Cover Page for Protocol

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NCT number	NCT02670915
Sponsor trial ID:	NN1218-4101
Official title of study:	Efficacy and Safety of Faster-acting Insulin Aspart compared to NovoRapid® both in Combination with Insulin Degludec in Children and Adolescents with Type 1 Diabetes
Document date:	17 August 2018

16.1.1 Protocol and protocol amendments

List of contents

Redacted protocol
Includes redaction of personal identifiable information only.

.

Protocol

Trial ID: NN1218-4101

Efficacy and Safety of Faster-acting Insulin Aspart compared to NovoRapid® both in Combination with Insulin Degludec in Children and Adolescents with Type 1 Diabetes

onset®7

Trial phase: 3b

Protocol originator

[redacted]

[redacted] Insulin, GH & Devices

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List of abbreviations

ADA	American Diabetes Association
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BG	blood glucose
CGM	continuous glucose monitoring
CRO	contract research organisation
DUN	dispensing unit number
eCRF	electronic case report form
EMA	European Medicines Agency
EoT	End of treatment
FAS	full analysis set
FDA	Food and Drug Administration
FPG	fasting plasma glucose
FSFV	first subject first visit
GCP	Good Clinical Practice
HbA_{1c}	glycosylated haemoglobin
hCG	human chorionic gonadotropin
HDL	high density lipoprotein
I:Carb	insulin:carbohydrate ratio
IB	Investigator's Brochure
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee
IMP	investigational medicinal product
IG	interstitial glucose
IRB	Institutional Review Board
ISPAD	International Society for Paediatric and Adolescent Diabetes

IV/WRS	interactive voice/web response system
LAR	legally acceptable representative
LDL	low density lipoprotein
LSLV	last subject last visit
MAR	missing at random
NPH	Neutral Protamine Hagedorn
PG	plasma glucose
PP	per protocol
PPG	postprandial glucose
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
s.c	subcutaneous
SmPC	summary of product characteristics
SMPG	self-measured plasma glucose
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment emergent adverse event
T1DM	type 1 diabetes mellitus

1 Summary

Primary objective:

To confirm the effect of treatment with meal-time faster-acting insulin aspart in terms of glycaemic control by comparing it to meal-time NovoRapid®, both in combination with insulin degludec using a non-inferiority approach in children and adolescents with type 1 diabetes.

Secondary objectives

To confirm the effect of treatment with post-meal faster-acting insulin aspart in terms of glycaemic control by comparing it to meal-time NovoRapid®, both in combination with insulin degludec, using a non-inferiority approach in children and adolescents with type 1 diabetes.

To confirm superiority of treatment with meal-time faster-acting insulin aspart in terms of glycaemic control by comparing it to meal-time NovoRapid®, both in combination with insulin degludec in children and adolescents with type 1 diabetes.

To compare the effect and safety of treatment with meal-time faster-acting insulin aspart vs. meal-time NovoRapid® both in combination with insulin degludec in children and adolescents with type 1 diabetes.

To compare the effect and safety of treatment with post-meal faster-acting insulin aspart vs. meal-time NovoRapid® both in combination with insulin degludec in children and adolescents with type 1 diabetes.

Primary endpoint

- Change from baseline in HbA_{1c} 26 weeks after randomisation

Key secondary endpoints

26 weeks after randomisation:

Change from baseline in 8-point self-measured plasma glucose (SMPG) profile (8-point profile):

- Mean postprandial glucose (PPG) and PPG increment over all three meals

- Change from baseline in fasting plasma glucose (FPG)

- Number of treatment emergent adverse events (AEs)

Trial design

This is a 26-week randomised, partly double-blind, multicentre, multinational, active controlled, treat-to-target, three-armed parallel group trial with a 12-week run-in period comparing the effect and safety of meal-time faster-acting insulin aspart vs. meal-time NovoRapid® both in combination with insulin degludec once daily in a basal-bolus regimen in type 1 diabetes mellitus Subjects from 1 year to less than 18 years of age. The trial will also include a 26-week open-label post-meal faster-acting insulin aspart dosing arm in combination with insulin degludec.

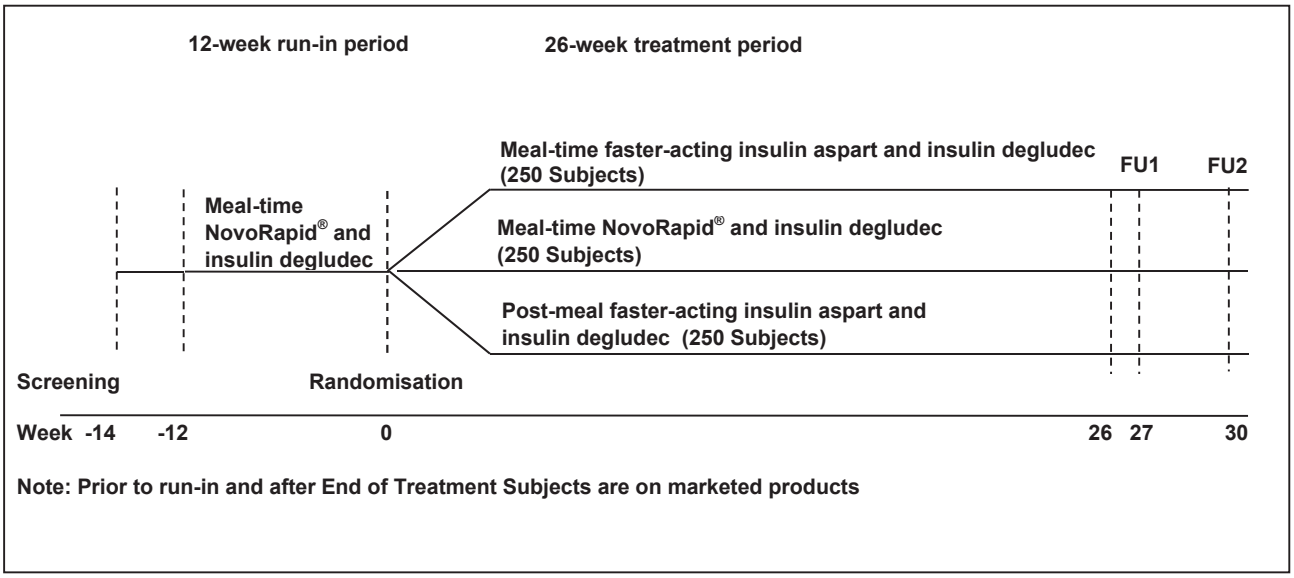


Figure 1–1 Trial design

Trial population:

A total of 833 Subjects with type 1 diabetes mellitus are planned to enter the run-in period, of which 750 are expected to enter randomised treatment.

Key inclusion criteria:

- Male or female, 1 ≤ age < 18 years at the time of signing informed consent and < 18 years at the time of randomisation
- Diagnosed with type 1 diabetes mellitus (based on clinical judgement and supported by laboratory analysis as per local guidelines)
- Ongoing daily treatment with a basal-bolus insulin regimen using basal insulin analogue or NPH insulin for at least 90 days prior to the screening visit
- $HbA_{1c} \leq 9.5\%$ (80 mmol/mol) analysed by the central laboratory at the screening visit

Key exclusion criteria:

- More than one episode of diabetic ketoacidosis requiring hospitalisation within the last 90 days prior to the screening visit
- Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria in a period of 90 days before screening

Key randomisation criterion:

- $HbA_{1c} \leq 9.5\%$ (80 mmol/mol) (at Visit 12 analysed by the central laboratory)

Key efficacy assessments:

- HbA_{1c}
- Mean postprandial glucose (PPG) and PPG increment (assessed from 8-point profile) over three meals
- Fasting plasma glucose (FPG)

Key safety assessment:

- Number of adverse events (AEs)

Trial product(s):

For this trial the following trial products will be provided:

- Faster-acting insulin aspart, 100 U/mL solution for subcutaneous (s.c.) injection (investigational medicinal product) administered with NovoPen Echo®

- NovoRapid®, 100 U/mL solution for s.c. injection (investigational medicinal product) administered with NovoPen Echo®

- Insulin degludec, 100 U/mL solution for s.c. injection (investigational medicinal product) administered with a pre-filled PDS290 pen-injector (FlexTouch®)

2 Flow chart

NN1218-4101	Protocol section	Screening	12-week run-in period												Randomisation	26-week treatment period																	Follow-up 1[c]	Follow-up 2[c]	Premature Discontinuation[c]
Visit (V) Phone contact (P)		V1	V2	P3	V4	P5	V6	P7	V8	P9	V10	P11	V12	P13	V14	P15	V16	P17	V18	P19 P20 P21	V22	P23 P24 P25	V26	P27 P28 P29	V30	P31 P32 P33	V34	P35 P36 P37	V38	P39	V40	V41	P42	V40A
Time of visit (week)		-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	17 18 19	20	21 22 23	24	25	26	+7 days after EoT	+30 days after EoT	
Visit window (days)[a]		+10	±3[b]	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+5	+5	
SUBJECT RELATED INFO/ASSESSMENTS																																		
Informed consent	8.1.1 18.2	x																																
Informed assent	8.1.1 18.2	x																																
In/exclusion criteria	6.2 6.3	x	x																															
Randomisation criteria	6.5														x																			
Run-in failure criteria	6.4			x	x	x	x	x	x	x	x	x	x	x	x																			
Criteria for premature discontinuation of trial product	6.6															x	x	x	x	x	x	x	x	x	x	x	x	x	x	x				
Demography	8.4.1	x													x[d]																			
Diagnosis of diabetes	8.4.2	x																																
Diabetes treatment history	8.4.5	x	x																												x	x	x	x
Concomitant illness/medical history	8.4.3	x																																
Concomitant medication	8.4.4	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
CLINICAL ASSESSMENTS																																		
4-point profile (SMPG)	8.5.6.1			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x[e]			x
8-point profile (SMPG)	8.5.6.2														x								x								x			x
Hypoglycaemic episodes	8.5.1.1		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x
Hyperglycaemic episodes	8.5.1.2		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x
Adverse events	12		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Injection site reactions	8.5.1.3		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x[f]	x
Technical complaints	12.4		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x[e]			
Height	8.5.2	x													x								x								x			x
Body weight	8.5.2	x													x								x								x			x

NN1218-4101	Protocol section	Screening	12-week run-in period													Randomisation	26-week treatment period																Follow-up 1[c]	Follow-up 2[c]	Premature Discontinuation[c]
Visit (V) Phone contact (P)		V1	V2	P3	V4	P5	V6	P7	V8	P9	V10	P11	V12	P13		V14	P15	V16	P17	V18	P19 P20 P21	V22	P23 P24 P25	V26	P27 P28 P29	V30	P31 P32 P33	V34	P35 P36 P37	V38	P39	V40	V41	P42	V40A
Time of visit (week)		-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	17 18 19	20	21 22 23	24	25	26	+7 days after EoT	+30 days after EoT	
Visit window (days)[a]		+10	±3[b]	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+5	+5	
Vital signs	8.5.7	x														x								x								x			x
Physical examination	8.5.5	x														x								x								x			x
Pubertal status (Tanner staging)	8.5.5.1															x								x								x			x
CGM[g]	8.5.3												x	x		x														x	x	x[e]			x
Meal test[g]	8.5.3															x																x[e]			x
LABORATORY ASSESSMENTS																																			
Fasting plasma glucose[h]	8.6.4															x								x								x			x
HbA_{1c}	8.6.6	x											x			x								x								x			x
1,5-anhydroglucitol	8.6.2															x								x								x			x
Biochemistry	8.6.3	x														x								x								x			x
Haematology	8.6.5	x														x								x								x			x
Antibodies	8.6.7															x								x								x			x
Lipids	8.6.8	x														x								x								x			x
Pregnancy test	8.6.9	x														x																x			x
TRIAL MATERIAL																																			
IV/WRS call	10	x	x				x				x					x				x		x		x		x		x		x		x[e]			x
Dispensing visit	8.1.3 8.1.5		x				x				x					x				x		x		x		x		x		x					
Dosing[l]	8.5.4		x													x																x			
Doses of trial insulin on the 3 days before visit	8.5.4			x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			x
New doses of trial Insulin	8.5.4		x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x				
Drug accountability	9.4						x				x					x				x		x		x		x		x		x		x			x
REMINDERS																																			
Hand out ID Card	8.1.2	x																																	
Training in diabetes and carbohydrate counting	8.7.2	x	x		x		x		x		x		x			x																			

NN1218-4101	Protocol section	Screening	12-week run-in period													Randomisation	26-week treatment period																Follow-up 1[e]	Follow-up 2[e]	Premature Discontinuation[e]
Visit (V) Phone contact (P)		V1	V2	P3	V4	P5	V6	P7	V8	P9	V10	P11	V12	P13		V14	P15	V16	P17	V18	P19 P20 P21	V22	P23 P24 P25	V26	P27 P28 P29	V30	P31 P32 P33	V34	P35 P36 P37	V38	P39	V40	V41	P42	V40A
Time of visit (week)		-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	17 18 19	20	21 22 23	24	25	26	+7 days after EoT	+30 days after EoT	
Visit window (days)[a]		+10	±3[b]	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+5	+5	
Training in trial products and pen handling	8.7.3		x		x		x		x		x		x			x		x		x		x		x		x		x		x				
Handout direction for use	9.2		x																																
Handout and instruct in BG meter use	8.5.6		x																																
Supply and instruct in diary/collection of diary	8.7.1 8.2		x		x		x		x		x		x			x		x		x		x		x		x		x		x		x[l]		x
Handout FPG home blood sampling kit	8.6.4												x									x								x					x[k]
Instruct in safety precautions and hand out supplies	8.7.4		x																																
End of Treatment	8.1.9																														x			x	
End of trial	8.1.9, 8.2, 8.3																														x[l]		x[m]		
Sign off case book	13																														x[l]		x[m]		

a) Visit windows are relative to the randomisation visit (Visit 14), except for the follow-up visits which are relative to last day on trial product
b) Visit 2 can take place as soon as the Subject has been found eligible and must take place no later than 13 days after the screening visit (Visit 1). The results of all the screening assessments must be available (including central laboratory results) and must have been reviewed by the Investigator before the Subject can enter the run-in period
c) Subjects who prematurely discontinue trial product will be asked to attend the premature discontinuation visit and subsequently FU1 and FU2 according to section 8.2
d) For Germany only: The only demographic data to be collected at Visit 14 is the Subject's age at randomisation (to be used for stratification)
e) The assessment is not applicable for premature discontinued Subjects, see section 8.2
f) Injection site reactions must be captured on the AE form (no additional injection site reaction information needs to be completed)
g) Only applicable for a subgroup of Subjects. In case of premature discontinuation please see Appendix B
h) Using the FPG home blood sampling kit
i) Start and stop date of trial product
j) Only collection of diary. For Subjects who prematurely discontinue trial product a new diary will be handed out at this visit
k) Site staff should provide FPG home blood sample kits to the Subject prior to the visit
l) Only for Subjects prematurely discontinuing trial product
m) Only for Subjects completed the full visit schedule. Subjects who prematurely discontinue trial product must have Visit 40 planned according to section 8.2

3 Background information and rationale for the trial

The trial will be conducted in compliance with this protocol, ICH Good Clinical Practice (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, can reduce the incidence of complications and delay the progression of existing complications in type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus[3,4]. Postprandial hyperglycaemia contributes significantly to the glycosylated haemoglobin (HbA_{1c}) level, and its control is essential for achieving the HbA_{1c} target level[5]. Basal-bolus insulin therapy aims at mimicking the normal physiological insulin response. 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[6]. However, unmet needs still exist within prandial insulin therapy for people with diabetes and an exogenous insulin with a faster glucose lowering effect is needed for tighter PPG control. 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. Although several insulin products are available on the market and can be used by paediatric patients, there is still a need for improvement of the treatment options to more closely resemble the physiological action profile of endogenous insulin and to reduce unwanted side effects such as hypoglycaemia. The pathophysiology of T1DM appears to be comparable between adults and paediatric patients, and consequently, the potential benefits of faster-acting insulin aspart for children and adolescents are believed to be similar to those for adults.

