completion of the subject's diary including the SMPG profiles, dose and hypoglycaemia reporting.

9 Trial supplies

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

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

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

9.1 Trial products

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

Table 9–1 Trial products

Trial product	Strength	Dosage form	Route of administration	Container/ delivery device
Faster aspart, (IMP), test product	100 U/ml	Solution for injection	Subcutaneously	3 ml prefilled pen
Insulin aspart (NovoRapid®) (IMP), reference therapy				
Insulin degludec (IMP), test product	100 U/ml	Solution for injection	Subcutaneously	3 ml prefilled pen

The following non-investigational medicinal products (NIMP) will not be provided by Novo Nordisk. However, they will be reimbursed if required according to local regulations.

- Rapid acting insulin analogues (NovoRapid® or marketed formulations of insulin lispro or insulin glulisine) in the run-in period
- Metformin, tablets for oral use

The comparator and active drug are visually identical.

9.2 Labelling

The trial products will be labelled in accordance with Annex 13[38], local regulations and trial requirements.

Each trial site will be supplied with sufficient trial products for the trial on an on-going basis controlled by the IWRS. Trial product will be distributed to the trial 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). Additionally, the pen differentiation guide must be provided to subjects at randomisation (Visit 14). Direction for use and pen differentiation guide can be provided as needed at the following dispensing visits.

9.3 Storage

Table 9–2 Storage conditions

Trial product	Storage conditions (not-in-use)	In-use conditions	In-use time[a]
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®)			
Insulin degludec	Store in refrigerator (2°C – 8°C) Do not freeze Protect from light	Do not store above 30°C Protect from light Can be stored in refrigerator (2°C – 8°C) Do not freeze	Use within 8 weeks

[a] In-use time starts when first dose is taken

The investigator must ensure that trial product is kept under proper storage conditions and 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). Additional details regarding handling of temperature deviations can be found in the TMM.

Trial product that has been stored improperly must not be dispensed to any subject before it has been evaluated and approved for further use by Novo Nordisk. The investigator must take appropriate action to ensure correct storage.

9.4 Drug accountability and destruction

Drug accountability of all trial products received at site is the responsibility of the investigator.

Returned trial product (used/partly used and/or unused), expired or damaged trial product can be stored at room temperature and must be stored separately from non-allocated trial product.

Non-allocated trial products (expired, damaged and available) must be accounted as unused at the latest at closure of the trial site.

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

Destruction of trial products can be performed on an on-going basis and will be done according to local procedures after accountability is finalised and reconciled by the monitor in the IWRS. Destruction of products must be documented in the IWRS.

9.5 Auxiliary supplies

The following will be provided by Novo Nordisk:

- Direction for use for the prefilled pens
- Novo Nordisk needles
- Standardised liquid meal (for the meal test)
- BG meter and strips, lancets and control solution for BG meter

Only needles provided by Novo Nordisk must be used for administration of trial product.

Please refer to the TMM for further auxiliary details.

10 Interactive voice/web response system

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

IWRS is used for:

- Medication arrival
- Screening
- Screening failure
- Run-in dispensing
- Run-in failure
- Randomisation
- Dispensing
- Dispensing Verification (when barcode scanner is used)
- Treatment discontinuation
- Completion
- Code break
- Drug accountability
- Data change

IWRS user manuals will be provided to each trial site.

11 Randomisation procedure and breaking of blinded codes

At randomisation (Visit 14) the subject will be randomised to either faster aspart or NovoRapid®, both in combination with once daily insulin degludec with or without metformin.

The randomisation will be carried out in a 1:1 manner to the 2 different treatment possibilities described below using the IWRS:

- Faster aspart and insulin degludec with or without metformin
- NovoRapid® and insulin degludec with or without metformin

The investigator, subject and sponsor will be blinded to the bolus treatment.

11.1 Breaking of blinded codes

The IWRS 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 IWRS, 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 IWRS is not accessible at the time of code break the IWRS helpdesk should be contacted. Contact details are listed in Attachment I.

If the code has been broken by investigator, the subject must discontinue treatment with trial product and a treatment discontinuation session must be completed in IWRS.

12 Adverse events, technical complaints and pregnancies

12.1 Definitions

12.1.1 Adverse event

An adverse event (AE) is any untoward medical occurrence in a subject administered a medicinal product, and which does not necessarily have a causal relationship with this treatment.

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

An AE includes:

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

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

- Pre-existing conditions, including those found as a result of screening or other trial procedures performed before exposure to trial product (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 8.4.2.

The following three definitions are used when assessing an AE:

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

  Relationship between an AE and the relevant trial product(s):
  - **Probable** - Good reason and sufficient documentation to assume a causal relationship.
  - **Possible** - A causal relationship is conceivable and cannot be dismissed.
  - **Unlikely** - The event is most likely related to aetiology other than the trial product.

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

12.1.2 Serious adverse event

A serious adverse event (SAE) is an experience that at any dose results in any of the following:

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

a. The term "life threatening" in the definition of SAE refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe.

b. The term "hospitalisation" is used when a subject:

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

[c.] A substantial disruption of a subject's ability to conduct normal life functions (e.g. following the event or clinical investigation the subject has significant, persistent or permanent change, impairment, damage or disruption in his/her body function or structure, physical activity and/or quality of life).

[d.] For example intensive treatment in an emergency room or at home of allergic bronchospasm, blood dyscrasia or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

The following AEs must always be reported as an SAE using the important medical event criterion if no other seriousness criteria are applicable:

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

12.1.3 Non-serious adverse event

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

12.1.4 Medication errors

A medication error concerning trial products is defined as:

- Administration of wrong drug.

  Note: Use of wrong dispensing unit number (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), misuse or abuse of trial product.
- Accidental administration of a lower or higher dose than intended. The administered dose must deviate from the intended dose to an extent where clinical consequences for the trial subject were likely to happen as judged by the investigator, although they did not necessarily occur.

Medication errors must be reported on an AE form and a specific event form, see Section 8.4.1.1.

12.1.5 Adverse events requiring additional data collection

AEs requiring additional data collection are AEs where the additional data will benefit the evaluation of the safety of the trial product.

In this trial the following AEs require the completion of specific event forms in the eCRF

- Injection site reaction

For details, see Section 8.4.1.2.

12.1.6 Technical complaints

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)
- All packaging material including labelling
- 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 (FU2). For subjects discontinuing trial products prematurely this also includes events after the post-treatment follow-up period until the last contact (Visit 30). 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.

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.

For all non-serious AEs, the applicable forms should be signed when the event is resolved or at the end of the trial at the latest.

Timelines for initial reporting of AEs:

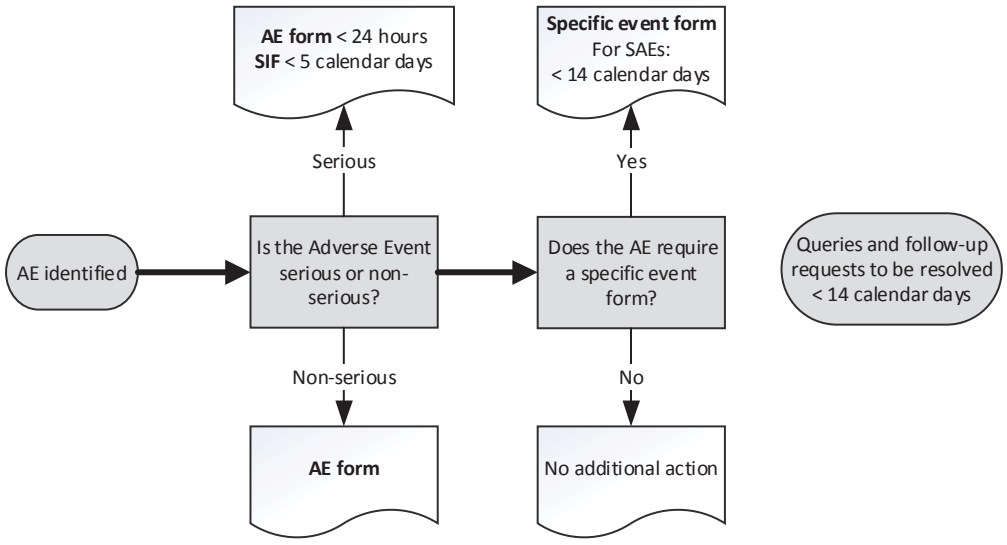
The investigator must complete the following forms in the eCRF within the specified timelines:

- **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.

  For SAEs requiring reporting on a specific event form: In addition to the above the specific event form within **14 calendar days** from the investigator's first knowledge of the AE.