3.2 Therapeutic area

T1DM is among the most common chronic diseases in childhood and adolescence and the children and adolescents with T1DM are dependent on insulin for survival. Intensive treatment is beneficial in terms of reducing the risk for long term complications. The International Society for Paediatric and Adolescent Diabetes (ISPAD) recommends an HbA_{1c} range for all age groups of < 7.5% (58 mmol/mol), and that each child should have their target individually determined with the goal of achieving a value as close to normal as possible while avoiding severe hypoglycaemia as well as frequent mild to moderate hypoglycaemia[7]. This treatment target was recently supported by the American Diabetes Association (ADA)[8].

3.3 NovoRapid®

Insulin aspart is marketed worldwide as NovoRapid® (marketed as NovoLog® in the US) and is a fast-acting insulin analogue indicated for the treatment of diabetes. In the remainder of this document the name NovoRapid® will be used.

NovoRapid® is homologous to human insulin, with the exception of the substitution of proline with aspartic acid at position B28. The rapid action of insulin aspart is related to a weakened tendency of the insulin molecules to self-associate due to this modification, and is thereby related to faster absorption as compared to human insulin. Compared with regular human insulin, insulin aspart has a faster onset and a shorter duration of action, resulting in superior postprandial glycaemic control by means of lowering total glucose excursion following a meal, both in Subjects with T1DM[9,10,11] and in Subjects with type 2 diabetes mellitus[12-14]. This also allows NovoRapid® to be injected immediately before a meal, in contrast to regular human insulin. NovoRapid® can be used in children in preference to regular human insulin when a rapid onset of action might be beneficial, e.g. in the timing of the injections in relation to meals. No studies have been performed in children below the age of 2 years. In line with current practice NovoRapid® will only be used in this age group under careful medical supervision.

For further details see the current version of the NovoRapid® summary of product characteristics (SmPC)[15]or the U.S. NovoLog® Label information[16].

3.4 Faster-acting insulin aspart

Faster-acting insulin aspart (also called faster aspart) is insulin aspart in a new formulation. Faster-acting insulin aspart is being developed with the objective of achieving an increased early absorption of insulin aspart compared to NovoRapid® thereby providing a faster insulin action. Faster-acting insulin aspart aims at mimicking the physiological prandial insulin secretion pattern better than currently available treatment and thereby more effectively controlling the PPG 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-acting insulin aspart and NovoRapid® have shown that faster-acting insulin aspart elicited an earlier onset of appearance and a greater early exposure to insulin aspart than NovoRapid® in Subjects with T1DM, with the largest difference found within the first 15 minutes after injection. Faster-acting insulin aspart also elicited a greater early glucose-lowering effect than NovoRapid®, but no statistically significant difference between faster-acting insulin aspart and NovoRapid® in total glucose-lowering effect[17]. Results from a clinical pharmacology trial comparing the pharmacokinetic and pharmacodynamic properties of faster-acting insulin aspart and NovoRapid® during a meal test in children (6-11 years), adolescents (12-17 years) and adults (18-64 years) with T1DM have shown that faster-acting insulin aspart elicited an earlier onset of exposure and a higher early insulin exposure whilst maintaining a similar total exposure and maximum concentration compared to NovoRapid® across all age groups.

Faster-acting insulin aspart had a larger glucose-lowering effect compared to NovoRapid® during the meal-test in children. In adolescents, a larger glucose-lowering effect for faster-acting insulin aspart was not demonstrated during the meal-test, despite a greater early insulin exposure. In adults, the glucose-lowering effect tended to be larger for faster-acting insulin aspart than for NovoRapid® during a meal-test. Overall, the glucose-lowering effect was comparable between age groups[17].

In a therapeutic confirmatory basal-bolus trial in adult Subjects with T1DM faster-acting insulin aspart taken with the meal effectively improved glycaemic control and the reduction in HbA_{1c} was statistically significantly larger than with NovoRapid®. For post-meal faster-acting insulin aspart, non-inferiority to meal-time NovoRapid® regarding lowering of HbA_1c was also confirmed. Meal-time faster-acting insulin aspart provided superior PPG control compared with 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 meal-time faster-acting insulin aspart. No statistically significant difference was seen in overall rate of severe or blood glucose confirmed hypoglycaemic episodes between meal-time faster-acting insulin aspart and NovoRapid®.The rate during the first 1 hour after start of a meal, constituting a smaller fraction of all severe or blood glucose (BG) confirmed hypoglycaemic episodes, was statistically significantly higher for meal-time faster-acting insulin aspart compared to NovoRapid®. The overall safety profile for faster-acting insulin aspart and NovoRapid® was similar and as expected for insulin aspart[17]. In this trial, the safety profile of faster-acting insulin aspart is expected to be similar to that of NovoRapid®. The insulin aspart molecule has a well-known safety profile based on more than 10 years of clinical experience. Compared to NovoRapid®, faster-acting insulin aspart contains excipients which results in a faster initial absorption of insulin aspart following s.c. injection. The added excipients are included in the Food and Drug Administration´s (FDA) list for approved drug products for injections, and no toxicological concerns have been predicted from s.c. use in humans at the proposed concentrations. For further details see the current version of the faster-acting insulin aspart Investigator Brochure (IB)[17].

3.5 Insulin degludec

Insulin degludec (marketed as Tresiba®) is a basal insulin with an ultra-long duration of action for once-daily s.c. administration at any time of the day, preferably at the same time every day. After s.c. injection, soluble and stable multi-hexamers are formed creating a depot of insulin in the s.c. tissue. Insulin degludec monomers gradually separate from the multi-hexamers thus resulting in a slow and continuous delivery of insulin degludec into the circulation, leading to the observed ultra-long pharmacokinetic and pharmacodynamic profiles and thereby a flat and stable glucose-lowering-effect. The duration of action of insulin degludec is beyond 42 hours within the therapeutic dose range. A clinical pharmacology study in children and adolescents with T1DM confirmed that the ultra-long acting properties of insulin degludec seen in adults are preserved in children and adolescents. Extent of exposure after a single fixed dose tends to be greater in children/adolescents than in adults; but as with other insulin products, insulin degludec should

always be titrated according to individual requirements[18]. In a recent study conducted in a paediatric population insulin degludec was shown to be safe and to effectively improve long-term glycaemic control in all Subjects[19]. Insulin degludec was recently approved for use in children and adolescents aged 1 to less than 18 years old in the EU.

For further details see the current version of the Tresiba® EU SmPC[20] or the U.S. Tresiba® Label information[21] and if not approved in the country of interest detailed information for insulin degludec is available in the current edition and any updates of the Investigator's Brochure (IB)[22].

At the time of this protocol issuance, degludec is approved in more than 60 countries, including USA, all of the EU countries, and marketed in 26 countries.

3.6 Rationale for the trial

This trial aims to confirm that the efficacy and safety profile of faster-acting insulin aspart can be demonstrated in the paediatric population with T1DM. In the European Medicines Agency (EMA) and FDA note for guidance on clinical investigation of medicinal products for the treatment of diabetes, HbA_{1c} is considered the most widely accepted measure of overall, long-term glucose control. Consequently, HbA_{1c} will be included as the primary endpoint[23,24].

The trial is also designed to investigate differences in glycaemic control between faster-acting insulin aspart and NovoRapid® based on data from a standardised meal test and continuous glucose monitoring (CGM) in a subgroup of Subjects.

In addition, this trial includes a post-meal faster-acting insulin aspart dosing arm in order to assess whether post-meal administration could prove effective in achieving glucose control to offer a clinically acceptable treatment option.

Together with the clinical pharmacology trial in children and adolescents, the current trial is conducted in order to fulfil the regulatory requirements for obtaining a paediatric indication for faster-acting insulin aspart[25].

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

4 Objectives and endpoints

4.1 Objectives

4.1.1 Primary objective

To confirm the effect of treatment with meal-time faster-acting insulin aspart in terms of glycaemic control by comparing it to meal-time NovoRapid® both in combination with insulin degludec using a non-inferiority approach in children and adolescents with type 1 diabetes.

4.1.2 Secondary objectives

To confirm the effect of treatment with post-meal faster-acting insulin aspart in terms of glycaemic control by comparing it to meal-time NovoRapid® both in combination with insulin degludec, using a non-inferiority approach in children and adolescents with type 1 diabetes.

To confirm superiority of treatment with meal-time faster-acting insulin aspart in terms of glycaemic control by comparing it to meal-time NovoRapid®, both in combination with insulin degludec in children and adolescents with type 1 diabetes.

To compare the effect and safety of treatment with meal-time faster-acting insulin aspart vs. meal-time NovoRapid® both in combination with insulin degludec in children and adolescents with type 1 diabetes.

To compare the effect and safety of treatment with post-meal faster-acting insulin aspart vs. meal-time NovoRapid® both in combination with insulin degludec in children and adolescents with type 1 diabetes.

4.2 Endpoints

4.2.1 Primary endpoint

- Change from baseline in HbA_{1c} 26 weeks after randomisation

4.2.2 Secondary endpoints

Change from baseline refers to the change from randomisation to 26 weeks after randomisation.

4.2.2.1 Supportive secondary efficacy endpoints

The following endpoints will be assessed 26 weeks after randomisation.

Change from baseline in 8-point self-measured plasma glucose (SMPG) profile (8-point profile):

- Mean PPG and PPG increment over all three meals*
- Individual meal (breakfast, lunch and main evening meal) PPG and PPG increment
- Mean of the 8-point profile
- Fluctuation in the 8-point profile

- Change from baseline in fasting plasma glucose (FPG)*
- Change from baseline in 1,5-anhydroglucitol
- Percentage of Subjects reaching HbA_{1c} target (HbA_{1c}<7.5 %) according to ISPAD guidelines
- Percentage of Subjects reaching HbA_{1c} target (HbA_{1c}<7.5 %) according to ISPAD guidelines, without severe hypoglycaemia
- Insulin dose (Units/day and Units/kg/day; total basal, total bolus and individual meal insulin dose)

4.2.2.2 Supportive secondary CGM related efficacy endpoints (subgroup):

26 weeks after randomisation:

- Change from baseline of time spent in low interstitial glucose (IG) (IG ≤ 3.9 mmol/L [70 mg/dL])
- Incidence of episodes and percentage of time spent with IG ≤ 2.5, 3.0, 3.9 mmol/L [45, 54, 70 mg/dL] and IG >10.0, 12.0 mmol/L [180, 216 mg/dL]
- Percentage of time spent within IG target 4.0-10.0 mmol/L [71-180 mg/dL] both included

4.2.2.3 Supportive secondary CGM and meal-characteristics efficacy endpoints (subgroup):

26 weeks after randomisation:

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

4.2.2.4 Supportive secondary meal test related efficacy endpoints (subgroup):

26 weeks after randomisation:

- Change from baseline in 30-minute PPG and PPG increment
- Change from baseline in 1-hour PPG and PPG increment
- Change from baseline in 2-hour PPG and PPG increment

4.2.2.5 Supportive secondary CGM and meal test related efficacy endpoints (subgroup):

26 weeks after randomisation:

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

4.2.2.6 Supportive secondary safety endpoints

26 weeks after randomisation:

- Number of treatment emergent hypoglycaemic episodes
    - According to ADA/ISPAD classification
    - According to Novo Nordisk/ISPAD classification
- Number of treatment emergent hypoglycaemic episodes subdivided into daytime and nocturnal (23:00-7:00, both included)
    - According to ADA/ISPAD classification
    - According to Novo Nordisk/ISPAD classification

- Number of treatment emergent meal related (from start of meal until 1, 2, and 4 hours after start of meal and from 2-4 hours after start of meal, respectively) hypoglycaemic episodes
    - According to ADA/ISPAD classification
    - According to Novo Nordisk/ISPAD classification

- Number of treatment emergent adverse events (AEs)*

- Number of treatment emergent injection site reactions

- Change from baseline in clinical evaluations:
    - Physical examination
    - Vital signs

- Change from baseline in body weight, height, body mass index and SD score of body weight and body mass index (z score)

- Change from baseline in laboratory assessments:
    - Haematology (haemoglobin, haematocrit, erythrocytes, thrombocytes, and leucocytes)
    - Biochemistry (creatinine, alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [AP], sodium, potassium, albumin, and total bilirubin)
    - Lipid profile (total cholesterol, high density lipoproteins [HDL], low density lipoproteins [LDL])

- Change from baseline in anti-insulin aspart (specific and cross-reacting with human insulin and total of these) antibody development

*Key supportive secondary endpoints prospectively selected for disclosure (e.g. clinicaltrials.gov and EudraCT).

5 Trial design

5.1 Type of trial

This is a 26-week randomised, partly double-blind, multicentre, multinational, active controlled, treat-to-target, parallel group trial with a 12-week run-in period comparing the efficacy and safety of meal-time faster-acting insulin aspart vs. meal-time NovoRapid® both in combination with insulin degludec once daily in a basal-bolus regimen in Subjects with T1DM from 1 year to less than 18 years of age. The trial will also include a 26-week open-label post-meal faster-acting insulin aspart dosing arm in combination with insulin degludec.

The randomisation will be stratified by age group ($1 \leq$ age < 3 years, $3 \leq$ age < 6 years, $6 \leq$ age < 12 years and $12 \leq$ age < 18 years) based on Subject's age at randomisation.

For each Subject, the total trial duration is approximately 45 weeks consisting of the following periods:

- Up to 2 weeks for screening
- A 12-week run-in period primarily with the aim of optimising the insulin degludec dose
- A 26-week treatment period
- A 7-day and a 30-day follow-up period

Throughout the run-in and treatment period there will be weekly site visits/phone contacts.

A subgroup of Subjects (150 in total), age ≥ 8 years old at screening (Visit 1) will have blinded CGM and a standardised meal test at two occasions during the trial leading up to Visit 14 and Visit 40. The Subjects will have the blinded CGM for at least 11 days and up to 13 days before randomisation and up to 13 days before the end of the 26-week treatment period. The standardised meal test will be performed at baseline (Visit 14) and at the End of Treatment. The CGM and meal test subgroup and procedures are described in Appendix B.

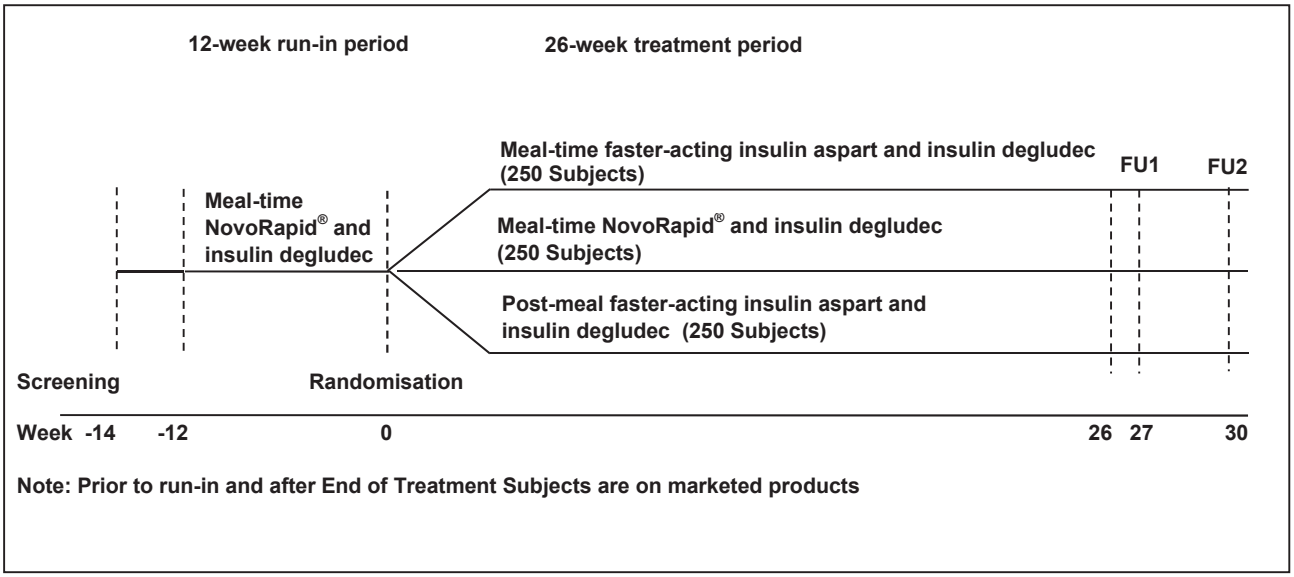


Figure 5–1 Trial design

The trial includes a screening visit to assess the Subject's eligibility. At Visit 2, the eligible Subjects will be enrolled in a 12-week run-in period where all Subjects will be switched from their previous insulin treatment to insulin degludec once daily and meal-time NovoRapid®. During the 12-week run-in period the Investigator will focus on optimisation of the basal insulin on a weekly basis to individual fasting plasma glucose (FPG) targets. After the run-in period, Subjects with $HbA_{1c} \leq$ 9.5% (80 mmol/mol) who based on the Investigator's judgement have shown ability and willingness to adhere to the trial protocol will be randomised (1:1:1) to receive meal-time faster-acting insulin aspart, post-meal faster-acting insulin aspart or meal-time NovoRapid®, all in combination with insulin degludec. In the 26-week treatment period, the Investigator should focus on optimising bolus insulin to individual pre-meal targets, in accordance with the titration guideline, as described in Appendix A. Adjustment of basal insulin dose should be minimized during the treatment phase. However, if necessary, basal insulin dose may be adjusted at the Investigator's discretion. The Investigator must attempt to achieve the glycaemic pre-meal target of 4.0 – 8.0 mmol/L (71 – 145 mg/dL), and the bedtime target of 6.7 – 10 mmol/L (120 – 180 mg/dL) as described in Appendix A[7].

5.2 Rationale for trial design

The 12-week run-in period has been included to ensure that the Subjects are being trained in the trial procedures and that the basal insulin titration is optimised safely. The randomisation will be stratified by age group (1 ≤ age < 3 years, 3 ≤age < 6 years, 6 ≤ age < 12 years and 12 ≤ age < 18 years) to ensure a comparable number of Subjects in each treatment group for each strata. The 26-week treatment period (double-blind with open-label arm) is needed to obtain as valid and unbiased effect and safety data as possible and the duration is considered sufficient to reach a stable HbA_{1c}

level in a basal-bolus setting. The post-meal dosing arm is open-label due to the difference in dosing timing from the two blinded arms. The high frequency of contacts has been chosen in order to ensure optimal titration of faster-acting insulin aspart and NovoRapid®.

A 30 days follow up visit is introduced in order to collect information on adverse events (AEs) occurring in the follow up period.

5.2.1 Rationale for the CGM and meal test subgroup

The rationale for the meal test is to evaluate PPG excursions after a standardised liquid meal when injecting faster-acting insulin aspart compared to NovoRapid®. The rationale for the CGM assessment is to get a thorough evaluation of the glycaemic control achieved with the different treatments in this trial, including during the meal test.

5.2.2 Rationale for choice of non-inferiority margin

Placebo control trials will usually be considered unethical to conduct in a T1DM diabetic population and it can therefore be difficult to assess the true insulin aspart effect. In a recently finalised faster-acting insulin aspart trial (NN1218-4049) in a bolus insulin naïve T2DM adult population comparing a basal insulin treatment in addition to metformin to a full basal bolus insulin treatment in addition to metformin the estimated treatment effect in change from baseline HbA_{1c} was - 0.94% [-1.17; -0.72] (data on file). In this trial the addition of 3 times daily faster-acting insulin aspart lead to a reduction in HbA_{1c} of 1.16% after 18 weeks of treatment. In a similar phase 4 trial [26] investigating the stepwise addition of insulin aspart 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 on file) with 3 times daily insulin aspart 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. Using a non-inferiority margin of 0.4, one of the suggested margins in the FDA guidance[27], an improvement of approximately 0.54% would have been preserved using the 0.4% non-inferiority margin. It is also worthwhile to state that the T1DM population would not have any endogenous insulin production and the true effect of insulin aspart might be even higher than what is seen in a T2DM population.

5.3 Treatment of Subjects

All Subjects will record 4-point SMPG profiles (4-point profiles) on the three days prior to a site visit/phone contact, in accordance with section 8.5.6.1, throughout the trial for the purpose of insulin titration. In the 26-week treatment period, the Investigator should focus on optimising bolus insulin on a weekly basis to individual pre-meal and bedtime targets. Adjustment of basal insulin dose should be minimised during the treatment phase. However, if necessary, basal insulin dose may be adjusted at the Investigator's discretion. Insulin doses should be titrated according to plasma glucose (PG) values as described in the titration guideline (Appendix A). No maximum dose is

specified. The Novo Nordisk insulin titration team will review glycaemic parameters during treatment and is blinded to Subject's trial treatment.

No concomitant diabetes medication except the trial products are allowed during the trial after Visit 2.

The Subjects must not wear their own real time CGM during the run-in and treatment periods.

5.3.1 Basal insulin titration

At Visit 2 Subjects will be switched from their previous basal insulin analogue or Neutral Protamine Hagedorn (NPH) insulin to insulin degludec, as described in the titration guideline (Appendix A). Insulin degludec should be administered once daily at any time of the day, preferably at the same time every day. During the 12-week run-in period the basal insulin will be titrated by the Investigator on a weekly basis to the pre-breakfast glycaemic target of 4.0 - 8.0 mmol/L (71 - 145 mg/dL) in accordance with the titration guideline (Appendix A). Further adjustments of the insulin degludec dose during the treatment period should be done at the discretion of the Investigator, if needed.

5.3.2 Bolus insulin titration

At Visit 2 Subjects will be switched from their pre-trial bolus insulin to meal-time NovoRapid®, as described in the titration guideline, see Appendix A. All Subjects should have additional diabetes training including training in carbohydrate counting as described in section 8.7.2. NovoRapid® will not be adjusted during the run-in period unless the Investigator finds it necessary to adjust the bolus insulin for safety reasons.

At randomisation (Visit 14) Subjects will be randomised to receive meal-time faster-acting insulin aspart, or post-meal faster-acting insulin aspart or to continue using meal-time NovoRapid®.

According to the discretion of the Investigator the Subjects will be instructed to titrate the bolus insulin doses using the principles of flexible bolus dosing based on the meal carbohydrate content or to use the pre-defined bolus dosing algorithms during the treatment period, see Appendix A. It is recommended that the Subjects use the method that they are most familiar with throughout the trial. The Subjects should continue using the dosing method that they use when they enter the trial, however if switching dosing method is to the benefit of the Subjects, as judged by the Investigator, the Subjects may change dosing method during the trial. In the treatment period the bolus insulin will be titrated to the pre-meal target of 4.0 – 8.0 mmol/L (71 – 145 mg/dL), and the bed-time target of 6.7 – 10 mmol/L (120 – 180 mg/dL) in a treat-to-target fashion.

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

Timing of dosing should be according to randomisation and should be as described:

- Meal-time dosing is defined as injecting 0 - 2 minutes before the meal.
- Post-meal dosing, is defined as injecting 20 minutes after the start of the meal

Timing of bolus insulin injection should be part of the "training in trial products and pen handling" and should be reinforced at each contact.

Details regarding titration of bolus insulin (pre-defined dosing algorithm and principles of flexible bolus dosing) are described in the titration guideline, see Appendix A.

5.4 Treatment after discontinuation of trial product

When discontinuing trial products the Subject should be switched to suitable marketed products at the discretion of the Investigator. Doses of subsequent antidiabetic treatment should be carefully titrated based on blood glucose measurements, considering the stable effect and long half-life of insulin degludec. Doses of subsequent antidiabetic treatment should be captured in the eletronic case report form (eCRF) according to section 8.4.5 at each contact after discontinuation.

5.5 Rationale for treatment

Based on the currently available pharmacokinetic data on faster-acting insulin aspart it is anticipated that treatment with faster-acting insulin aspart as a meal-time insulin will enable insulin therapy to more closely mimic a physiologic insulin secretory pattern. Consequently, the PPG excursions may be more effectively controlled. For further details see the current version of the faster-acting insulin aspart IB[17].

NovoRapid® will be used as a comparator to faster-acting insulin aspart in order to compare the effect and safety of faster-acting insulin aspart to the currently marketed insulin aspart formulation. For further details see the current version of the NovoRapid® SmPC[15] or the U.S. NovoLog® Label information[16]. As this is a partly double-blind trial, NovoRapid® and faster-acting insulin aspart will be titrated following the same recommendations.

Insulin degludec has been chosen as the basal insulin because it is a once-daily basal insulin and as efficacy and safety has been studied in adult Subjects and recently in a paediatric population[19]. The flat and stable glucose-lowering effect of insulin degludec makes it an optimal insulin when assessing the properties of bolus insulin (faster-acting insulin aspart compared to NovoRapid®). For further details see the current version of the Tresiba® EU SmPC[20] and if not approved in the country of interest see the insulin degludec IB[22].

The treatment targets are aligned with the current ISPAD Clinical Practice Consensus Guidelines[7].

6 Trial population

6.1 Number of Subjects

Number of Subjects planned to be screened: 1004

Number of Subjects planned to be included in the run-in period: 833

Number of Subjects planned to be randomised: 750

A screening failure rate of approximately 17 % and a run-in failure rate of approximately 10% are anticipated for this trial. The Investigators must strive to include Subjects in the youngest age groups (age < 6), to enable investigation of the efficacy and safety of faster-acting insulin aspart in these age groups. It will be attempted to include at least 20 Subjects below 6 years of age in each treatment arm.

6.2 Inclusion criteria

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

1. Informed consent and child assent, as age-appropriate, 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. Legally Acceptable Representative (LAR) of the Subject must sign and date the Informed Consent Form (according to local requirements). The child must sign and date the Child Assent Form or provide oral assent, if required according to local requirements

2. Male or female, 1 ≤ age < 18 years at the time of signing informed consent and < 18 years at the time of randomisation

3. Diagnosed with type 1 diabetes mellitus (based on clinical judgement and supported by laboratory analysis as per local guidelines)

4. Ongoing daily treatment with a basal-bolus insulin regimen using a basal insulin analogue or NPH insulin for at least 90 days prior to the screening visit

5. Ability and willingness to take at least 3 daily meal-time related bolus insulin injections throughout the trial (Subject and LAR(s) should be evaluated as a unit)

6. Total daily dose of insulin ≤ 2.0 U/kg prior to the screening visit

7. HbA_{1c} ≤ 9.5% (80 mmol/mol) analysed by the central laboratory at the screening visit

8. Ability and willingness to adhere to the protocol, including performing self-measured plasma glucose profiles (Subject and LAR(s) should be evaluated as a unit)

9. Willingness to NOT use real time CGM during the trial

6.2.1 Additional inclusion criteria for the CGM and meal test subgroup

For a Subject to be eligible for the CGM and meal test subgroup, all the below additional inclusion criteria must be answered "yes".

10. Male or female, age ≥ 8 years at the time of screening (Visit 1)

11. Weight ≥ 20.0 kg (44.0 lbs) measured at the time of screening (Visit 1)

12. Ability and willingness to use the principles of flexible bolus dosing based on carbohydrate counting, as judged by the Investigator (Subject and LAR(s) should be evaluated as a unit)

6.3 Exclusion criteria

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

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

2. Previous participation in this trial. Participation is defined as signed informed consent

3. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using adequate contraceptive methods (adequate contraceptive measures as required by local regulation or practice)
   For EU only: Adequate contraceptive measures are implants, injectable, combined oral contraceptives, hormonal IUD, sexual abstinence or vasectomised partner.
   For Japan only: Adequate contraceptive measures are abstinence (not having sex), diaphragm, condom (by the partner), intrauterine device, sponge, spermicide or oral contraceptives.

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

5. Anticipated initiation or change in concomitant medication in excess of 14 days known to affect weight or glucose metabolism (e.g. orlistat, thyroid hormones, corticosteroids)

6. Any condition, which, in the opinion of the Investigator, might jeopardise the Subject's safety or compliance with the protocol (Subject and LAR(s) should be evaluated as a unit)

7. Diagnosis of malignant neoplasms within the last five years prior to the screening visit

8. Known hypoglycaemic unawareness or recurrent severe hypoglycaemic episodes as judged by the Investigator

9. More than one episode of diabetic ketoacidosis requiring hospitalisation within the last 90 days prior to the screening

10. Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria in a period of 90 days before screening

6.4 Run-in failure criteria

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

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

2. Pregnancy

3. Intention of becoming pregnant

4. Participation in another clinical trial throughout the run-in period

Subjects fulfilling any of the above criteria or withdrawing consent prior to randomisation are considered as run-in failures and should be completed as described in section 8.1.3.1.