If the eCRF is unavailable, the concerned AE information must be reported on a paper AE form 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 form into the eCRF.

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



Timelines are for the completion of forms from the time of investigator's awareness.
AEs requiring specific event forms are descibed in Section 12.1.4 and 12.1.5.

AE: Adverse Event SIF: Safety Information form

Figure 12–1 Reporting of AEs

Novo Nordisk assessment of AE expectedness:

Novo Nordisk assessment of expectedness is performed according to the following reference documents:

- Faster aspart IB[22] current version and any updates thereto.
- Insulin degludec Company Core Data Sheet current version and any updates thereto.
- NovoRapid®, Company Core Data Sheet current version and any updates thereto.

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.[1] 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 IRBs/IECs of trial product-related SUSARs in accordance with local requirement and ICH GCP[1], unless locally this is an obligation of the investigator.

Novo Nordisk and non-Novo Nordisk products used as concomitant medication or non-investigational medicinal product:

If an AE is considered to have a causal relationship with a non-Novo Nordisk and Novo Nordisk marketed product used as NIMP (NovoRapid® in run-in period) and metformin or concomitant medication in the trial, it is important that the suspected relationship is reported to Novo Nordisk, e.g. in the alternative aetiology section on the safety information form. Novo Nordisk may need to report this AE to relevant regulatory authorities.

12.3 Follow-up of adverse events

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

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

- **SAEs:** All SAEs must be followed until the outcome of the event is "recovered/resolved", "recovered/resolved with sequelae" or "fatal", and until all queries have been resolved. Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome "recovering/resolving" or "not recovered/not resolved". Cases can be closed with the outcome of "recovering/resolving" when the subject has completed the follow-up period and is expected by the investigator to recover.

The SAE follow-up information should only include new (e.g. corrections or additional) information and must be reported **within 24 hours** of the investigator's first knowledge of the

information. This is also the case for previously non-serious AEs which subsequently become SAEs.

- **Non-serious AEs:** Non-serious AEs must be followed until the outcome of the event is "recovering/resolving", "recovered/resolved" or "recovered/resolved with sequelae" or until the end of the follow-up period stated in the protocol, whichever comes first, and until all queries related to these AEs have been resolved. Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome "recovering/resolving" or "not recovered/not resolved". Cases can be closed with the outcome of "recovering/resolving" when the subject has completed the follow-up period and is expected by the investigator to recover.

The investigator must ensure that the recording of 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.

SAEs after end of trial: If the investigator becomes aware of an SAE with a suspected causal relationship to the IMP occurring to a subject after the subject has ended the trial, the investigator should report this SAE within the same timelines as for SAEs during the trial.

12.4 Technical complaints and technical complaint samples

12.4.1 Reporting of technical complaints

For Novo Nordisk Products

All technical complaints on any of the following products:

- Faster aspart, 100 U/mL solution for subcutaneous injection, 3 mL PDS290 pen injector (blinded)
- NovoRapid®, 100 U/mL solution for subcutaneous injection, 3 mL PDS290 pen injector (blinded)
- Insulin degludec, 100U/mL solution for subcutaneous 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 and/or SAEs.

Technical complaints must be reported on a separate technical complaint form:

- One technical complaint form must be completed for each affected DUN
- If DUN is not available, a technical complaint form for each batch, code or lot number 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.

Only technical complaints related to AEs will be reported in the clinical trial report.

12.4.2 Collection, storage and shipment of technical complaint samples

For Novo Nordisk Products

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 copy of the technical complaint form must be included in the shipment of the sample. If several samples are returned in one shipment, the individual sample and the corresponding technical complaint form must be clearly separated.

The investigator must ensure that the technical complaint sample contains the batch, code or lot number and, if available, the DUN. All parts of the DUN should be returned.

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.

12.5 Pregnancies in female subjects

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.

<u>Forms and timelines for reporting AEs:</u>
Non-serious AEs:

- AE form[a] **within 14 calendar days** of the investigator's first knowledge of the initial or follow-up information to the non-serious AE.

SAEs:

- AE form[a] **within 24 hours** of the investigator's first knowledge of the SAE.
- 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.

[a] 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. If the AE occurred in the foetus or newborn infant, the AE can only be reported on paper AE and safety information form.

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 8.4.2). 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 aspart IB[22], Insulin degludec IB[24] and for NovoRapid®, please refer to the current versions of the SmPC[19] or U.S. Novolog® Label Information.[20]

12.7 Committees related to safety

12.7.1 Novo Nordisk safety committee

Novo Nordisk will constitute an internal faster aspart safety committee to perform ongoing safety surveillance. The faster 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 case report forms (CRFs):

- Pregnancy forms

The following will be provided as paper CRFs to be used when access to the eCRF is revoked or if the eCRF is unavailable:

- AE forms
- Safety information forms
- Technical complaint forms (also to be used to report complaints that are not subject related (e.g. discovered at trial site before allocation)

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. The SMPG values and corresponding insulin doses for titration purposes should be entered **within 24 hours** on week days after the site visit/telephone contact throughout the trial.

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

14 Monitoring procedures

Monitoring will be conducted using a risk based approach including risk assessment, monitoring plans, centralised monitoring and visits to trial sites. 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 and to monitor drug accountability. The first monitoring visit will be performed as soon as possible after first patient first visit at the trial site and no later than 4 weeks after. The monitoring visit intervals will depend on the outcome of the centralised monitoring of the eCRFs (remote assessment of data by Novo Nordisk), the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP, but will not exceed 12 weeks until LPLV at the trial site.

The monitor must be given direct access to all 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.

Data collected prior to the discontinuation of the glycaemic data collection system (the combined use of the MyGlucoHealth BG-meter and an electronic diary):
Data entered by the subject in the eDiary device will be recorded directly in the device. All data entered in the eDiary device will be automatically transferred to a 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 database is regarded as source data. For data entered by the investigator through the webportal the source documentation can be the medical records but if entered directly into the webportal, the database is regarded as 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.

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.
- Screen failure date and reason
- Date of visit
- Demography (date of birth, sex and race (according to local regulation))
- Eligibility criteria
- SAE

Monitors will review the subject's medical records and other source data to ensure consistency and/or identify omissions compared to the eCRF. If discrepancies are found, the investigator must be questioned about these.

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 (CRO).

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

Data from central laboratories will be transferred electronically. 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.

Data collected prior to the discontinuation of the glycaemic data collection system (the combined use of the MyGlucoHealth BG-meter and an electronic diary):
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 may be written in addition to the protocol, including a more technical and detailed elaboration of the statistical analyses. The statistical analysis plan will be finalised before database lock.

General considerations

In general, for endpoints evaluated as a change from baseline and/or where a baseline adjustment is made, baseline is defined as information collected at randomisation (Visit 14). In case a measurement is not available at randomisation, the most recent measurement prior to randomisation will be used as baseline.

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

- In-trial: The observation period from date of randomisation and until last trial -related subject-site contact. The in-trial observation period includes data collected after treatment discontinuation.
- On-treatment: The observation period from date of first dose of randomised NovoRapid®/faster aspart and to 7 days after the first occurrence of:
    - The day of last dose of randomised NovoRapid®/faster aspart
    - The day before initiation of ancillary treatment

All efficacy endpoints will be summarised and analysed using the full analysis set (FAS), unless otherwise stated. Safety endpoints will be summarised using the safety analysis set and analysed using the FAS. The FAS is defined in section 17.2.

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

Data collected before randomisation (Visit 14) will only be summarised descriptively.

The primary objective of the trial is to confirm the effect of treatment with faster aspart compared to NovoRapid®, both in combination with insulin degludec with or without metformin in adults with T2DM in terms of glycaemic control, using a non-inferiority approach.

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

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

The steps in the hierarchical testing procedure are as follows:

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

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

Step 3: HbA_{1c} superiority of faster aspart versus NovoRapid®

Step 4: 1,5-anhydroglucitol superiority of faster aspart versus NovoRapid®

Estimands

Primary estimand

The primary estimand is defined as the treatment difference between subjects randomised to faster aspart and NovoRapid® both in combination with insulin degludec with or without metformin, in adults with T2DM not optimally controlled with a basal-bolus regimen assessed by change from baseline in HbA_{1c} 16 weeks after randomisation for all randomised subjects regardless of treatment discontinuation or use of ancillary treatment.

The primary estimand assesses the expected benefit a future population with T2DM can achieve if prescribed to faster aspart as compared to NovoRapid®. 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 treatment reflects clinical practice. Thereby the primary estimand provides a treatment difference for clinicians concerning the glycaemic effect of faster aspart compared to NovoRapid® in the day to day life in subjects with T2DM in an adult population.

Secondary estimand

A secondary estimand is defined as the treatment difference in change from baseline in HbA_{1c} 16 weeks after randomisation between treatment with faster aspart and treatment with NovoRapid® both in combination with insulin degludec with or without metformin in adult subjects with T2DM

not optimally controlled with a basal-bolus regimen if all subjects had adhered to randomised treatment and did not receive ancillary treatment.

The condition 'adhered to randomised treatment and did not receive ancillary treatment' should be interpreted as the exclusion of information collected after initiation of antidiabetic treatment that can mask or exaggerate the effect of the initially randomised treatment. Only data collected prior to discontinuation of trial product or initiation of ancillary treatment is used to draw inference. This avoids confounding effects of ancillary treatment.

The two estimands will be repeated for the confirmatory endpoints

- Change from baseline in 1-hour PPG increment (meal test) 16 weeks after randomisation
- Change from baseline in 1,5-anhydroglucitol 16 weeks after randomisation

17.1 Sample size calculation

The sample size is determined to ensure a sufficient power for step 1 and step 2 in the hierarchical testing procedure for the primary estimand presented in section 17. The power for step 3 and 4 in the hierarchical testing procedure will also be presented. The sample size is determined using a non-inferiority limit of 0.4% in step 1, which was chosen as described in section 5.2.1. The statistical evaluation will be done as described in section 17.3.

In previous confirmatory trials where faster aspart has been investigated, the completion rates have been high. Therefore it will be expected that treatment discontinuation might be as low as 10% where trial discontinuation constitutes half of these and with similar withdrawal reasons in the treatment arms.

Power for the non-inferiority step (Step 1) is based on a t-statistic under the assumption of a one-sided test of size 2.5% for the FAS. A mean treatment difference of -0.1% for the comparison between faster aspart and NovoRapid® in favour of faster aspart is expected. As trials in this population where data from treatment withdrawn subjects is retrieved is limited, a conservative estimate of the standard deviation (SD) in change from baseline in HbA_{1c} of 0.8% was chosen. The power for superiority in step 3 will be calculated using the same assumptions as for step 1 but without the non-inferiority margin.

For determination of power in step 2 in the hierarchical testing, where change from baseline in 1-hour PPG increment 16 weeks after randomisation is compared between faster aspart and NovoRapid® a t-statistic with a two-sided test of size 5% is used, where the treatment difference is expected to be at least 0.6 mmol/L [11 mg/dL]. The SD=3.5 mmol/L [63 mg/dL] in change from baseline in 1-hour PPG increments 16 weeks after randomisation based on laboratory analysed PG in a standardised meal test will be considered reasonable based on trials NN1218-3852 and NN1218-3853.

The power in step 4, where superiority of faster aspart over NovoRapid® in change from baseline in 1,5-anhydroglucitol 16 weeks after randomisation is tested a t-statistic with a two-sided test of size 5% is used. The mean treatment difference is expected to be at least 0.2 µg/mL and an SD of 3.5µg/mL will be used based on trials NN1218-3852 and NN1218-3853.

The power calculations are done using proc power in SAS 9.4. Please refer to Table 17–1 for assumptions for the sample size calculation.

Table 17–1 Specifications assumed for sample size calculations

	Statistical test	Significance level	Analysis population	Non-inferiority margin	SD	Mean difference	Randomisation scheme
Step 1	2-group t-test	One-sided 2.5 %	FAS	0.4 % (absolute)	0.8 %	-0.1 %	1:1
Step 2	2-group t-test	Two-sided 5.0%	FAS	NA	3.5 mmol/L	0.6 mmol/L	1:1
Step 3	2-group t-test	Two-sided 5.0%	FAS	NA	0.8 %	-0.1 %	1:1
Step 4	2-group t-test	Two-sided 5.0%	FAS	NA	3.5 µg/mL	0.2 µg/mL	1:1

In Table 17–2 the sensitivity of the sample size to the power shown for three different sizes of FAS. Three different choices of the mean difference are used to calculate the power in step 2.

Table 17–2 Sensitivity of sample size to power

N total	N per arm	Step 1			Step 2			Step 3			Step 4		
FAS	FAS	Mean diff (%)	SD (%)	Power (%)	Mean diff (mmol/L)	SD (mmol/L)	Power (%)	Mean diff (%)	SD (%)	Power (%)	Mean diff (µg/mL)	SD (µg/mL)	Power (%)
		-0.1	0.8	>99.9	0.5	3.5	58.1	-0.1	0.8	47.4	0.2	3.5	13.9
920	460	-0.1	0.8	>99.9	0.6	3.5	73.8	-0.1	0.8	47.4	0.2	3.5	13.9
		-0.1	0.8	>99.9	0.7	3.5	85.8	-0.1	0.8	47.4	0.2	3.5	13.9
		-0.1	0.8	>99.9	0.5	3.5	64.7	-0.1	0.8	53.4	0.2	3.5	15.5
1072	**536**	**-0.1**	**0.8**	**>99.9**	**0.6**	**3.5**	**80.1**	**-0.1**	**0.8**	**53.4**	**0.2**	**3.5**	**15.5**
		-0.1	0.8	>99.9	0.7	3.5	90.5	-0.1	0.8	53.4	0.2	3.5	15.5
		-0.1	0.8	>99.9	0.5	3.5	70.4	-0.1	0.8	58.9	0.2	3.5	17.0
1224	612	-0.1	0.8	>99.9	0.6	3.5	85.0	-0.1	0.8	58.9	0.2	3.5	17.0
		-0.1	0.8	>99.9	0.7	3.5	93.8	-0.1	0.8	58.9	0.2	3.5	17.0

In conclusion, 1072 subjects in the FAS (536 subjects per group) will ensure a marginal power of >99.9% to show non-inferiority in step 1, given that the actual treatment difference is -0.1%, and a marginal power of 80.1% to show superiority in step 2, given that the actual treatment difference is 0.6 mmol/L.

Assuming a screening failure rate of 30% and run-in failure rate of 15%, 1803 subjects should be screened for inclusion in the trial.

17.2 Definition of analysis sets

The following analysis sets are defined in accordance with the ICH-E9 guidance [39].

- Full Analysis Set (FAS) includes all randomised subjects. In exceptional cases, randomised subjects may be excluded from the FAS. In such cases, the reason for exclusion will be justified and documented. Subjects in the FAS will contribute to the evaluation "as randomised"
- Per Protocol (PP) Analysis Set includes all subjects in the FAS, 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"
- Safety Analysis Set includes all subjects receiving at least one dose of randomised treatment. Subjects in the safety analysis set will contribute to the evaluation "as treated".

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

Before data are released for statistical review, a blinded review of all data will take place to identify serious non-adherence to the protocol that may potentially affect the results. Furthermore, extreme values and outliers will be identified by the statistician during programming and data review, according to ICH-E9.[39] This will be performed by using a fake randomisation.

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

17.3 Primary endpoint

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

Primary analysis:

1) The primary estimand will be addressed by the below primary analysis on all subjects included in the FAS and using the in-trial observation period. Note that if subjects withdraw

consent to contribute additional information or are completely lost to follow-up, missing data will occur. The primary analysis will be implemented as a statistical model using multiple imputations where the subjects without any available HbA_{1c} measurements at scheduled visits will have their HbA_{1c} value imputed from the available information from the treatment group the subject has been randomised to. Note that this resembles in essence a mixed model of repeated measurements analysis. Subjects without any 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 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 metformin use at baseline (Yes/No) as factors and baseline HbA_{1c} as covariate is fitted to the change in HbA_{1c} from baseline to week 4 for each treatment group separately. The estimated parameters, and their variances, from these models are used to impute missing values at week 4 for subjects in each treatment group, based on region, metformin use at baseline (Yes/No) and baseline $HbA_{1c.}$

- In the third step, for each of the 100 copies of the dataset, missing values at week 8 are imputed in the same way as for week 4. The imputations are based on an analysis of variance model with region and metformin use at baseline (Yes/No) as factors and baseline HbA_{1c} and change from baseline in HbA_{1c} at week 4 as covariates.

- This stepwise procedure is then repeated sequentially for week 12 and 16.

- For each of the complete data sets, the change from baseline to week 16 is analysed using an analysis of variance model with treatment, region and metformin use at baseline (Yes/No) as factors, and baseline HbA_{1c} 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:

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

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

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

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

Non-inferiority of faster aspart 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

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

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

Note that as the anticipated number of subjects discontinuing treatment, but not trial is low, multiple imputations based on such subjects is not expected to be suitable.