6.5 Randomisation criteria

To be randomised, the below randomisation criteria must be answered “yes”.

1. Age < 18 years at the time of randomisation

2. $HbA_{1c} \leq 9.5\%$ (80 mmol/mol) (at Visit 12 analysed by the central laboratory)

3. Subjects must have demonstrated ability and willingness to adhere to the protocol during the run-in period, based on the Investigator’s judgement (Subject and LAR(s) should be evaluated as a unit)

6.5.1 Additional randomisation criterion for the CGM and meal test subgroup

For a Subject to be eligible for the CGM and meal test subgroup, the below additional randomisation criterion must be answered "yes".

4. Subject has shown ability and willingness to use the principles of flexible bolus dosing based on carbohydrate counting throughout the run-in period, as judged by the Investigator (Subject and LAR(s) should be evaluated as a unit)

6.6 Criteria for premature discontinuation of trial product

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

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

1. Included in the trial in violation of the inclusion and/or exclusion and/or randomised in violation of the randomisation criteria
2. Pregnancy
3. Intention of becoming pregnant
4. Participation in another clinical trial throughout the trial

Subjects discontinued from trial product after randomisation will be followed as described in section 8.2.

6.7 Withdrawal from trial

The Subject may withdraw at will at any time either by the Subject or by the Subject's LAR(s). The Subject's request to discontinue must always be respected.

If the Subject considers withdrawing consent the Investigator must underline to the Subject the importance of continuing in the trial despite trial product discontinuation. If the Subject agrees to discontinue trial product but to stay in the trial, procedures similar to those described in section 8.2 must be followed.

If a Subject decides to withdraw informed consent the Subject should be encouraged to undergo procedures as described in section 8.3

A Subject included in the trial in violation of the inclusion and/or exclusion criteria and/or randomised in violation of the randomisation criteria must discontinue treatment with trial product, but will not be withdrawn from the trial and will be followed as described in section 8.2

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

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

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible
- The site must re-train the subject in the importance of maintaining the scheduled visits
- In cases in which the subject is deemed lost to follow-up the investigator must make every effort to regain contact with the subject (e.g. telephone calls to friends or family members, e-mails or certified letter to the subject as applicable). These contact attempts should 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"

6.8 Subject replacement

Subjects who are withdrawn will not be replaced.

6.9 Rationale for trial population

For children and adolescents diagnosed with T1DM, insulin therapy is indicated, and data from the The Diabetes Control and Complications Trial Research Group (DCCT) show that intensive treatment is beneficial in terms of the risk of developing long term complications[3]. As the disease usually presents in early childhood and adolescence, the assessment of safety and efficacy of new insulins is appropriate in all ages including childhood and adolescence.

The trial population consist of children and adolescents with T1DM, $1 \leq$ age < 18 years with an $HbA_{1c} \leq 9.5$ % (80 mmol/mol) at screening and at randomisation. Infants below the age of 1 year are not eligible for this trial since most cases of diabetes diagnosed at this very young age are cases of neonatal diabetes. Neonatal diabetes is a distinct form of diabetes requiring specialized diagnosis and management beyond the scope of this trial.

In diabetes, a likely cause of elevated HbA_{1c} is poor compliance with treatment regimens or atypical course of the disease; consequently individuals with an HbA_{1c} greater than 9.5% (80 mmol/mol) are not included in this trial. The 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 where focus is not on bolus titration.

During the last 3 months prior to Visit 1 the Subjects must have been on an ongoing daily treatment with a basal-bolus insulin regimen using basal insulin analogue or NPH insulin in order to ensure a smooth switch from prior treatment to trial treatment, and to ensure that optimal adjustment of basal insulin can be done during the 12-week run-in period.

For safety reasons, Subjects with more than one episode of diabetic ketoacidosis requiring hospitalisation within the last 90 days prior to the screening visit are not eligible for this trial.

7 Milestones

Planned duration of recruitment period (FSFV – LSFV): 38 weeks

End of trial is defined as Last Subject Last Visit (LSLV).

The duration of the recruitment period will depend on the screening rate, and the screening- and run-in failure rates.

Recruitment will be followed closely via the interactive voice/web response system (IV/WRS) in order to estimate when to stop the screening, taking into account the number of Subjects currently in screening/run-in, and previous screening/run-in failure rates. All Subjects who are in screening/run-in when recruitment closes will be randomised if eligible. All Investigators will be notified immediately when the recruitment period ends, after which no further Subjects may be screened, and the IV/WRS will be closed for further screening.

Trial registration:
Information of the trial will be disclosed at clinicaltrials.gov, novonordisk-trials.com and the Clinical Trials Information JapicCTI site clinicaltrials.jp. 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 Food and Drug Administration Amendment Act (FDAAA)[30], European Requirements[31-33] and other relevant recommendations or regulations. If a Subject requests to be included in the trial via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the Investigator's contact details to the Subject. As a result of increasing requirements for transparency, some countries require public disclosure of Investigator names and their affiliations.

8 Methods and assessments

In order to safeguard the Subjects and to prevent discomfort to the largest extent possible, the number of assessments and blood samplings for analysis during the trial will be kept to a minimum.

From section 8.1.2 and throughout the protocol, Subject refers to the Subject and LAR(s) as a whole, if applicable, depending on the age and the capability of the Subject to perform the required trial procedures.

If applicable and agreed with the LAR(s), other Family members, relatives or persons close to the Subject are allowed to support the Subject with performing the trial related procedures as well as to accompany the Subject to site visits.

8.1 Visit procedures

Procedures for the visits and phone contacts are described in the section below. Timing of the different assessments and the visit windows are described in the flowchart in section 2.

8.1.1 Informed Consent and child assent

Before any screening activities take place, the Subject and the LAR(s) must be provided with written and oral information about the trial and the procedures involved. The Subject and LAR(s) must be fully informed, orally and in writing about their responsibilities and rights while participating in the trial, in accordance with local requirements. The Subject and LAR(s) will also be informed about possible advantages and disadvantages when being treated with trial products. All information will be presented to the Subject in an age-appropriate language. The Subject and LAR(s) will have the opportunity to ask questions and have ample time to consider participation.

The informed consent form must be signed and dated by one or both Parents/LAR(s) according to local requirements before any trial-related procedures commence. Trial-related activities are any procedures that would not have been performed during the normal management of the Subject. If required according to local legislation, oral assent must be provided by the Subject, or if required a child assent form must be dated and signed by the Subject, as age-appropriate. The Subject and LAR(s) must be provided with a copy of their own signed and dated Subject information/ informed consent form and child assent form.

If the minor reaches legal age during the conduct of the trial, the Subject has to re-consents to the standard (adult) SI/IC. This is done by using the SI/IC signature sheet for Subject turning legal age included in the standard (adult) SI/IC form.

If the Investigator is not the Subject's primary physician the Investigator should if possible notify the primary physician about the Subject's trial participation. If required, permission must be given by the Subject and the LAR(s).

The process for providing trial information and obtaining informed consent is described further in section 18.2.

8.1.2 Screening visit

Screening will take place within 17 days prior to the run-in visit (Visit 2). Before any screening related trial procedures are performed informed consent must be obtained by the Subject, according to section 8.1.1 and 18.2.

Each Subject will be assigned a unique 6-digit Subject number which will remain the same throughout the trial. A screening session must be performed in the IV/WRS.

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

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

After Visit 1, any clinically significant deterioration of a pre-existing condition, as well as any new clinically significant signs or symptoms, should be reported as an AE in accordance with section 12.

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.

The Investigator must keep a Subject screening log, a Subject identification code list and a Subject enrolment log. The Subject screening log and Subject enrolment log may be combined in one list.

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

8.1.2.1 Screening failures

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

For screening failures the screening failure form in the eCRF must be completed with the reason for not continuing in the trial. Serious adverse events (SAEs) from screening failures must be transcribed by the Investigator into the eCRF. Follow-up of SAEs must be carried out according to section 12.

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

8.1.2.2 Re-screening

Rescreening is NOT allowed.

8.1.3 Run-in

If the Subject is found eligible to continue in the trial the Subject will enter a 12-week run-in period (Visit 2). Visit 2 can take place as soon as the Subject has been found eligible and must take place no later than 17 days after the screening visit (Visit 1). The results of all the screening assessments must be available (including central laboratory results) and must have been reviewed by the Investigator before the Subject can enter the run-in period.

At Visit 2 the Subject will receive trial products and no other anti-diabetic treatment is allowed from Visit 2 until the End of Treatment visit .

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

For procedures to be performed in the run-in period see flowchart, section 2.

8.1.3.1 Run-in failures

If the Subject decides to discontinue from the trial during the run-in period, or is fulfilling one of the run-in failure criteria, or has not met the randomisation criteria then the Subject will be considered a run-in failure. Consequently, a run-in failure session must be made in the IV/WRS and a run-in failure form must be completed in the eCRF together with the reason for not continuing in the trial. No further visits or assessments should take place, however the Subject should be instructed to return all used, unused and partly used trial product to the site. Final drug accountability must be performed in the IV/WRS.

Medical events of special interest (MESIs), SAEs and non-serious AEs from run-in failures must be transcribed by the Investigator into the eCRF. Follow-up of AEs should be carried out according to section 12.3. The last date of trial product treatment must be captured in the IV/WRS.

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

8.1.4 Randomisation

Randomisation (Visit 14) should occur after the 12-week run-in period has been completed. If the Subject meets the randomisation criteria and none of the run-in failure criteria, the Subject will be randomised into one of the three treatment arms by using IV/WRS, as described in section 10. The Subject will keep the same Subject number as allocated at screening. Stop date of NovoRapid® from run-in and start date of the randomised trial product will be recorded in the eCRF.

In the morning of Visit 14 the Subject should collect a capillary blood sample for FPG central laboratory analysis using the FPG home sampling kit provided at Visit 12. The Subject must be fasting for the capillary FPG blood sample, as described in section 8.6.4. If the Subject has performed the FPG blood sampling at home fasting is not required for Visit 14. Subjects participating in the CGM and meal test subgroup must attend Visit 14 fasting, as described in section 8.1.7 and in Appendix B.

Subjects must attend Visit 14 without having taken any insulin for at least 8 hours prior to the visit as required for insulin antibody blood sampling.

For randomisation visit procedures (Visit 14), see flowchart, section 2.

8.1.5 Site visits

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

Scheduled dispensing of trial products should be performed at the visits indicated in the flowchart section 2. A dispensing session must be performed in the IV/WRS when dispensing. Drug accountability must be performed at each dispensing visit after Visit 2 and at the End of Treatment visit.

The discontinuation from trial product criteria must be reviewed to ensure the Subject's eligibility to continue in the trial.

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

8.1.6 Phone contacts

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

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

The premature discontinuation from trial product criteria must be reviewed to ensure the Subject's eligibility to continue in the trial. For assessments performed at the phone contacts see flowchart section 2.

8.1.7 Fasting visits

Fasting is defined as no intake of drink or food for at least 8 hours prior to blood sampling (only water is allowed). Medication which should be taken with or after a meal should be withheld until blood sampling has been performed. No insulin must be taken for at least 8 hours prior to insulin antibody blood sampling. Any other concomitant medication can be taken as usual.

If the Subject has performed the FPG blood sampling at home fasting is not required for any site visits, except for Subjects included in the CGM and meal test subgroup.

The Subjects included in the CGM and meal test subgroups must attend Visit 14 and Visit 40 fasting.

8.1.8 Rescheduled visits

If the Subjects included in the CGM and meal test subgroup attend Visit 14 and Visit 40 in a non-fasting condition, the visit should be rescheduled within the visit window, see Appendix B.

8.1.9 End of Treatment

At End of Treatment, the randomised treatment with trial product should be discontinued and a Completion session must be performed in the IV/WRS.

The Subject should be switched to suitable marketed product(s) at the discretion of the Investigator and should be recorded on the concomitant diabetes medication form in the eCRF, as described in section 8.4.4 .

For procedures to be performed at End of Treatment, see flowchart in section 2.

Subjects in the CGM and meal test subgroup should undergo the meal test before discontinuing trial product.

8.1.10 Follow-up periods

Follow-up visit 1 (FU1) (Visit 41) is a site visit and must take place 7-12 days after the actual date of an End of Treatment. Follow-up visit 2 (FU2) (Phone Contact 42) must take place 30-35 days after the End of Treatment.

8.1.10.1 Follow-up Visit 1

After the first follow-up period (7 days) the following data will be collected:

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

- Hyperglycaemic episodes
- Injection site reactions

The diary, handed out at the End of Treatment visit for collection of hypoglycaemic and hyperglycaemic episodes, should be returned by the Subject at this visit.

8.1.10.2 Follow-up Visit 2

After the last follow-up period (30 days) the following data will be collected during the phone contact:

- AEs
- Concomitant medication
- Current diabetes medication

8.2 Premature discontinuation of trial product

If a Subject is prematurely discontinued from trial product after randomisation (Visit 14), the Investigator must ensure every possible effort is made to undertake procedures for Visit 40A, as soon as possible.

A ”treatment discontinuation” session must be made in the IV/WRS and reason for discontinuation of trial product must be specified in the first part of the End-of-Treatment/Trial form in the eCRF. For CGM and Meal test subgroup the ”treatment discontinuation” session must be performed after the meal test has been finalised.

Final drug accountability must be performed. The Subject should be switched to a suitable marketed product at the discretion of the Investigator. The medication should be recorded on the concomitant diabetes medication form in the eCRF, as described in 5.4 and 8.4.4 at each contact after discontinuation.

The Subject should also complete the follow-up visits (Visit 41 and Phone Contact 42).

In addition, Subjects prematurely discontinued from trial product should continue with the per protocol planned visits after 12 weeks (Visit 26) and 26 weeks (Visit 40) from randomisation depending on when the Subject discontinues trial product. The following assessments are not applicable for prematurely discontinued Subjects at V40: 4-point profile, technical complaints, CGM and meal test, IV/WRS call.

Phone contact after premature discontinuation of trial product:
The Investigator must establish telephone contact with the Subject at least once halfway through the premature discontinuation visit period, if the Subjects discontinue the trial treatment prior to Visit 30. Phone contact will only be recorded in source data and will not be captured in eCRF.

The Subject should be notified that they will be contacted according to the protocol.

All attempts to contact the Subject must be documented in the source document.

At each contact the Investigator should as a minimum capture/evaluate:

- Any assessment of hypo/hyperglycaemic episodes
- Adverse events
- Change in diabetes medication

In case of any findings, these must be captured in the eCRF.