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

Sensitivity analysis for the primary analysis addressing the primary estimand

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

2) First the primary analysis in 1) will be repeated, but excluding all factors except from treatment in the model. This analysis will explore the influence of the different factors.
3) The primary analysis approach chosen for this trial relies on the assumption that missing data is missing at random (MAR). This assumption implies that the HbA_{1c} for subjects leaving the trial, after their withdrawal, develops in a similar way as the HbA_{1c} for similar subjects that remain in the trial (not necessarily on treatment) and had similar development of HbA_{1c} before withdrawal. The MAR assumption may be questionable for subjects withdrawing at own will. Therefore the statistical models using multiple imputation will be repeated with the following alteration:

a) Imputations will be done from the treatment arm that the subject was randomised to and a value of 0.4% (non-inferiority margin) is added to the change from baseline in HbA_{1c} at week 16 for subjects randomised to faster aspart who withdrew from the trial.[40]

b) Imputations will be done from the comparator arm (NovoRapid®). This will serve as a supplementary sensitivity analysis for the superiority analysis. It does not rely on the MAR assumption, but assumes that all subjects who withdraw from the trial in the faster aspart arm shift to NovoRapid®. The imputation will be done conditional on observed information for subjects that withdraw from the faster aspart arm such that the treatment effect diminishes gradually after trial discontinuation (copy reference/conditional imputation). The analysis will use data from the in-trial observation period.

c) Imputation will be done from the comparator arm (NovoRapid®). This will serve as a supplementary sensitivity analysis for the superiority analysis. It does not rely on the MAR assumption, but it is assumed that all subjects who withdraw from the trial in the faster aspart arm respond at week 16 as if they have been treated with NovoRapid® for the entire trial. That is, all collected post-randomisation data for subjects who withdraw from the trial in the faster aspart arm will be set to missing. The analysis will use data from the in-trial observation period.

Analyses addressing the secondary estimand

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

4) The secondary estimand will be analysed using the same statistical model using multiple imputations as the primary analysis in 1) except using the on-treatment observation period.
5) A tipping point analysis based on a statistical model using multiple imputation model similar to 1), using the on-treatment observation period, will be made. In this analysis observations for subjects that discontinue randomised treatment are imputed based on the treatment arm they were randomised to and subjects discontinuing treatment in the faster aspart group are given a penalty. This is done to investigate the robustness of the conclusion in the p rimary analysis with respect to the MAR assumption and mimics a scenario where the HbA_{1c} of the subjects discontinuing treatment in the faster aspart groups evolve less favourably than predicted. As a first step imputations will be done without penalty assuming MAR in the treatment group. Second, the imputed values for week 16 in the faster aspart group will be added a penalty. This is done repeatedly, gradually increasing the penalty until the conclusion from the non-inferiority analysis no longer holds. This will serve as a sensitivity analysis for the non-inferiority analysis and the specific value of the penalty that changes the conclusion will be used to evaluate the robustness of the conclusion of the non-inferiority analysis.

6) A tipping point analysis based on a statistical model using multiple imputation, similar to 5) but with the modification that subjects discontinuing treatment due to non-eligibility (Subjects discontinuing randomised treatment prematurely due to criteria 1, 2, 3, and 4, which are defined in section 6.6) in the faster aspart group will not have a penalty added. These analyses are motivated by the fact that data from subjects prematurely discontinuing randomised treatment due to non-eligibility can reasonably be assumed to be missing completely at random.
7) The same statistical model using multiple imputations as the analysis in 4), but using the PP analysis set and analysed using the on-treatment observation period. This analysis will investigate the situation that subjects might have deviated from the inclusion and exclusion criteria and will serve as sensitivity analysis for the non-inferiority analysis.

17.4 Secondary endpoints

17.4.1 Confirmatory secondary endpoints

If the effect of treatment with faster aspart can be confirmed in the primary analysis, the trial also aims to confirm effect of treatment with faster aspart for a number of secondary confirmatory endpoints using a hierarchical (fixed sequence) testing procedure as described in section 17 (General consideration). 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 aspart.

The confirmatory secondary endpoints are:

- Change from baseline in 1-hour PPG increment 16 weeks after randomisation (meal test)
- Change from baseline in 1,5-anhydroglucitol 16 weeks after randomisation

The steps in the hierarchical testing procedure are as follows:

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

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

Step 3: HbA_{1c} superiority of faster aspart versus NovoRapid®

Step 4: 1,5-anhydroglucitol superiority of faster aspart versus NovoRapid®

The primary estimand for the primary endpoint will be repeated for the confirmatory secondary endpoints, change from baseline in 1-hour PPG increment (meal test) and change from baseline in 1,5-anhydroglucitol 16 weeks after randomisation. The analyses related to these estimands are

defined below and will be used for the decisions to continue or not, throughout the hierarchical testing procedure. These analyses will be based on the FAS and use the in-trial observation period.

As sensitivity analysis the secondary analysis 4) will also be repeated for the confirmatory secondary endpoints. The analyses will be based on the FAS and using the on-treatment observation period.

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

As the second step of the hierarchical testing procedure changes from baseline in 1-hour PPG increment (meal test) 16 weeks after randomisation will be tested for superiority of faster aspart compared to NovoRapid®.

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

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

- An analysis of variance model with region and metformin use at baseline (Yes/No) as factors and baseline 1-hour PPG increment as covariate is fitted to the change from baseline in 1-hour PPG increment at week 16 for the NovoRapid® group only. The estimated parameters, and the variance, from this model are used to impute missing values using stochastic simulation at week 16 for subjects in both treatment groups in order to generate 100 complete datasets.
- For each of the complete data sets, the change from baseline to week 16 is analysed using an analysis of variance model with treatment, region and metformin use at baseline (Yes/No) as factors, and baseline 1-hour PPG increment as covariate.
- The estimates and standard deviations for the 100 data sets are pooled to one estimate and associated standard deviation using Rubins formula. From this, the pooled estimates and 95% confidence interval for the treatment difference is calculated.

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

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

Step 3 in the hierarchical testing procedure is to confirm superiority of change from baseline HbA_{1c} 16 weeks after randomisation of the effect of treatment with faster aspart compared to NovoRapid®. Superiority will be based on the same 95% CI that was used for addressing the primary analysis. Superiority will be confirmed if the upper boundary of the two-sided 95% confidence interval of the mean treatment difference (faster aspart minus NovoRapid®) is below 0%.

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

Step 4 in the hierarchical testing procedure is to confirm superiority of change from baseline 1,5-anhydroglucitol 16 weeks after randomisation of the effect of treatment with faster aspart compared to NovoRapid®. The endpoint will be analysed based on all planned post baseline measurements until or at 16 weeks after randomisation using a model similar to the primary analysis 1), but with baseline 1,5-anhydroglucitol as covariate. Superiority will be confirmed if the upper boundary of the two-sided 95% confidence interval of the mean treatment difference (faster aspart minus NovoRapid®) is below 0.

17.4.2 Supportive secondary endpoints

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 the safety analysis set and will therefore only use the on-treatment observation period.

Change from baseline in FPG 16 weeks after randomisation

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

If a subject achieves HbA_{1c} target 16 weeks after randomisation

HbA_{1c} < 7.0%

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

This responder endpoint will be analysed based on a logistic regression model using treatment , region and metformin use at baseline (Yes/No) as factors, and baseline HbA_{1c} as covariate. In analysis of the in-trial observation period subjects without an HbA_{1c} measurement at week 16 will

be treated as non-responders. In the analysis using the on-treatment observation period both subjects who discontinue randomised treatment or withdraw from trial is included as non-responders.

HbA_{1c} < 7.0% without severe hypoglycaemia

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

This responder endpoint will be analysed based on a logistic regression model using treatment , region and metformin use at baseline (Yes/No) as factors and baseline HbA_{1c} as covariate. In the analysis of the in-trial observation period subjects without an HbA_{1c} measurement at week 16 will be treated as non-responders. In the analysis using the on-treatment observation period both subjects who discontinue randomised treatment or withdraw from trial will be included as non-responders.

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

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

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

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

In general, analyses will be based on the entire 7-9-7-point SMPG profile except for the analyses of nocturnal endpoints where information in the 9-point SMPG profile will be utilised.

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

Pre-prandial PG and PPG will be recorded by the subjects as part of the 7-9-7-point SMPG profile prior to three defined visits. Individual mean mealtime PPG (post-breakfast, post-lunch, post-main evening meal) will be derived from the three profiles. Overall mean PPG will be derived from the individual derived mealtime PPG values.

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

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

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

  Change from baseline in the mean of the 7-9-7-point SMPG profile 16 weeks after randomisation will be analysed based on all planned post baseline measurements until or at 16 weeks after randomisation using a model similar to 1) except with the corresponding baseline value as covariate.

- Change from baseline in PPG and PPG increment (mean, breakfast, lunch and main evening meal)

  Change from baseline in PPG and PPG increment endpoints 16 weeks after randomisation for mean over all three meals and the individual meals will be analysed separately based on all planned post baseline measurements until or at 16 weeks after randomisation using a model similar to 1) except with the corresponding baseline value as covariate.

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

  The fluctuation in the 7-9-7-point SMPG 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. It will be calculated using the linear trapezoidal technique.

  Fluctuation in the 7-9-7-point SMPG profile will be logarithmically transformed and analysed based on all planned post baseline measurements until or at 16 weeks after randomisation using a model similar to 1) except with the corresponding log-transformed baseline value as covariate. Estimated treatment means and the estimated treatment differences with corresponding 95% CI will be back-transformed to the original scale, resulting in estimated geometric means, a treatment ration and a 95% CI for the treatment ratio.

- Change from baseline in nocturnal SMPG measurements

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

  Change from baseline in nocturnal SMPG measurements 16 weeks after randomisation will be analysed based on all planned post baseline measurements until or at 16 weeks after randomisation using a model similar to 1) except with the corresponding baseline values as covariate.

If a subject achieves PPG target (based on overall mean of daily PPG measurements in 7-9-7-point SMPG profile) 16 weeks after randomisation:

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

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

This responder endpoint will be analysed based on a logistic regression model using treatment , region and metformin use at baseline (Yes/No) as factors, and baseline overall 1-hour mean PPG as covariate. In analysis of the in-trial observation period subjects without an overall mean 1 hour PPG at week 16 will be treated as non-responder. In the on- treatment observation period analysis both subjects who discontinue randomised treatment or withdraw from trial will be included as non-responders.

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

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

This responder endpoint will be analysed based on a logistic regression model using treatment , region and metformin use at baseline (Yes/No) as factors, and baseline mean 1-hour PPG as covariate. In analysis of the in-trial observation period subjects without an overall mean 1 hour PPG at week 16 will be treated as non-responders. In the on- treatment observation period analysis both subjects who discontinue randomised treatment or withdraw from trial will be included as non-responders.

Insulin dose (Units/day and Units/kg/day; total basal, total bolus, total daily insulin dose and individual meal insulin dose) 16 weeks after randomisation

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

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

Change from baseline in lipid endpoints (total cholesterol, HDL cholesterol, LDL cholesterol) will be logarithmically transformed and analysed separately based on all planned post baseline measurements until or at 16 weeks after randomisation using a model similar to 1) except with the corresponding log-transformed baseline 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.

17.4.2.2 Safety endpoints

In terms of AEs, as a minimum, SAEs will be tabulated separately 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

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

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

TEAEs are summarised descriptively, whereas AEs 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 technical complaint, premature treatment discontinuation due to AEs, AEs leading to withdrawal from trial and outcome.

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

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

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

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

Number of treatment emergent injection site reactions

Treatment emergent injection site reactions occurring during the trial will be summarised and listed.

Classification of Hypoglycaemia

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

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

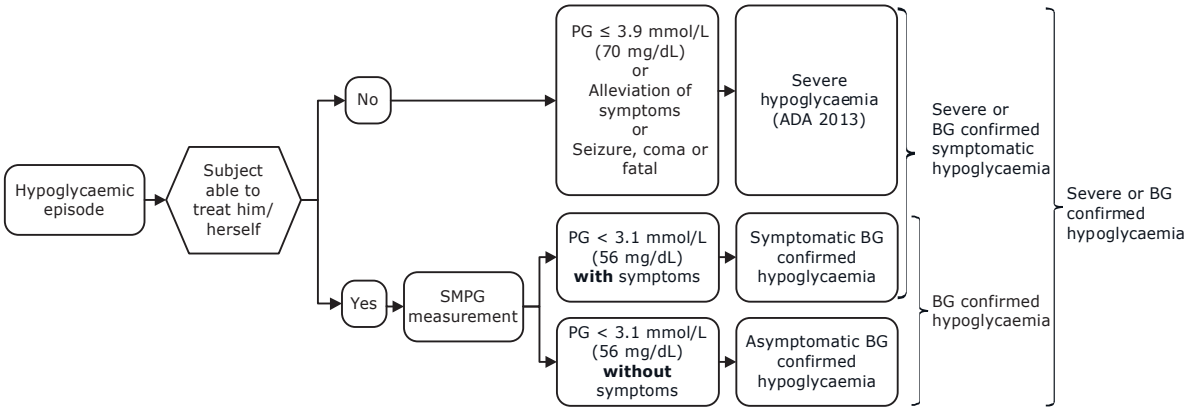
Hypoglycaemic episodes are classified according to the Novo Nordisk classification of hypoglycaemia (see Figure 17–1) and the ADA classification of hypoglycaemia (see Figure 17–2).

Novo Nordisk classification of hypoglycaemia

In normal physiology, symptoms of hypoglycaemia occur below a PG level of 3.1 mmol/L (56 mg/dL).[41] Therefore, Novo Nordisk has included hypoglycaemia with PG levels below this cut-off point in the definition of BG confirmed hypoglycaemia.

Novo Nordisk uses the following classification (see Figure 17–1) in addition to the ADA classification:

- Severe hypoglycaemia according to the ADA classification.[34]
- Severe or BG confirmed hypoglycaemia: An episode that is severe according to the ADA classification[34] or BG confirmed by a PG value <3.1 mmol/L (56 mg/dL) **with** or **without** symptoms consistent with hypoglycaemia.



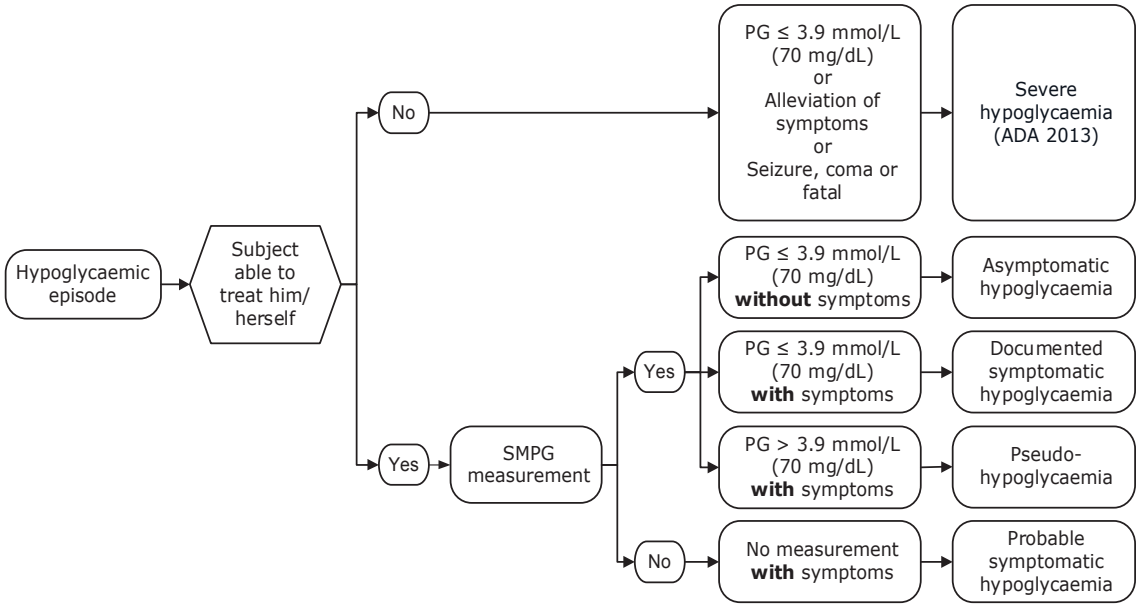
Note: Glucose measurements are performed with capillary blood calibrated to plasma equivalent glucose values

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

Figure 17–1 Novo Nordisk classification of hypoglycaemia

ADA classification[34] of hypoglycaemia

- 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 PG to normal is considered sufficient evidence that the event was induced by a low PG concentration.
- Asymptomatic hypoglycaemia: An episode not accompanied by typical symptoms of hypoglycaemia, but with a measured PG concentration ≤ 3.9 mmol/L (70 mg/dL).
- Documented symptomatic hypoglycaemia: An episode during which typical symptoms of hypoglycaemia are accompanied by a measured PG concentration ≤ 3.9 mmol/L (70 mg/dL).
- Pseudo-hypoglycaemia: An episode during which the person with diabetes reports any of the typical symptoms of hypoglycaemia with a measured PG concentration > 3.9 mmol/L (70 mg/dL) but approaching that level.
- Probable symptomatic hypoglycaemia: An episode during which symptoms of hypoglycaemia are not accompanied by a PG determination but that was presumably caused by a PG concentration ≤ 3.9 mmol/L (70 mg/dL).