Follow-up contact after premature discontinuation of trial product:
Subjects that prematurely discontinue trial product will be asked to attend an End of Treatment visit (Visit 40A) and follow-up visit 1 (FU1) 7-12 days after visit 40A and follow-up visit 2 (FU2) 30-35 days after V40A.

In the following situations where two visits are close to each other, only one visit should take place:

- If V40A is more than 10 weeks after randomisation and before the planned V26, only V40A should be performed
- If V26 and FU2 visit windows overlap according to visit schedule, only V26 should be performed
- If V40 and FU1 visit windows overlap according to visit schedule, only V40 should be performed
- If V40 and FU2 visit windows overlap according to visit schedule, only V40 should be performed

Diary records after premature discontinuation of trial product:
The Subject will be handed out premature discontinuation diaries to fill in:

- Date, actual clock time and value of the SMPG measurements performed as part of the 8-point profiles on the two consecutive days just before Visit 26 and Visit 40
- Hypoglycaemic episodes. The following information should be recorded:

- Start date and time of hypoglycaemic episode
- Time and value of plasma glucose level before treating the episode (if available) and any follow up measurements.
- Whether the episode was symptomatic (Yes/No)

  A hypoglycaemic episode starting without symptoms should be updated to symptomatic if the Subject experience symptoms later during the episode.
- Was the hypoglycaemic episode associated with severe neuroglycopenia, usually resulting in coma or seizure and requiring parenteral therapy (glucagon or intravenous glucose)[34]? (Layman language used in the Subject diaries: Was the low blood glucose episode associated with symptoms severe enough to result in unconsciousness or a seizure and was glucagon (an injection) or IV glucose/sugar (drip) needed for your child to recover?)

- Hyperglycaemic episodes (see section 8.5.1.2)

Hypoglycaemic and/or hyperglycaemic episode must be reported in the diary until Visit 40 has been completed.

8.3 Withdrawal from trial

If a Subject withdraws consent after randomisation (Visit 14), the Investigator should ensure every possible effort is made to undertake procedures similar to those for Visit 40, including the meal test for the Subjects included in the CGM and meal test subgroup, as soon as possible. The Subject must also complete the follow-up visits (Visit 41 and Phone Contact 42).

The End-of-Treatment/Trial form must be completed in the eCRF and final drug accountability must be performed even if the Subject is not able to come to the site. A "Treatment Discontinuation" session must be made in IV/WRS and reason for withdrawal must be specified on the End of Treatment/Trial form in the eCRF. Final drug accountability must be performed even if the Subject is not able to come to the trial site.

Although a Subject is not obliged to give his/her reason(s) for withdrawing from a trial, the Investigator should make every effort to ascertain the reason(s), while fully respecting the Subject's rights. Where the reasons are obtained, the primary reason for discontinuing trial product and not completing the trial must be specified on the End-of-Treatment/trial form in the eCRF.

In case a premature discontinuation Subject choose to withdraw after completing Visit 40A, FU1 and FU2, the Visit 40 should be performed but FU1 and FU2 visit is not to be completed again.

8.4 Subject related information

8.4.1 Demography

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

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

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

8.4.2 Diagnosis of type 1 diabetes mellitus

Date of diagnosis of diabetes will be obtained and recorded in the Diabetes History in the eCRF.

8.4.3 Concomitant illness and medical history

A **concomitant illness** is any illness except T1DM that is present at the start of the trial (i.e. at the screening visit) or found as a result of the screening procedures. Any abnormal and clinically significant findings at Visit 1 must be recorded on the medical history/concomitant illness form in the eCRF. Information about diabetes complications must also be recorded if present.

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

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

For female Subjects, it must be documented in the Subject's medical record if they are premenarcheal.

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 as described in section 12.

8.4.4 Concomitant medication

A **concomitant medication** is any medication, other than trial product(s) and diabetes medication which should be reported in accordance with section 8.4.5, which is taken during the trial, including in the screening, run-in and the follow-up periods.

Details of any concomitant medication must be recorded in the eCRF at the first visit (Visit 1). Changes in concomitant medication must be recorded at each visit as they occur.

The information collected for each concomitant medication includes (as a minimum) trade name or generic name, indication, start date and stop date or continuation.

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

8.4.5 Diabetes treatment history

Any diabetes medication taken at screening, after end of treatment, or during any unplanned events, e.g. hospitalisation must be recorded as concomitant diabetes medication in the eCRF including the trade name or generic name, total daily dose, start date, stop date or continuation. At the run-in visit (Visit 2) all diabetes medication should be discontinued and a stop date recorded.

8.5 Clinical Assessments

8.5.1 Adverse events requiring special forms in the eCRF

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

- Hypoglycaemic episodes
- Hyperglycamic episodes
- Injection site reactions
- Medication error (described in section 12.1.4)

8.5.1.1 Hypoglycaemic episodes

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

All plasma glucose values:

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

should be reported in the diary according to the instructions below throughout the trial from Visit 2 to Visit 41. Upon onset of a hypoglycaemic episode the Subject is recommended to measure plasma glucose every 15 minutes until the SMPG value is >3.9 mmol/L (70 mg/dL) or symptoms have been resolved in accordance to current guidelines[35].

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 will per default be considered as one hypoglycaemic episode until a succeeding SMPG value is >3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved. One hypoglycaemic episode form is to cover these measurements and/or symptoms. However, each hypoglycaemic episode form will cover a period of maximum 60 minutes after onset of a hypoglycaemic episode.

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

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

The record should include the following information:

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

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

- Whether the episode was symptomatic (Yes/No)

  A hypoglycaemic episode starting without symptoms should be updated to symptomatic if the Subject experience symptoms later during the episode.

- Was the hypoglycaemic episode associated with severe neuroglycopenia, usually resulting in coma or seizure and requiring parenteral therapy (glucagon or intravenous glucose)[34]? (Layman language used in the Subject diaries: Was the low blood glucose episode associated with symptoms severe enough to result in unconsciousness or a seizure and was glucagon (an injection) or IV glucose/sugar (drip) needed for your child to recover?)

  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 basal insulin dose prior to episode
- Date, time and dose of last bolus insulin dose prior to episode
- Date and time of last meal prior to episode
- Whether the episode occurred in relation to physical activity
- Any sign of fever or other intercurrent disease (e.g. gastrointestinal infections)
- Whether the Subject was asleep when the episode occurred

  If yes: Whether the symptoms of the episode woke up the Subject

If the question "Was the hypoglycaemic episode associated with severe neuroglycopenia, usually resulting in coma or seizure and requiring parenteral therapy (glucagon or intravenous glucose)?" is answered "YES" the hypoglycaemic episode is classified as “severe”[34], and the following additional information should be recorded:

- Who assisted in the treatment of the hypoglycaemic episode (i.e. medical person or non-medical person)
- Where the treatment was administered (in clinic/emergency room/ hospital or other. If the Subject was treated in clinic/emergency room/hospital whether they were transported in an ambulance or not)
- Type of treatment provided by other person (i.e. oral carbohydrates, glucagon, IV glucose or other)
- Were symptoms alleviated by the administration of treatment?
- Factors contributing to the episode (i.e. physical activity, missed meal, diet changed, medication error (i.e. overdose, mix-up between products), miscalculation of insulin dose, other factors not listed or unknown)
- Did the Subject experience seizure?[34]
- Did the Subject experience loss of consciousness?[34]
- Did the Subject experience any of the following symptoms (modified from table 1[34]) (layman term used in the diary is specified in brackets if different from the protocol term)?
    - Autonomic: Shakiness, sweatiness, trembling, palpitations (Rapid and irregular heart beat) and pallor (extreme paleness)
    - Neuroglycopenic: Poor concentration, blurred or double vision, disturbed colour vision, difficulty hearing, slurred speech, poor judgment and confusion, problems with short-term memory, dizziness and unsteady gait
    - Behavioural signs and symptoms: Irritability, erratic behaviour, agitation (restlessness associated with irritability and tension), nightmares, inconsolable crying
    - Non-specific symptoms: Hunger, headache, nausea, tiredness
- Did the Subject experience other symptoms?

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

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

The Investigator must review the diary for low SMPG values not reported as hypoglycaemic episodes at each contact. The Subject must be questioned whether any of the low values were severe i.e. whether the hypoglycaemic episode was associated with severe neuroglycopenia . If the hypoglycaemic episode was associated with severe neuroglycopenia it has to be reported as a severe hypoglycaemic episode on a hypoglycaemic episode form.

Low SMPG values for non-severe hypoglycaemic episodes not having a hypoglycaemic episode form completed within 7 days since the SMPG measurement should be reported on a hypoglycaemic episode form with as much information as possible. Due to decreased validity of such data Novo Nordisk will not query for additional data except for the date, SMPG value and whether the hypoglycaemic episode was associated with severe neuroglycopenia[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 must also be filled in, as described in section 12.

8.5.1.2 Hyperglycaemic episodes

The Subject should be instructed to always perform an SMPG measurement when there is suspicion of a hyperglycaemic episode. If the SMPG value is > 14.0 mmol/L (250 mg/dL) and the Subject looks/feels ill, the Subject should be instructed to do the following:

- Measure blood ketones using a BG meter or
- Measure urine ketones using a urine stick

If the Subject experiences a hyperglycaemic episode where the Subject looks/feels ill and with either a SMPG > 14.0 mmol/L (250 mg/dL) and blood ketones > 1.5 mmol/L or SMPG >14.0 mmol/L (250 mg/dL) and urine ketones above "moderate", the Subject should record this in the diary as a hyperglycaemic episode and should be instructed to contact the site staff as soon as possible for further guidance on titration. Symptoms should be treated in accordance with instructions from the Investigator.

Multiple (>1) hyperglycaemic values of an SMPG >14mmol/L (250mg/dL) are considered as one hyperglycaemic episode until the SMPG is ≤14mmol/L (250 mg/dL). One episode is set to a maximum of 24 hours from the first SMPG >14 mmol/L (250 mg/dL). If new high SMPG values and blood or urine ketones are measured more than 24 hours after the first reported high values it is considered as a new hyperglycaemic episode and a new hyperglycaemic episode form is to be filled in.

In case of several high SMPG and ketone values within the 24 hours interval, the highest value for SMPG and ketone respectively is the one that will be reported as the SMPG and ketone value for the hyperglycaemic episode; but the start time of the episode will remain as the time for the first high SMPG value

Information on hyperglycaemic episodes will be collected throughout the trial from Visit 2 to Visit 41. The following must be reported in the hyperglycaemic episode form in the diary and eCRF:

- Start date and time of the hyperglycaemic episode
- Whether the Subject looked/felt ill prior to the episode
- The SMPG value before treating the episode and any follow-up measurements
    - The highest value measured during the hyperglycaemic episode will be reported as the plasma glucose value for the episode, the remaining values will be kept as source data
- Result from urine ketone test or blood ketone test , preferably before treating the episode and any follow-up measurements
    - The highest value measured during the hyperglycaemic episode will be reported as the ketone value for the episode, the remaining values will be kept as source data.
- Any factors contributing to the episode:
    - Physical activity
    - Diet change
    - Medication error (i.e. too low dose, mix-up between products)
    - Miscalculation of dose of antidiabetic medication
    - Change in any concomitant illness
    - Any signs of fever or other acute disease
    - Missed or change in dose of concomitant medication
    - Other
    - Unknown

The Investigator must review the diary data at each contact for correct reporting of hyperglycaemic episodes. High SMPG values and/or ketones not having a hyperglycaemic episode form completed within 7 days since the SMPG and/or ketone measurement should be reported on a hyperglycaemic episode form with as much information as possible (as a minimum the date and SMPG value); hyperglycaemic episodes will not be queried for additional information retrospectively due to decreased validity of such data [36,37].

The subject must be re-trained in how to report hyperglycaemic episodes if the Investigator identifies high SMPG and/or ketone values not reported as part of a hyperglycaemic episode.

If the hyperglycaemic episode fulfils the criteria for an SAE then an AE form and a safety information form must be filled in, as described in section 12.

8.5.1.3 Injection site reactions

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

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

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

The injection site reaction form should only be used for events with an onset date between Visit 2 and Visit 41. The Investigator has to evaluate whether further actions are needed (e.g. extra visits, supervised injection, discontinuation of trial product, dermatologist consultation).

8.5.2 Body measurements

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

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

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

Body Mass Index (BMI) will automatically be calculated by the eCRF.

Body measurements will be assessed as described in the flowchart in section 2. All values of the body measurements will be recorded in the eCRF.

8.5.3 Continuous glucose monitoring (CGM) and meal test in a subgroup

At selected sites a number of the Subjects will undergo an assessment of their IG levels by wearing a blinded CGM device for at least 11 days and up to 13 days in connection to Visit 14 and Visit 40. At Visit 14 and Visit 40 the Subjects will undergo a standardised liquid meal test in connection to wearing the CGM. Both assessments will be mandatory for an agreed number of Subjects at the selected sites.

A detailed description of the assessments is described in the CGM and meal test protocol Appendix B.

8.5.4 Insulin dose

During the trial, starting at the run-in visit (Visit 2), the Subject should be instructed to record the date and doses (units) of the breakfast, lunch, and main evening meal bolus insulin on the three days prior to a site visit/phone contact in the diary. In addition, for extra insulin boluses, date, actual clock time, dose (units), time of the previous meal, and reason for the extra bolus should be recorded.

The Subjects should also be instructed to report the date and the dose (units) of the basal insulin in the diary on the three days prior to the scheduled site visits/phone contact.

The recommended insulin doses will be individually calculated in the eCRF based on the SMPG values and the doses taken in accordance with the titration guideline, described in Appendix A. If the Subject is using the principles of flexible bolus dosing based on the carbohydrate content of the meal to adjust the bolus dose, only the basal insulin dose will be calculated in the eCRF as described in Appendix A.

Doses of trial products must be recorded in the eCRF.

8.5.5 Physical examination

Physical examination will be assessed as described in the flowchart in section 2 and 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
- General appearance

Any abnormal, clinically significant findings at the screening visit (Visit 1) must be recorded as a concomitant illness (see section 8.4.3) and the Investigator must add a comment in the Subject's medical record.

Any clinically and significant worsening from screening, as well as any new abnormal and clinically significant findings, must be reported as an AE in accordance with section 12.2.

8.5.5.1 Pubertal status (Tanner staging)

Pubertal status will be assessed as described in the flowchart in section 2 by Tanner staging in accordance with stages I-V[38] and will be recorded in the eCRF.

8.5.6 Self-measured plasma glucose

At the run-in visit (Visit 2), the Subject will be supplied with a BG meter, and ancillaries for the BG meter. The Subject will be instructed in how to use the device according to the manufacturer's instructions. The Subject will also be provided with written instructions. Sites will, as necessary, review the instructions for use with the Subject during site visits. Throughout the trial, only the BG meter provided by Novo Nordisk must be used to measure the PG values to be recorded in the diary, and for calibrating the CGM device used in the CGM and meal test subgroup.

The BG meter 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 in the display. These are the values to be used for dose adjustment.

The Subject should be instructed in how to record the results of the SMPGs in the diaries. The record of each SMPG should include date and value. All 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 should be corrected.

Additional SMPG values recorded by the Subject in the diary should not be transcribed to the eCRF except the following SMPG values which should be recorded as hypoglycaemic or hyperglycaemic episodes:

- SMPG values ≤ 3.9 mmol/L (70 mg/dL)
- SMPG values > 3.9 mmol/L (70 mg/dL) when they occur in conjunction with hypoglycaemic symptoms
- SMPG values > 14.0 mmol/L (250 mg/dL) if the criteria described in section 8.5.1.2 was fulfilled

The Investigator must check if the Subject has recorded all hypoglycaemic and hyperglycaemic episodes in the hypoglycaemia and hyperglycaemia sections of the diary. If not done the missing information should be provided by the Subject, if possible.

8.5.6.1 4-point profile

The Subjects will be instructed to record 4-point profiles in the diary on the three days prior to a scheduled site visit/phone contact every week throughout the trial for insulin titration purposes, starting at run-in (Visit 2). The record of each SMPG should include date and PG value. The SMPG values for the 4-point profile should be recorded at the following time points:

- Before breakfast
- Before lunch

- Before main evening meal
- At bedtime

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

The 4-point profile can be part of the 8-point profiles if actual clock times of the SMPG measurements are recorded.

8.5.6.2 8-point profile

The Subject will be instructed to perform an 8-point profiles prior to selected visits as described in the flowchart in section 2 and record these in the diary, as outlined in the flowchart in section 2. The 8-point profiles will be used for effect analysis as part of the trial.

Measurement of the 8-point profile should be performed on the 2 consecutive days just before the visit as outlined in Table 8–1.

Table 8–1 8-point SMPG profile (8-point profile)

Time point	Day -2	Day -1	Day of visit
Before breakfast	√	√[a]	√
60 minutes after start of breakfast	√	√	
Before lunch	√	√	
60 minutes after start of lunch	√	√	
Before main evening meal	√	√	
60 minutes after start of evening meal	√	√	
At bedtime	√	√	

[a]The last SMPG value of the first 8-point profile will be the first SMPG value of the last 8-point profile.

For each measurement, the SMPG value, actual clock time and date should be recorded in the diary.

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

If the Subject does not fulfil the randomisation criteria of an $HbA_{1c} \leq 9.5$ mmol/l (80 mmol/L) measured at Visit 12 (analysed by the central laboratory) the 8-point profile should not be performed.

8.5.7 Vital signs

Diastolic blood pressure, systolic blood pressure and pulse should preferable be assessed while the Subject is in a sitting position after 5 minutes of rest. Vital signs will be assessed as described in the flowchart in section 2 .

Any abnormal and clinically significant findings at Visit 1 must be recorded on the medical history/concomitant illness form in the eCRF as described in section 8.4.3.

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

8.6 Laboratory assessments

Except for urine pregnancy testing which will be performed locally at site and ketone measurements (blood and urine in case of hyperglycaemic episodes) which will be performed by the Subjects, 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 arrange transportation of all blood samples taken during the trial. The central laboratory may utilise subcontractors.

A detailed description of assay methods, reference ranges, and procedures for obtaining 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 stated in the flowchart in section 2.

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

Laboratory results will be made available by the central laboratory. Laboratory reports must be reviewed, dated and signed by the Investigator on the day of evaluation. It must be specified by the Investigator if out of range results are clinically significant.

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. See the laboratory manual for further guidance. To minimise the volume of blood collected from the Subject only the affected sample(s) should be retaken. Before repeating any blood sampling the Investigator must ensure that the total volume of blood collected from the Subject is in accordance with the guideline as described in section 8.6.1.

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

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.

If any clinically significant abnormalities occur at screening (Visit 1) or as a result of the screening procedures then these must be recorded on the medical history/concomitant illness form in the eCRF, as described in section 8.4.3. Any clinically significant deterioration of a pre-existing condition as well as any new clinically significant signs or symptoms occurring hereafter should be reported as an AE in accordance with section 12.

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 must be reported to the Investigator.

The Investigator must review all laboratory results for concomitant illnesses and AEs and report these according to this protocol. The Investigator will not be able to review the antibody results for AEs as the antibody samples will be analysed after LSLV.

Laboratory samples will be destroyed on an ongoing basis except antibody samples as described in section 24.2.

8.6.1 Blood volumes for blood sampling

The volume of blood to be collected for trial blood sampling will be minimised, in accordance with the EMA and FDA guidelines[39,40]. Table 8–2 lists the blood volume required to be collected for the scheduled trial blood samples. The blood volume to be collected at each blood sampling visit will not exceed 1% of the Subject's total blood volume and the blood volume to be collected over a period of four weeks will not exceed 3% of the Subject's total blood volume[41].

The volume of the FPG capillary blood samples is insignificant and will not be considered.

Table 8–2 Approximate blood volumes collected during the trial

	2 < Age (mL)	2 ≤ Age < 6 years (mL)	6 ≤ Age < 18 (mL)	Age ≥ 8 and in CGM and meal test subgroup (mL)
Visit 1	3.0	5.0	6.5[a]	6.5[a]
Visit 12	0.5	1.2	2.0	2.0
Visit 14	5.8	8.4	10.0[a]	10.0[a]/[b]
Visit 26	5.8	8.4	10.0	10.0
Visit 40[c]	5.8	8.4	10.0[a]	10.0[a]/[b]
Total blood volume collected	20.9	31.4	38.5	38.5

[a] Including blood volume for performing hCG pregnancy test for females of childbearing potential only (females having had menarche).

[b] including four PG blood samples collected during the meal test

[c] Same blood volume applicable for Visit 40A

It is the responsibility of the Investigator to ensure that the blood volume limits are respected based on the age and weight of the Subject[42].

In case of re-sampling only the affected blood sample(s) should be collected and the Investigator must ensure that no more than 3% of the Subject's total blood volume is collected over a period of four weeks[42].

If the Subject's weight is less than 20.0 kg (44.0 lbs) at screening (Visit 1) the Subject is not eligible for the CGM and meal test subgroup.

8.6.2 1,5-anhydroglucitol

Blood samples will be drawn as described in the flowchart in section 2 to determine the level of 1,5-anhydroglucitol in order to evaluate postprandial glycaemic fluctuations.

8.6.3 Biochemistry

Blood samples for biochemistry will be collected as described in the flowchart in section 2 and analysed to determine:

- Alanine aminotransferase (ALT)
- Albumin
- Alkaline phosphatase
- Aspartate aminotransferase (AST)
- Creatinine
- Potassium
- Sodium
- Total bilirubin

8.6.4 Fasting plasma glucose

FPG will be measured in order to evaluate metabolic control.

Capillary blood samples for FPG will be taken at home using a home blood sampling kit in the morning on the day of the visits, as described in the flowchart in section 2.

The Subject will receive a home blood sampling kit and instruction on how to use it. The Subject will bring the blood sample to the site visit and the sample will be handled by the site staff in accordance with the instructions described in the laboratory manual. If preferred, the FPG blood sampling can be performed at the site provided that the Subject is fasting for the site visit.

The FPG capillary blood sample must be taken while the Subject is fasting, in accordance with the fasting definition described in section 8.1.7 and before administration of insulin on that day. If these conditions cannot be met, collection of the FPG sample should be rescheduled within the permitted visit window, except for the capillary FPG sample to be collected at the randomisation visit (Visit 14). If no FPG sample is available at the randomisation visit the randomisation visit should be rescheduled within the visit window.

FPG results ≤ 3.9 mmol/L (70 mg/dL) should not be reported as hypoglycaemic episodes in the eCRF but as an AE related to the procedure (e.g. if the FPG result is 2.9 mmol/L (52 mg/dL), please report as ‘low plasma glucose of 2.9 mmol/L (52 mg/dL)’).

8.6.5 Haematology

Blood samples for haematology will be collected as described in the flowchart in section 2 and analysed to determine:

- Erythrocytes
- Haematocrit
- Haemoglobin
- Leucocytes
- Thrombocytes

8.6.6 HbA_{1c}

Blood samples will be collected as described in the flowchart in section 2 to determine HbA_{1c} level in order to evaluate metabolic control. The HbA_{1c} blood sample collected at Visit 1 will be used to determine if the Subject is eligible to enter the trial (the run-in period) and the HbA_{1c} blood sample collected at Visit 12 will be used to determine if the Subject is eligible for randomisation i.e. fulfils the randomisation criterion.

8.6.7 Insulin antibodies

On the day of insulin antibody sampling as described in the flowchart in section 2 the Subject need not to be fasting but must attend the visit without having taken any kind of insulin for at least 8 hours before insulin antibody blood sampling. The Subject should bring the trial product to the site visit and the insulin can be administered after the blood sampling has been performed.

If the Subject has taken insulin less than 8 hours before insulin antibody blood sampling, the insulin antibody blood sampling must be rescheduled within the visit window.

Anti-insulin aspart antibodies (specific and cross-reacting with human insulin and total of these) will be measured. Antibody samples may be retained until drug approval by U.S. Food and Drug Administration (FDA) and/or European Medicins Agency (EMA). The retained antibody samples may be used for further charcterisation for antibody response towards drug if required by health authorities or for safety reasons, see section 24.2

8.6.8 Lipids

Blood samples for lipids will be collected as described in the flowchart in section 2 and analysed to determine:

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

8.6.9 Pregnancy testing

For females of childbearing potential (females having had menarche), a blood Human Chorionic Gonadotropin (hCG) pregnancy test will be performed as described in the flowchart in section 2. In addition, urine pregnancy tests will be performed locally, at site, during the trial if a menstrual period is missed, if menarche occurs or if deemed necessary by the Investigator or required by local law. A positive urine test should be followed by a confirmatory serum-hCG (central laboratory).

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

8.7 Other assessments and procedures

8.7.1 Diary

At each site visit, starting at the run-in visit (Visit 2), the Subjects will be provided with a new diary. The diary should be collected at the next site visit, and retained at the site as source data in accordance with section 14. No diary will be handed out for the 30-day follow-up visit (between FU1 and FU2) and consequently source data will be the notes written in Subject's medical record for FU2.

The Investigator must carefully instruct the Subject in how to fill in the diary. The Subject should bring the diary at each visit to the site and there the Investigator or delegated site personnel must review the diary together with the Subject to ensure consistency/compliance. The information in the diary is considered as source data and must be transcribed into the eCRF by the site personnel. In case some information is missing in the diary and is available in the medical records, this information can be used.

The Subjects should be instructed to record the following in the diary:

- Date, time point and value of the SMPG measurements performed on the three days prior to each site visit/phone contact (4-point profiles)
- Date, actual clock time and value of the SMPG measurements performed as part of the 8-point profiles on the two consecutive days just before Visit 14, Visit 26 and Visit 40
- Date, time point and doses (units) of bolus insulin on the three days prior to each site visit/phone contact throughout the trial
- Date and dose (units) of basal insulin on the three days prior to each site visit/phone contact throughout the trial
- For extra insulin boluses: Date, actual clock time, dose (units), time and type of previous meal and reason for the extra bolus
- Carbohydrate content per meal on the three days prior to each site visit/phone contact throughout the trial, if the Subject is using principles of flexible dosing.
- Prescribed doses of trial products during the phone contacts

- I:Carb ratio and insulin correction factor (sensitivity factor) per type of meal (breakfast, lunch and main evening meal), at each phone contact (applicable for flexible dosing Subjects).
- Date for first dose of trial products.
- Date of last dose of bolus insulin in run-in period
- Hypoglycaemic episodes (see section 8.5.1.1)
- Hyperglycaemic episodes (see section 8.5.1.2)
- A comment for the reason for deviating from the titration algorithm, if applicable

The Investigator should record the following in the diary:

- Prescribed doses of trial products during the site visits
- I:Carb ratio and insulin correction factor (sensitivity factor) per type of meal (breakfast, lunch and main evening meal), at each site visit (applicable for flexible dosing Subjects).
- Time and date of next visit and/or phone contact
- Subject number
- Site contact details

The temporary transferral of data between the Subject and the Investigator for titration purposes can be performed electronically e.g. by sending a picture file or a scanned copy of the relevant diary pages by email in addition to the scheduled phone contacts. The diary will act as source at any time.

When the Subject comes in for the following site visit, and if there is a discrepancy between the data in the diary and the transferred data, then the diary will be considered source data. The eCRF should be updated accordingly, and a comment explaining that the titration was based on wrong values should be entered into the eCRF.

Review of the diaries must be documented either on the front page of the documents and/or in the Subject's medical record.

If clarification of entries in the diary is needed then the Subject should be questioned and a conclusion made in the medical record. Care should be taken not to bias the Subject.

8.7.2 Training in diabetes and carbohydrate counting

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

It is the Investigators responsibility to ensure that the Subject is adequately trained 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 oral carbohydrates
- Ability to sum up the carbohydrate content of a meal

8.7.3 Training in trial product and pen handling

The Subjects should be trained in how to handle the insulin pen system when handed out the first time. The Subjects must demonstrate for the Investigator at the following visit after NovoPen Echo® and the pre-filled PDS290 pen-injector (FlexTouch®) has been handed out, that the Subject can use the pen correctly. Training should be repeated during the trial if necessary. It is important to emphasise that the Subject should remember the following:

- Always use a new needle for each injection as this will prevent contamination and blocked needles
- Priming to ensure the insulin flow
- The needle should be kept in the skin while counting slowly to 6 after the dose counter has returned to zero after injection. If the needle is removed too early then the full dose may not have been delivered

Important:
The Subjects should be thoroughly trained in distinguishing between the basal insulin and the bolus insulin. The pens will come in different colours and types, so they can be differentiated. The bolus insulins are to be injected with a durable pen (NovoPen Echo®) and should be loaded with a Penfill® before use. The basal insulin is to be injected with a pre-filled PDS290 pen-injector (FlexTouch®). The Subjects must be instructed to always check the name on the label before administering the insulin.

8.7.4 Safety precautions

The Investigator must instruct the Subjects always to carry the following supplies in case of hypoglycaemic episodes and need for ketone measurement (as described in section 8.5.1.1 and 8.5.1.2):

- Glucagon for injection, according to local practice
- A fast-acting glucose preparation (e.g. tablets or powder)
- Urine sticks for ketone monitoring

The Subject must be trained in how and when to use the supplies.

8.8 Subject compliance

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

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

9 Trial supplies

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

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:

Table 9–1 Trial Products

Trial product	Strength	Dosage form	Route of administration
Faster aspart (blinded for the meal-time arm)[a] *(IMP)*[b]	100 U/mL	Penfill® 3 mL	s.c.
Faster aspart (open-label for the post-meal arm)[a] *(IMP)*[b]	100 U/mL	Penfill® 3 mL	s.c.
Insulin aspart (NovoRapid®) (blinded for the treatment period) *(IMP)*[b]	100 U/mL	Penfill® 3 mL	s.c.
Insulin aspart (NovoRapid®) (open- label for the run-in period)	100 U/mL	Penfill® 3 mL	s.c.
Insulin degludec (open-label) *(IMP)*[b]	100 U/mL	Pre-filled PDS290 pen-injector 3 mL	s.c.