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

PG: plasma glucose SMPG: Self-measured plasma glucose

Figure 17–2 ADA classification of hypoglycaemia

Treatment emergent hypoglycaemic episodes are presented in terms of the number of subjects with at least one event (N), the percentage of subjects with at least one event (%), the number of events (E) and the event rate per 100 years of exposure (R). Separate summaries are made by severity considering all episodes, nocturnal and daytime episodes using Novo Nordisk and ADA classified episodes. All episodes will also be summarised by category, including summaries in relation to time since start of meal, as occurring during1, 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 hours, 4 hours and from 2 hours (exclusive) to 4 hours (inclusive) after start of the meal) will be analysed based on the FAS using a negative binomial regression model with a log - link function and the logarithm of the time period in which a hypoglycaemic ep isode is considered treatment emergent as offset. The model will include treatment, region and metformin use at baseline (Yes/No) as factors. To the extent where data allow, separate analysis will be performed for severe hypoglycaemic episodes.

Change from baseline in clinical evaluations 16 weeks after randomisation:

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 using the on-treatment period. 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 the on-treatment period and both actual values as mean change and change from baseline.

Electrocardiogram

ECG findings will be summarised descriptively using the on-treatment period and 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

Fundoscopy/fundus photography findings will be summarised descriptively using the on-treatment period and 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.

Change from baseline in clinical laboratory assessments 16 weeks after randomisation

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

- Haematology (erythrocytes, haematocrit, haemoglobin, leucocytes, thrombocytes)
- Biochemistry (ALT, AST, albumin, alkaline phosphatase, creatinine, potassium, sodium, total bilirubin)

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

Change from baseline in body weight and body mass index 16 weeks after randomisation

The measurements will be summarised descriptively using the on-treatment period and the actual values as mean change.

Change from baseline in body weight will be analysed based on all planned post baseline measurements until or at 16 weeks after randomisation using a statistical model similar to 1) except with the corresponding baseline measurement as covariate.

18 Ethics

18.1 Benefit-risk assessment of the trial

All subjects included in the trial will be treated with basal-bolus regimen with insulin degludec as the basal insulin. Inclusion and exclusion criteria have been chosen to ensure that subjects enrolling in the trial have T2DM at a stage where basal-bolus treatment is needed (i.e. subjects must have been diagnosed with T2DM for 10 years or more and must have been on a basal-bolus treatment regimen at least 365 days prior to screening).

Subjects taking metformin at the enrolment in the trial should continue the metformin treatment unchanged. Metformin plus basal/bolus insulin is a recommended treatment for subjects with T2DM[9] and the combination of metformin and basal-bolus insulin therapy with faster aspart or NovoRapid® as the bolus insulin was included in the phase 3A faster aspart trials in T2DM.

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 in case of low BG measurement.

Trial products will be provided by Novo Nordisk free of charge during the trial. When treatment with trial products ends, the subject and investigator will decide on the best available treatment on the market. Novo Nordisk will not offer any free medications after the completion of the trial.

Summary of clinical pharmacology

The pharmacokinetic and pharmacodynamic profiles of faster aspart consistently demonstrated a left shift compared to that of NovoRapid® in subjects with T1DM and the profiles for faster aspart and NovoRapid® were similar in overall shape. Faster aspart produced a faster onset of exposure and increased initial absorption rate compared to NovoRapid® resulting in a faster onset of action and increased early glucose-lowering effect. Overall, the differences in the pharmacokinetic and pharmacodynamic properties for faster aspart compared to NovoRapid® were consistent across trials.[22] No safety concerns were raised during any of the trials.

Similar clinical pharmacology trials have not been performed in subjects with T2DM, however the phase 3A programme for faster aspart included trials in bolus naïve T2DM subjects. Non-inferiority to NovoRapid® with regard to HbA_{1c} change from baseline was demonstrated. In subjects with T2DM faster aspart statistically significantly improved control of the 1-hour PPG increment when compared to NovoRapid®.[22] No safety issues for faster aspart have been identified based on data from the clinical development programme, and the safety profile is similar to NovoRapid®.[22]

Clinical benefits and risk considerations for the trial

The purpose of this trial is to confirm the effect and compare safety of faster aspart compared to NovoRapid® both in combination with insulin degludec with or without metformin in subjects with T2DM treated with a basal-bolus regimen.

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, subjects 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 will provide the opportunity for optimising the titration of basal and bolus insulin based on SMPG values and thereby may contribute to obtaining improved HbA_{1c} results. All subjects will have reinforced dietary training including simple carbohydrate counting.

For the individual subjects, the anticipated risks include hypoglycaemia, hyperglycaemia, systemic allergic reactions, injection site reactions, lipodystrophy, 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. A phase 3A trial with faster aspart in T2DM showed a slight shift in distribution of the occurrence of hypoglycaemic episodes in relation to a meal when comparing to NovoRapid®. A statistical significant higher rate of hypoglycaemic episodes was seen during the first 2 hours after a meal for faster aspart. This is not unexpected and reflects the pharmacokinetic and pharmacodynamic properties of faster aspart.[22]

All treatments are contraindicated in case of hypersensitivity to the active substances or any of the excipients. The risk of hypersensitivity is partly mitigated by excluding subject with known hypersensitivity towards any trials products or related products.

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. Lipodystrophy (including lipohypertrophy, lipoatrophy) at the injection site can occur. Continuous rotation of the injection site within the particular injection area may help to reduce the risk of developing these reactions.

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

Subjects in this trial will be using bolus and basal insulin administered via two differently colour-coded prefilled 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. Subjects will be trained in distinguishing between the pens. 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.

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 aspart in non-clinical and clinical studies taken together with review of the additional excipients in the faster aspart formulation have not revealed any safety issues that would prohibit the administration of faster 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 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[1] and the requirements in the Declaration of Helsinki.[2]

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

- Data already collected and any data collected at the end-of-trial visit including follow-up visits will be retained by Novo Nordisk, entered into the database and used for the clinical 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 subjects 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 the 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

19.1 Protocol deviations

Deviations from the protocol should be avoided.

If deviations do occur, the investigator must inform the monitor and the implications of the deviation must be reviewed and discussed.

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

Documentation on protocol deviations must be kept in the investigator trial master file and sponsor trial master file.

19.2 Prevention of missing data

The importance of subject retention will be addressed by Novo Nordisk in the training and communication with the trial sites.

The subjects will be carefully informed about the trial procedures before signing informed consent, so that they know the implications of participating in the trial. The run-in period in this trial will reduce the likelihood of drop-outs as only those who adhere to the protocol requirements will undergo randomisation. Subjects will during the run-in period get an understanding of what is expected from them when taking part in the trial and thereby minimise discontinuation from trial product post randomisation. In addition, only absolutely necessary criteria for premature discontinuation of trial products primarily focusing on subjects safety are included and thereby reducing the number of discontinuations and limiting the amount of missing data.

Close surveillance of subject retention will be performed throughout the trial by Novo Nordisk with focus on reasons for premature discontinuation of trial products or withdrawal of consent to secure early mitigations in collaboration with the trial sites.

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[36, 37]; however a 7 days' timeline is applied for reporting of missing hypoglycaemic episode, The subject will be retrained in correct completion of the diary if missing data is identified.

The investigator will make every effort to ensure that all assessments are performed and data is collected. If missing data does occur the reason will be collected via the protocol deviation process, see section 19.1. Novo Nordisk will monitor protocol deviations on an on-going basis throughout the trial followed by appropriate actions (e.g. re-training of site staff).

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, written notification from Novo Nordisk must be received and 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
- 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 Investigational new drug (IND)
- All US investigators, as described above, will sign FDA Form 1572

For sites outside the US:

- Intended for participating sites outside of the US
- Not conducted under the Investigational new drug (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 agreement, each investigator agrees to comply fully with ICH GCP[1], applicable regulatory requirements and the Declaration of Helsinki.[2]

By signing the protocol agreement, each investigator also agrees to allow Novo Nordisk to make investigator's name and information about site name and address publically available if this is required by national or international regulations.

22 Responsibilities

The investigator is accountable for the conduct of the trial at his/her site and must ensure adequate supervision of the conduct of the trial at the trial site. If any tasks are delegated, the investigator must maintain a log of appropriately qualified persons to whom he/she has delegated specified trial-related duties. The investigator must ensure that there is adequate and documented training for all staff participating in the conduct of the trial. It is the investigator's responsibility to supervise the conduct of the trial and to protect the rights, safety, and well-being of the subjects.