[a] Faster aspart is the short name for faster-acting insulin aspart and will be used as text on the labels.

[b] Investigational medical product

All bolus insulins will be administered with NovoPen Echo®. Penfill® is the cartridge used for durable Novo Nordisk pens. Basal insulin will be administrated with a pre-filled PDS290 pen-injector (FlexTouch®).

9.2 Labelling

Labelling of the trial products will be in accordance with Annex 13[43], local regulations and trial requirements.

Labelling will include the product related requirements and precautions.

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

The Investigator must document that direction for use is given to the Subject orally and in writing at each dispensing visit. Direction for use must as a minimum be provided to the Subject in writing at the first dispensing visit (Visit 2).

9.3 Storage

Table 9–2 Storage of trial products

Trial product	Storage conditions (not-in-use)	In-use conditions[a]	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 Can be stored in refrigerator (2°C – 8°C) Do not freeze Protect from light	Use within 8 weeks

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

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

Trial product that has been stored improperly must not be dispensed to any Subject and should be made temporarily unavailable in the IV/WRS and stored separately (quarantined) within the correct

temperature range until it has been evaluated and approved for further use by Novo Nordisk. The Investigator must take appropriate action to ensure correct storage.

9.4 Drug accountability and destruction

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

Subjects are instructed to return all used, partly used and unused trial product at each dispensing visit. See flowchart in section 2 for timing of the dispensing visits.

Returned trial product (used/partly used or unused including empty packaging material) can be stored at room temperature and must be stored separately from non-allocated trial product. The Monitor will reconcile the drug accountability using the IV/WRS Drug Accountability module. The Monitor is responsible for ensuring that there is a process for the destruction of used and unused trial products. The destruction of trial products will be recorded on a Destruction Form, which will be signed by the person responsible for destruction. Destruction of products must be documented.

9.5 Auxiliary supplies

9.5.1 Auxiliaries supplied by Novo Nordisk A/S

The following auxiliaries will be supplied by Novo Nordisk A/S:

- NovoPen Echo®
- Direction for use
- BG meters, and ancillary for BG meters
- Needles, the size of the needle will be a maximum of 8 mm
- Standardised liquid meal (for the subgroup only)
- CGM supplies as described in Appendix B (for the subgroup only)
- Strips for ketone measurement
- A fast-acting glucose preparation (e.g. tablets or powder)

10 Interactive voice/web response system

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

IV/WRS is used for:

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

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

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

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

11 Randomisation procedure and breaking of blinded codes

At randomisation (Visit 14) the Subject will be randomised to either faster-acting insulin aspart or NovoRapid®, both in combination with insulin degludec.

The randomisation will be carried out in a 1:1:1 manner to the three different treatment arms described below using the IV/WRS:

- Meal-time faster-acting insulin aspart and insulin degludec
- Meal-time NovoRapid® and insulin degludec
- Post-meal faster-acting insulin aspart and insulin degludec

The randomisation will be stratified according to age at randomisation (Visit 14):

- $1 \leq$ age < 3
- $3 \leq$age < 6
- $6 \leq$ age < 12
- $12 \leq$ age < 18

The Investigators must strive to include Subjects in the youngest age groups (age < 6), to enable investigation of the efficacy and safety of faster-acting insulin aspart in these age groups. It will be attempted to include at least 20 Subjects below 6 years of age in each treatment arm.

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

11.1 Breaking of blinded codes

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

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

When the code is broken, the treatment allocation will be accessible to the Investigator and the Novo Nordisk Global Safety department. If IV/WRS is not accessible at the time of code break the IV/WRS vendor helpdesk should be contacted. The IV/WRS vendor helpdesk is available at all hours. Contact details are listed in Attachment I.

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

12 Adverse events, and 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 product, and which does not necessarily have a causal relationship with this treatment.

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

An AE includes:

- A clinically significant worsening of a concomitant illness.

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

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

- Pre-existing conditions, including those found as a result of screening procedures (pre-existing conditions should be reported as medical history or concomitant illness).
- Pre-planned procedures unless the condition for which the procedure was planned has worsened from the first trial related activity after the Subject has signed the informed consent.
- Non-serious hypoglycaemia is an AE, but is reported on a hypoglycaemic episode form instead of on an AE form, see section 8.5.1.1.
- Non-serious hyperglycaemia is an AE, but is reported on a hyperglycaemic episode form instead of on an AE form, see section 8.5.1.2

The following three definitions are used when assessing an AE:

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

- Final outcome of an AE
    - 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 dyscrasias or convulsions that do not result in hospitalisation or development of drug dependency or drug abuse.

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

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

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 Medical event of special interest

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

Medication errors concerning trial products:

- Administration of wrong drug.
- Wrong route of administration, such as intramuscular instead of s.c.
- Administration of an overdose with the intention to cause harm (e.g. suicide attempt).
- Accidental administration of a lower or higher dose than intended. That is a dose that deviates from the intended dose to an extent where clinical consequences for the trial Subject were likely to happen as judged by the Investigator, although not necessarily did happen.

12.1.5 Technical complaint

A technical complaint is any written, electronic, or oral communication that alleges product (medicine or device) defects. The technical complaint may be associated with an AE, but does not concern the AE itself.

Examples of technical complaints:

- The physical or chemical appearance of trial products (e.g. discoloration, particles or contamination)
- The packaging material (e.g. leakage, cracks, rubber membrane issues or errors in labelling text)
- Problems related to devices and/or needles (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. The events must be recorded in the applicable CRF forms in a timely manner, see timelines below and Figure 12–1.

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

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

- Faster-acting insulin aspart: IB. Current version and any updates hereof [17]
- NovoRapid®: Company Core Data Sheet. Current version and any updates hereof
- Insulin degludec: Insulin degludec IB. Current version and any updates hereof [22]

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

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

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

The AE form for a non-serious AE should be signed when the event is resolved or at the end of the trial.

12.2.1 Timelines for initial reporting of AEs:

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

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

  Both forms must be signed within 7 calendar days from the date the information was entered in the eCRF.

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

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

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

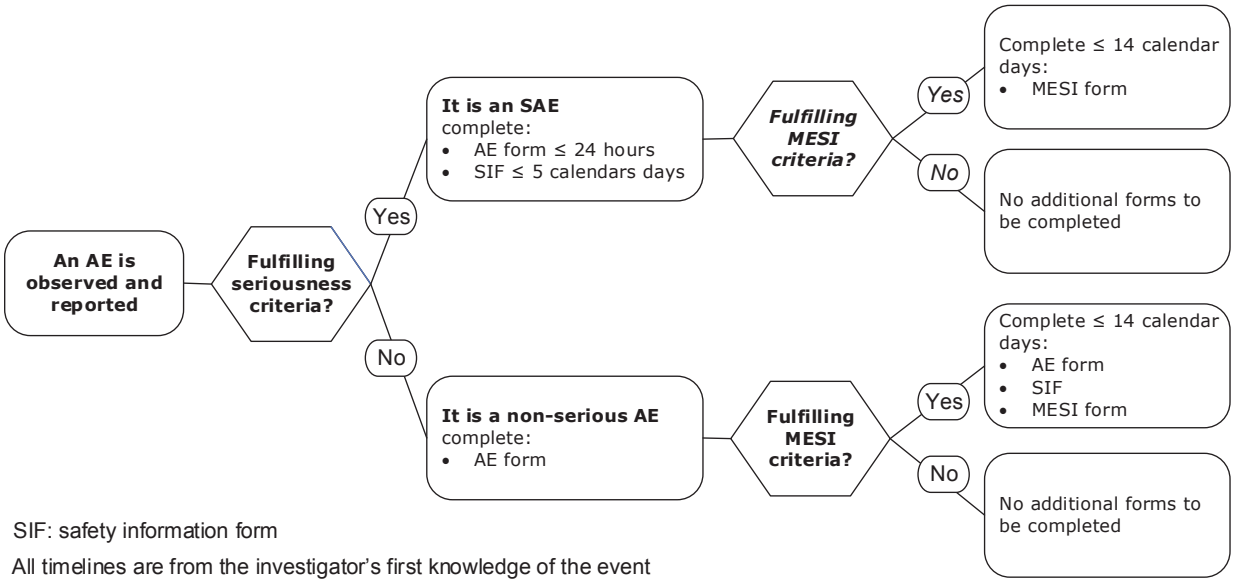


Figure 12–1 Initial reporting of AEs

12.2.2 Reporting of trial product-related SUSARs by the sponsor:

Novo Nordisk will notify the Investigator of trial product-related suspected unexpected serious adverse reactions (SUSARs) in accordance with local requirements and 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 Institutional Review Boards (IRBs)/independent ethics committees (IECs) of trial product-related SUSARs in accordance with local requirement and GCP[1], unless locally this is an obligation of the Investigator.

12.2.3 Novo Nordisk products used as concomitant medication:

If an SAE and/or MESI is considered to have a causal relationship with a Novo Nordisk marketed product used as concomitant medication in the trial, it is important that the suspected relationship is reported to Novo Nordisk, e.g. in the alternative aetiology section on the safety information form. Novo Nordisk may need to report this adverse event to relevant regulatory authorities.

12.3 Follow-up of adverse events

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

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

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

  The SAE follow-up information should only include new (eg corrections or additional) information and must be reported **within 24 hours** of the Investigator's first knowledge of the information. This is also the case for previously non-serious AEs which subsequently become SAEs.

- **Non-serious AEs:** Non-serious AEs must be followed until the outcome of the event is "recovering/resolving", "recovered/resolved" or "recovered/resolved with sequelae" or until the end of the follow-up period stated in the protocol, whichever comes first, and until all queries related to these AEs have been resolved. Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome

"recovering/resolving" or "not recovered/not resolved". Cases can be closed with the outcome of "recovering/resolving" when the Subject has completed the follow-up period and is expected by the Investigator to recover.

- **Non-serious AE fulfilling the MESI criteria:** Non-serious AE fulfilling the MESI criteria must be followed as specified for non-serious AEs. Follow-up information on MESIs should only include new (e.g. corrections or additional) information and must be reported **within 14 calendar days** of the Investigator's first knowledge of the information. This is also the case for previously reported non-serious AEs which subsequently fulfil the MESI criteria.

The Investigator must ensure that the worst case severity and seriousness of an event is kept throughout the trial. A worsening of an unresolved AE must be reported as follow up with re-assessment of severity and/or seriousness of the event.

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

12.4 Technical complaints, and technical complaint samples

12.4.1 Reporting of technical complaints

All technical complaints on any of the following products:

- Faster-acting insulin aspart (insulin aspart), 100 U/mL Penfill® 3 mL
- Insulin aspart (NovoRapid®), 100 U/mL Penfill® 3 mL
- Insulin degludec, 100 U/mL, pre-filled PDS290 pen-injector 3 mL
- NovoPen Echo®
- Novo Nordisk needles

which occur from time of delivery of the product until the time of the last usage of the product, must be collected and sent to Customer Complaint Center, Novo Nordisk.

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

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

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

The Investigator must complete the technical complaint form in the eCRF within the following timelines of the trial site obtaining knowledge of the technical complaint:

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

If the eCRF is unavailable or when reporting a technical complaint that is not Subject related, the information must be provided on a paper form by fax, e-mail or courier to Customer Complaint Center, Novo Nordisk, within the same timelines as stated above. When the eCRF becomes available, the Investigator must enter the information on the technical complaint form in the eCRF.

12.4.2 Collection, storage and shipment of technical complaint samples

The Investigator must collect the technical complaint sample and notify the Monitor **within 5 calendar days** of obtaining the sample at trial site. The Monitor must coordinate the shipment to Customer Complaint Center, Novo Nordisk (the address is provided in Attachment I) and ensure that the sample is sent as soon as possible. A print or copy of the technical complaint form from the eCRF must be sent with the sample.

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

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

Storage of the technical complaint sample must be done in accordance with the conditions prescribed for the product. The shipment of the technical complaint sample should be done in accordance with the same conditions as for storage (see section 9.3).

12.5 Pregnancies

12.5.1 Pregnancies in female Subjects

Female Subjects must be instructed to notify the Investigator immediately if they become pregnant during the trial. 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 (eg 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 (ie 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:

- Paper AE form* **within 14 calendar days** of the Investigator's first knowledge of the initial or follow-up information to the non-serious AE.

SAEs:

- Paper AE form* **within 24 hours** of the Investigator's first knowledge of the SAE.
- Paper safety information form **within 5 calendar days** of the Investigator's first knowledge of the SAE.
- **SAE follow-up information** to the AE form and/or safety information form **within 24 hours** of the Investigator's first knowledge of the follow-up information.

* It must be clearly stated in the AE diagnosis field on the AE form if the event occurred in the Subject, foetus or newborn infant.

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

12.6 Precautions and/or overdose

During treatment with insulin, there is a risk of hypoglycaemia (see section 8.5.1.1). Symptoms of hypoglycaemia usually occur suddenly and may include cold sweat, tremor, unusual tiredness, confusion, difficulty in concentration, excessive hunger, temporary vision changes, headache, nausea and palpitation. Prolonged or severe hypoglycaemia can lead to spasms, and/or unconsciousness and, in extreme cases, death. In small children symptoms of hypoglycaemia can in addition to the above be erratic behaviour, nightmares, inconsolable crying, trembling, pounding heart, difficulty hearing, slurred speech and seizure[34].

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.

See the current version of the faster-acting insulin aspart IB[17]. For NovoRapid® see the current versions of the SmPC[15] or local labelling. For insulin degludec see the Tresiba® EU SmPC, current version[20] and if not approved in the country of interest see the insulin degludec IB[22].

12.7 Committees related to safety

12.7.1 Novo Nordisk safety committee

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

12.7.2 Data Monitoring Committee

No external data monitoring committee is planned.

13 Case report forms

Novo Nordisk will provide a system for the electronic case report forms (eCRF). This system and support services to the system will be supplied by an external supplier

The Investigator must 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 (eg is not applicable), indicate this according to the data entry instructions. 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.

The following will be provided as paper CRF:

- Pregnancy forms
- AE forms
- Safety information forms
- Technical complaint forms

The paper AE forms, safety information forms and technical complaint forms must be used when access to the eCRF is revoked or if the eCRF is unavailable.

On the paper CRF forms print legibly, using a ballpoint pen. Ensure that all questions are answered, and that no empty data blocks exist. Ensure that no information is recorded outside the data blocks. If a test/assessment has not been done and will not be available, indicate this by writing "ND" (not done) in the appropriate answer field in the CRF. If the question is irrelevant (eg 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 CRF data may be made by the Investigator or the Investigator's delegated staff. An audit trail will be maintained in the CRF 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 authorised staff after the date the Investigator has signed the case book, the case book must be signed and dated again by the Investigator.