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

The investigator 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 must 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.

One investigator will be appointed by Novo Nordisk to review and sign the clinical trial report (signatory investigator) on behalf of all participating investigators. The signatory investigator will be appointed based upon the criteria defined by the International Committee of Medical Journal Editors for research publications.[42]

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.[28]

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.

Authorship

Authorship of publications should be in accordance with the Uniform Requirements of the International Committee of Medical Journal Editors[42] (sometimes referred to as the Vancouver Criteria).

Site-specific publication(s) by investigator(s)

For a multi-centre clinical trial, analyses based on single-site data usually have significant statistical limitations and frequently do not provide meaningful information for healthcare professionals or subjects, and therefore may not be supported by Novo Nordisk. It is a Novo Nordisk policy that such individual reports do not precede the primary manuscript and should always reference the primary manuscript of the trial.

Novo Nordisk reserves the right to prior review of such publications. Further to allow for the primary manuscript to be published as the first, Novo Nordisk asks for deferment of publication of individual site results until the primary manuscript is accepted for publication. As Novo Nordisk wants to live up to the industry publication policy, submission of a primary publication will take place no later than 18 months after trial completion.

23.2 Investigator access to data and review of results

As owner of the trial database, Novo Nordisk has the discretion to determine who will have access to the database.

Individual investigators will have their own research subjects' data, and will be provided with the randomisation code after results are available.

24 Retention of clinical trial documentation

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 and/or electronic devices supplied by Novo Nordisk. These data must be retained by the trial site. If the provided data (e.g. the CD-ROM) is not readable during the entire storage period, the investigator can request a new copy. A copy of all data will be stored by Novo Nordisk.

Novo Nordisk will maintain Novo Nordisk documentation pertaining to the trial for at least 20 years after discontinuation of the marketing authorisation, termination of the trial or cancellation of the research project whichever is longest.

The files from the trial site/institution must be retained for 15 years after end of trial as defined in Section 7, or longer if required by local regulations or Novo Nordisk. In any case trial files cannot be destroyed until the trial site/institution is notified by Novo Nordisk. The deletion process must ensure confidentiality of data and must be done in accordance with local regulatory requirements.

25 Institutional Review Boards/Independent Ethics Committees and regulatory authorities

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:

Poland: Novo Nordisk carries liability for the trial exclusively in the scope defined by the applicable laws and in particular by the Civil Code and the Pharmaceutical Law dated 6 September 2001 (uniform version Journal of Laws of 2008 No. 45 item 271 with amendments). In order to support potential claims for liability attributable to the trial, Novo Nordisk and the investigators are covered by the insurance policy issued according to applicable Polish law.

Russia: Federal law of 12 April 2010 No. 61-FZ 'On Medicinal Drugs' Circulation and Ministry of Healthcare of Russian Federation' order of 01 April 2016 No. 200n "Approval of rules of good clinical practice.

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Appendix A: Titration Guideline

Trial ID: NN1218-4113

Efficacy and Safety of Fast-acting Insulin Aspart Compared to NovoRapid® both in Combination with Insulin Degludec with or without Metformin in Adults with Type 2 Diabetes (onset® 9)

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1 Introduction

The goal of insulin therapy is to achieve near normoglycaemia, i.e. to reach a pre-defined HbA_{1c} 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® /fast-acting insulin aspart (faster 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 12 weeks the Investigator will focus on adjusting the basal insulin dose according to Section 3.2.

In addition, the subjects will continue their pre-trial bolus insulin analogue with or without metformin at Visit 2. No adjustments of bolus insulin should be performed by the Investigator unless for safety reasons during the run-in period.

At randomisation (after 12 weeks) eligible subjects will be randomised 1:1 into two parallel treatment groups:

1. mealtime faster aspart + insulin degludec
2. mealtime NovoRapid® + insulin degludec

During the following 16 weeks treatment period the Investigator will focus on adjusting the bolus insulin dose according to Section 3.5.

2.1 Injection area

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

Faster aspart or NovoRapid® 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.

Faster aspart or NovoRapid® should be given 0-2 minutes prior to main meals.

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

3.1 Initiation of insulin degludec (Visit 2)

Subjects' previous basal insulin should be switched to insulin degludec once daily on unit-to-unit basis at Visit 2 by the Investigator's discretion. However, when switching from Toujeo® or twice daily basal insulin, 20% dose reduction in basal dose should be considered.

3.2 Titration insulin degludec during run-in

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.

Insulin degludec should not be used to correct the postprandial glucose excursions.

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
4.0 – 5.0	**71 – 90**	**No adjustment**
5.1 – 7.0	91 – 126	+ 2
7.1 – 8.0	127 – 144	+ 4
8.1 – 9.0	145 – 162	+ 6
> 9.0	> 162	+ 8

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
<3.1	< 56	- 4

3.3 Treatment with bolus insulin during run-in

Subjects should continue their pre-trial bolus insulin analogue with or without metformin at Visit 2, and no adjustments of bolus insulin should be performed by the Investigator unless for safety reasons during the run-in period.

3.4 Initiation of faster aspart or NovoRapid® at Visit 14

Subjects should be switched to faster aspart or NovoRapid® (blinded) unit-to-unit from previous mealtime bolus doses at Visit 14 by the Investigator's discretion.

3.5 Titration of faster aspart or NovoRapid® from randomisation (Visit 14)

Titration of bolus insulin (faster aspart or NovoRapid®) should be performed from randomisation (Visit 14) and onwards while no adjustments of basal insulin dose(s) should be performed by the Investigator unless for safety reasons during the treatment period.

Subjects will be instructed to perform 4-point profiles at pre-breakfast, pre-lunch, pre- main evening meal and bedtime every day during the conduct of the trial for titration purposes.

Faster aspart or NovoRapid® should be titrated twice weekly to reach the glycaemic target of pre-prandial and bedtime plasma glucose between 4.0-6.0 mmol/L (71 - 108 mg/dL) in a treat-to-target fashion.

1) At the scheduled visit/phone contact, adjustment of faster aspart or NovoRapid® doses should be performed by investigator and based on pre-prandial and/or bedtime SMPG values which are measured during last 3-4 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 aspart or NovoRapid® doses based on SMPG values measured on the remaining 4 – 3 days between scheduled visits/phone contacts.

The adjustments should be according to Table 3

- Breakfast faster aspart or NovoRapid® will be titrated according to pre-lunch SMPG values measured on previous days

- Lunch faster aspart or NovoRapid® will be titrated according to pre-dinner SMPG values measured on previous days
- Main evening meal faster aspart or NovoRapid® will be titrated according to bedtime SMPG values measured on previous days

Table 3 Faster aspart or NovoRapid® dose adjustment algorithm

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
4.0 – 6.0	**71 -108**	**0**	**0-1 SMPG above target** **No SMPGs below target**
> 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 'extra bolus insulin'.

3.6 Deviations from the algorithm

It is recommended that the algorithm is followed. However, it is also important that the decision to adjust the insulin degludec, faster aspart or NovoRapid® doses are based on all relevant information as described in Section 3. A reason for deviating from the algorithm should be entered into the eDiary web portal by the Investigator as applicable.

4 Data collection

The titration data and hypoglycaemic episodes 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 or to request entry of missing data.

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

During the trial HbA_{1c} 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_{1c}. This will be done in an unbiased and whenever possible in a blinded manner.

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Appendix A: Titration Guideline

Trial ID: NN1218-4113

Efficacy and Safety of Fast-acting Insulin Aspart Compared to NovoRapid® both in Combination with Insulin Degludec with or without Metformin in Adults with Type 2 Diabetes (onset® 9)

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1 Introduction

The goal of insulin therapy is to achieve near normoglycaemia, i.e. to reach a pre-defined HbA_{1c} 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® /fast-acting insulin aspart (faster 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 12 weeks the Investigator will focus on adjusting the basal insulin dose according to Section 3.2.

In addition, the subjects will continue their pre-trial bolus insulin analogue with or without metformin at Visit 2. No adjustments of bolus insulin should be performed by the Investigator unless for safety reasons during the run-in period.

At randomisation (after 12 weeks) eligible subjects will be randomised 1:1 into two parallel treatment groups:

1. mealtime faster aspart + insulin degludec
2. mealtime NovoRapid® + insulin degludec

During the following 16 weeks treatment period the Investigator will focus on adjusting the bolus insulin dose according to Section 3.5.

2.1 Injection area

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

Faster aspart or NovoRapid® 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.

Faster aspart or NovoRapid® should be given 0-2 minutes prior to main meals.

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

3.1 Initiation of insulin degludec (Visit 2)

Subjects' previous basal insulin should be switched to insulin degludec once daily on unit-to-unit basis at Visit 2 by the Investigator's discretion. However, when switching from Toujeo® or twice daily basal insulin, 20% dose reduction in basal dose should be considered.

3.2 Titration insulin degludec during run-in

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 last two days prior to and on the day of contact in accordance with Table 1.

Insulin degludec should not be used to correct the postprandial glucose excursions.

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
4.0 – 5.0	**71 – 90**	**No adjustment**
5.1 – 7.0	91 – 126	+ 2
7.1 – 8.0	127 – 144	+ 4
8.1 – 9.0	145 – 162	+ 6
> 9.0	> 162	+ 8

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
<3.1	< 56	- 4

3.3 Treatment with bolus insulin during run-in

Subjects should continue their pre-trial bolus insulin analogue with or without metformin at Visit 2, and no adjustments of bolus insulin should be performed by the Investigator unless for safety reasons during the run-in period.

3.4 Initiation of faster aspart or NovoRapid® at Visit 14

Subjects should be switched to faster aspart or NovoRapid® (blinded) unit-to-unit from previous mealtime bolus doses at Visit 14 by the Investigator's discretion.

3.5 Titration of faster aspart or NovoRapid® from randomisation (Visit 14)

Titration of bolus insulin (faster aspart or NovoRapid®) should be performed from randomisation (Visit 14) and onwards while no adjustments of basal insulin dose(s) should be performed by the Investigator unless for safety reasons during the treatment period.

Subjects will be instructed to perform 4-point profiles at pre-breakfast, pre-lunch, pre- main evening meal and bedtime every day during the conduct of the trial for titration purposes.

Faster aspart or NovoRapid® should be titrated twice weekly to reach the glycaemic target of pre-prandial and bedtime plasma glucose between 4.0-6.0 mmol/L (71 - 108 mg/dL) in a treat-to-target fashion.

1) At the scheduled visit/phone contact, adjustment of faster aspart or NovoRapid® doses should be performed by investigator and based on pre-prandial and/or bedtime SMPG values which are measured during last 3-4 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 aspart or NovoRapid® doses based on SMPG values measured on the remaining 3-4 days between scheduled visits/phone contacts.

The adjustments should be according to Table 3

- Breakfast faster aspart or NovoRapid® will be titrated according to pre-lunch SMPG values measured on the previous three days

- Lunch faster aspart or NovoRapid® will be titrated according to pre-dinner SMPG values measured on the previous three days
- Main evening meal faster aspart or NovoRapid® will be titrated according to bedtime SMPG values measured on the previous three days

Table 3 Faster aspart or NovoRapid® dose adjustment algorithm

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
4.0 – 6.0	**71 -108**	**0**	**0-1 SMPG above target** **No SMPGs below target**
> 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 eCRF 'extra bolus insulin'.

3.6 Deviations from the algorithm

It is recommended that the algorithm is followed. However, it is also important that the decision to adjust the insulin degludec, faster aspart or NovoRapid® doses are based on all relevant information as described in Section 3. A reason for deviating from the algorithm should be entered into the eCRF .

4 Data collection

The following data should be entered into the eCRF within 24 hours (on weekdays) after a site visit/phone contact:

- Per protocol pre-prandial and bedtime SMPG values measured since the last visit/phone contact as described in sections 3.2 and 3.5
- Basal and bolus insulin doses taken.
- New insulin doses prescribed after titration
- Reasons for deviation from the titration algorithms, if applicable

5 Review procedure

Surveillance of titration data will be performed centrally by Novo Nordisk in an unbiased manner. It is important that data regarding dose titration is entered into the eCRF within 24 hours (on weekdays). 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 data listed in section 4 will be reviewed by Novo Nordisk within 24 hours (on weekdays).

The reviewer may contact the investigator to get clarification regarding the reason for deviation or to request entry of missing data.

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

During the trial HbA_{1c} 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_{1c}. 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-naive people with type 2 diabetes. Diabetologia. 2008;51(3):408-16.
2. Hermansen K, Davies M, Derezinski T, Ravn GM, Clauson P, Home P, et al. 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-naive people with type 2 diabetes. Diabetes Care. 2006;29(6):1269-74.
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):1569-81.
4. Riddle MC, Rosenstock J, Gerich J, Insulin Glargine Study Investigators. 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):3080-6.
5. Garber AJ, King AB, Del Prato S, 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):1498-507.
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):1489-97.

Global and country key Novo Nordisk staff

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

Content: Global key staff and Country key staff

Protocol Amendment

no 1
to Protocol, final version 2.0
dated 28 March 2017

Trial ID: NN1218-4113

Efficacy and Safety of Fast-acting Insulin Aspart Compared to NovoRapid® both in Combination with Insulin Degludec with or without Metformin in Adults with Type 2 Diabetes (onset® 9)

Trial phase: 3b

Applicable to all countries

Amendment originator:

[redacted]

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1 Introduction including rationale for the protocol amendment

This global 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

6.6 Criteria for premature discontinuation of trial products

Efforts must be made so that subjects attend and complete all scheduled visit procedures. Subjects should stay in the trial irrespective of lack of adherence to randomised treatment, lack of adherence to visit schedule or missing assessments. Only subjects who decline any further contact with the site in relation to the trial will be considered as withdrawn from the trial (see Section 6.7).

The subject may be prematurely discontinued from trial products at the discretion of the investigator due to a safety concern.

The subject must be prematurely discontinued from trial products if the following applies after randomisation:

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. Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product
5. *Lack of efficacy defined as fulfilment of **all** 4 below criteria:*
   - *No reduction in HbA_{1c} measured by central laboratory from screening (Visit 1) to visit 18, 22 or 26 **AND***
   - *A daily average of 4-point SMPG readings (before breakfast, before lunch, before dinner and at bed time) on 3 consecutive days higher than 240 mg/dL (13.3 mmol/L) within the last two weeks period **AND***
   - *A confirmatory FPG exceeding 240 mg/dL (13.3 mmol/L) or a confirmatory random PG exceeding 300 mg/dL (16.7 mmol/L) measured by central laboratory **AND***
   - *No treatable intercurrent cause (e.g. non-compliance) for the hyperglycaemia at the investigator's judgment*
6. *Unacceptable adverse event (including toxicity) that cannot be solved by any medical intervention or considered as non-acceptable risk at the investigator's judgment.*

Protocol Amendment

no 2

to Protocol, version 3.0 dated 09 June 2017

Trial ID: NN1218-4113

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1 Introduction including rationale for the protocol amendment

Discontinuation of the glycaemic data collection system

Due to an unusual data reporting pattern of hypoglycaemia and glycaemic values in two ongoing randomised clinical trials (NN1250-4252 and NN1218-4113), Novo Nordisk has decided to discontinue the glycaemic data collection system (i.e. the combined use of a BG-meter and eDiary) in trials using this system to protect the safety of the trial participants. This affects the NN1250-4252, NN1218-4113 and NN1250-4300 trials.

This protocol amendment has been created in alignment with the above decision to replace the electronic glycaemic data collection system with a paper diary solution and a new trial BG meter.

2 Changes

The discontinuation of the glycaemic data collection system necessitates update of many sections. Therefore, track-changes version of the protocol, titration guideline and SI-IC serves as documentation of the changes.

2.1 High-level summary of changes:

- Replacement of eDiary requirements with paper diary requirements (in alignment with the protocol template) including change of trial BG-meter. Throughout the protocol "eDiary" has been replaced with "diary"
- Clarification to titration guideline section 3.2. Information was provided to investigators in a memo dated 30-Nov-2017 to make it clear that insulin degludec titration is based on SMPGs two days prior to and on day of contact instead of three days prior to contact
- In agreement with SI-IC SOP author it was decided to include the new statements regarding Personal Data Protection in the amended SI-IC according to updated SI-IC template version 10.0
- Minor clarifying updates to protocol text

2.2 Primary protocol sections affected

- 2 Flowchart
- 8.1.2 Run-in
- 8.1.9 Premature discontinuation of trial products
- 8.1.11 Review of results
- 8.3.2 Discontinuation of MyGlucoHealth BG-meter and eDiary (new section)
- 8.3.3 Self-measured plasma glucose
- 8.3.4 Insulin dose
- 8.4.2 Hypoglycaemic episodes

- 8.6.3 Diary
- 9.5 Auxiliary supplies
- 12.4.1 Reporting of technical complaints
- 12.4.2 Collection, storage and shipment of technical complaint samples
- 13.1 Corrections to case report forms
- 14 Monitoring procedures
- 16 Computerised systems