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

Corrections necessary after the CRFs have been removed from the trial site must be documented on a data clarification form (DCF) or a monitor-initiated discrepancy form (MIDF).

13.2 Case report form flow

The Investigator must ensure that data is recorded in the eCRF/paper CRFs as soon as possible after the visits and phone contacts, preferably within 5 days. At the end of the trial at the site all data should be recorded no later than 24 hours after the last Subject’s last visit. Once data has been entered, it will be available to Novo Nordisk for data verification and validation purposes.

14 Monitoring procedures

During the course of the trial, the Monitor will visit the trial site to ensure that the protocol is adhered to, that all issues have been recorded, to perform source data verification and to monitor drug accountability. The first monitoring visit will be performed as soon as possible after FSFV at the trial site and no later than 4 weeks after. The monitoring visit intervals will depend on the outcome of the remote monitoring of the CRFs, the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP, but will not exceed 8 weeks

14.1 Source data verification

The Monitor must be given direct access to source documents (original documents, data and records). Direct access includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are important to the evaluation of the trial. If the electronic medical record does not have a visible audit trail, the Investigator must provide the Monitor with signed and dated printouts. In addition the relevant trial site staff should be available for discussions at monitoring visits and between monitoring visits (e.g. by telephone).

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

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

Data recorded in the Subject’s diary is considered source data with respect to:

- SMPG values and corresponding dates and time points for the 4-point profiles
- SMPG values and corresponding dates and actual clock times for the 8-point profiles
- Date, time point and doses of bolus injections
- Date and doses of basal injections
- Hypoglycaemic episodes
- Hyperglycaemic episodes
- Carbohydrate content of the meal, if applicable
- I:Carb ratio and sensitivity (correction) factor, if applicable

For the CGM and meal test subgroup additional data is considered source data as described in Appendix B.

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 verify that the eCRFs are completed and that paper CRFs are collected, if applicable.

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

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

15 Data management

Data management is the responsibility of Novo Nordisk. Data management may be delegated under an agreement of transfer of responsibilities to an external 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. Novo Nordisk will collect information on the practical use of these systems within the conduct of this clinical trial.

17 Statistical considerations

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

General considerations

In general, for endpoints evaluated as a change from baseline and/or where a baseline adjustment is made, baseline is defined as information collected at the randomisation visit (Visit 14). In case a measurement is not available at the randomisation visit, the most recent measurement prior to the randomisation visit will be used as baseline. Two observation periods are defined, "in trial" and "on treatment", and will be specified for each statistical analysis.

- 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-acting insulin aspart and no later than 7 days after the day of last dose of NovoRapid®/faster-acting insulin aspart. The on treatment observation period includes data collected up to and including 7 days after treatment discontinuation.

The primary objective, confirming the effect of treatment with meal-time faster-acting insulin aspart in children and adolescents with type 1 diabetes will be assessed using a non-inferiority approach comparing the change from baseline HbA_{1c} to meal-time NovoRapid®, where both treatments are combined with insulin degludec . More specifically the upper limit of the 95% confidence interval should be compared to a non-inferiority margin of 0.4. If it is below 0.4 non-inferiority will be considered established and the effect demonstrated.

The trial also aims to confirm the effect of treatment with post-meal faster-acting insulin aspart and to confirm superiority of meal-time faster-acting insulin aspart both in combination with insulin degludec in children and adolescents with type 1 diabetes. In order to control the family-wise type I error rate in the strong sense a hierarchical (fixed sequence) testing procedure will be deployed. This is based on a priority ordering of the null-hypotheses, and testing them in this order using the two-sided 95% confidence interval approach until an insignificant result appears. The effect is that rejection of the null hypothesis only will be confirmed for analyses where all previous null-hypotheses have been rejected in favour of faster-acting insulin aspart. This is done using a hierarchical testing procedure with three steps:

Step 1: HbA_{1c} non-inferiority of meal-time faster-acting insulin aspart versus meal-time NovoRapid® both in combination with insulin degludec

Step 2: HbA_{1c} non-inferiority of post-meal faster-acting insulin aspart versus meal-time NovoRapid® both in combination with insulin degludec

Step 3: HbA_{1c} superiority of meal-time faster-acting insulin aspart versus meal-time NovoRapid® both in combination with insulin degludec

Primary estimand

The primary estimand is defined as the treatment difference between Subjects randomised to faster-acting insulin aspart and NovoRapid® both in combination with insulin degludec, in children and adolescents with type 1 diabetes assessed by change from baseline HbA_{1c} 26 weeks after randomisation for all randomised Subjects regardless of treatment discontinuation or use of ancillary therapies. This estimand is a de facto estimand addressing effectiveness.

The primary estimand assesses the expected glycaemic benefit a Subject can achieve if prescribed to faster-acting insulin aspart as compared to NovoRapid® both in combination with insulin degludec in children and adolescents with type 1 diabetes. 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. Thereby the primary estimand provides a clinically relevant treatment difference for clinicians concerning the glycaemic effect of faster-acting insulin aspart compared to NovoRapid® in the day to day life in individual children and adolescents with type 1 diabetes, where both treatments are combined with insulin degludec.

Secondary estimand

As an alternative to the primary estimand, a secondary estimand is defined as the treatment difference in change from baseline HbA_{1c} 26 weeks after randomisation between faster-acting insulin aspart and NovoRapid® both in combination with insulin degludec in children and adolescents with type 1 diabetes aged 1 to less than 18 years if Subjects continue on treatment until 26 weeks. This estimand is a de jure estimand, addressing efficacy.

The de-jure treatment difference is the difference if all Subjects adhered and did not use ancillary medication. This estimand provides a more hypothetical treatment difference, but may also be the most sensitive for a non-inferiority comparison, since the intake of ancillary medication may equalize the treatment effect resulting in a difficult assessment if a difference is seen with respect to ancillary medication. Hence the analyses associated with this estimand will serve as sensitivity analyses for the non-inferiority analyses.

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

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

For endpoints measured over time mean values will be plotted to explore the trajectory over time. For survival endpoints, e.g. drop-out pattern, Kaplan-Meier plots are presented for each treatment. Data collected before randomisation will only be summarised descriptively.

Selected tables and figures will also be presented by strata (age).

17.1 Sample size calculation

The primary objective of the trial is to confirm the effect of treatment with meal-time faster-acting insulin aspart in terms of glycaemic control measured by change from baseline in HbA_{1c} 26 weeks after randomisation by comparing it to treatment with meal-time NovoRapid®, both in combination with insulin degludec, using a non-inferiority approach in children and adolescents with type 1 diabetes. The sample size is determined using a non-inferiority limit of 0.4%.

The trial also aims to confirm the effect of treatment with post-meal faster-acting insulin aspart and to confirm superiority of meal-time faster-acting insulin aspart, both in combination with insulin degludec in children and adolescents with type 1 diabetes. This is done using a hierarchical testing procedure with three steps:

Step 1: HbA_{1c} non-inferiority of meal-time faster-acting insulin aspart versus meal-time NovoRapid® both in combination with insulin degludec

Step 2: HbA_{1c} non-inferiority of post-meal faster-acting insulin aspart versus meal-time NovoRapid® both in combination with insulin degludec

Step 3: HbA_{1c} superiority of meal-time faster-acting insulin aspart versus meal-time NovoRapid®, both in combination with insulin degludec

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

Power for the non-inferiority steps are based on a t-statistic under the assumption of a one-sided test of size 2.5%. A zero mean treatment difference for the comparison between meal-time faster-acting insulin aspart and meal-time NovoRapid® is expected, and for the comparison of post-meal faster-

acting insulin aspart and meal-time NovoRapid® a mean difference of 0.05% in favour of meal-time NovoRapid® is expected.

Based on experience from previous trials, and taking into account that the in trial observation period includes data collected after treatment discontinuation, the standard deviation for change in HbA_{1c} is assumed to be 1.3%. With this standard deviation, a sample size of 250 Subjects per group (750 in total) will ensure more than 93% power to show non-inferiority, given that the actual treatment difference is 0%. This sample size will ensure a power of 85% to show non-inferiority of post-meal faster-acting insulin aspart compared to meal-time NovoRapid®.

The number of subjects to prematurely discontinue trial product is expected to be less than 10% based on previous trials. The number of subject to withdraw from trial is expected to be less than 5%.

17.1.1 Sample size calculation for the CGM and meal test subgroup

The CGM and meal test subgroup is included in the trial in order to compare additional assessments for evaluation of postprandial and overall glucose regulation between the treatment arms. As this additional assessment is exploratory in nature, this subgroup is not strictly powered to demonstrate a statistical significant difference between treatment arms in any particular endpoint. Fifty (50) Subjects per treatment arm have been chosen as this number is considered enough to provide sufficient information for evaluation in this exploratory analysis, and as this is a similar number to what have been included in previous trials using CGM subgroups.

17.2 Definition of analysis sets

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

- FAS includes all randomised Subjects. In exceptional cases randomised Subjects may be excluded from the FAS. In such cases the reason for exclusion will be justified and documented. Subjects in the FAS will contribute to the evaluation “as randomised”

- Per Protocol (PP) Analysis Set includes all Subjects in the full analysis set that comply with inclusion and exclusion criteria. Subjects in the PP set will contribute to the evaluation “as treated”

- SAS includes all Subjects receiving at least one dose of the investigational product or its comparator. Subjects in the safety set will contribute to the evaluation “as treated”.

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

Before data are released for statistical review after 26 weeks, a blinded review of all data will take place to identify protocol deviations that may potentially affect the results. Furthermore, extreme values and outliers will be identified by the statistician during programming and data review, according to ICH-E9[44].

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 to address all three confirmatory objectives is:

- Change from baseline in HbA_{1c} 26 weeks after randomisation

Primary analysis:

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

    - In the first step, intermittent missing values are imputed using a Markov Chain Monte Carlo 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 strata as factors and baseline HbA_{1c} as covariate is fitted to the change in HbA_{1c} from baseline to week 12 for each treatment group separately. The estimated parameters, and their variances, from these models are used to impute missing values at week 12 for Subjects in each treatment group, based on region, strata, and baseline HbA_{1c}.

    - In the third step, for each of the 100 copies of the dataset, missing values at week 26 are imputed in the same way as for week 12. The imputations are based on an analysis of

variance model with region and strata as factors and baseline HbA_{1c} and HbA_{1c} at week 12 as covariates.

- For each of the complete data sets, the change from baseline to week 26 is analysed using an analysis of variance model with treatment, region and strata 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:

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

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

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

All 3 objectives will be addressed by treatment differences and associated 95% confidence interval obtained from the same primary statistical model described above.

Non-inferiority of meal-time faster-acting insulin 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: $D > 0.4\%$ against H_A: $D \leq 0.4\%$,

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

If the primary objective is confirmed the effect of treatment with post-meal faster-acting insulin aspart in terms of glycaemic control is to be investigated by showing that post-meal faster-acting insulin aspart is non-inferior to NovoRapid® both in combination with insulin degludec in terms of glucose lowering effect as assessed by change from baseline in HbA_1c 26 weeks after randomisation. This will be determined in the same way as above where treatment difference is set to (post-meal faster-acting insulin aspart minus meal-time NovoRapid®).

Finally, if both the primary and the first secondary confirmatory objective are fulfilled, the superiority of the meal-time faster-acting insulin aspart as compared to meal-time NovoRapid® will be tested in terms of glycaemic control. This will be assessed by comparing the upper limit of the

95% CI from the primary analysis to 0. If the upper 95% CI is below 0 then superiority will be confirmed.

Sensitivity analyses for the primary estimand:

2) The internal validity of the primary estimand will first be evaluated by repeating the primary analysis in 1), but excluding all factors and covariates except from treatment in the model. This analysis will explore the influence of the different factors and covariates. The analysis will use the in trial observation period.

3) The primary analysis approach chosen for this trial relies on the assumption that missing data is missing at random (MAR). This assumption implies that the HbA_{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 or at the discretion of the Investigator. Therefore the statistical model using multiple imputation will be repeated with the following alterations:

    a. Imputation will be done from the treatment arm that the Subject was randomised to and a value of 0.4% (the non-inferiority limit) is added to the change in HbA_{1c} at 26 weeks for Subjects, on either of the faster-acting insulin aspart arms, withdrawing from the trial[45]. This will serve as a sensitivity analyses for the non-inferiority analyses. The analysis will use the in trial observation period.

    b. Imputation will be done from the comparator arm (NovoRapid®). This will serve as a sensitivity analysis for the superiority analysis. It does not rely on the MAR assumption, but assumes that all Subjects that withdraw the trial in the faster-acting insulin aspart arms shift to NovoRapid®. The imputation will be done such that the treatment effect diminishes gradually after trial discontinuation (copy reference). The analysis will use 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 assumes that all Subjects that withdraw the trial in the faster-acting insulin aspart arms shift to NovoRapid®. The imputation will be done such that the treatment effect diminishes immediately after trial discontinuation (jump to reference). The analysis will use the in trial observation period.

Analyses for the secondary estimand

4) The secondary estimand will be analysed using the same statistical model using multiple imputation as the primary analysis in 1) except using the on treatment observation period. The analysis will use the FAS.

5) A tipping point analysis will be implemented based on a statistical model using multiple imputation, using the FAS and the on treatment observation period. In this analysis Subjects that discontinued treatment are imputed based on the treatment arm they were randomised to and Subjects discontinuing treatment in the faster-acting insulin aspart groups are given a penalty. This is done to investigate the robustness of the conclusion in the primary analysis with respect to the MAR assumption and mimics a scenario where the HbA_{1c} of the Subjects discontinuing treatment in the faster-acting insulin aspart groups evolve less favourably than predicted. As a first step imputations will be done without penalty assuming MAR in the treatment groups. Second, the imputed values for week 26 in the faster-acting insulin aspart groups will be added a penalty. This is done repeatedly gradually increasing the penalty until the conclusion from the primary analysis no longer holds. The specific value of the penalty that changes the conclusion will be used to evaluate the robustness of the conclusion of the primary analysis.

6) A tipping point analysis will be implemented 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 trial product prematurely due to criteria 1, 2, 3, and 4) in the faster-acting insulin aspart groups will have their imputations based on parameters estimated from the faster-acting insulin aspart groups (and not the NovoRapid® group). These analyses are motivated by the fact that data from Subjects prematurely discontinuing trial product due to non-eligibility can reasonably be assumed to be missing completely at random. The analysis will use the on treatment observation period.

7) The same statistical model using multiple imputation as the primary analysis in 4), but using the PP analysis set and analysed using the on treatment observation period. This analysis will investigate the situation that Subjects deviate from the ideal treatment during the on treatment observation period and will serve as sensitivity analysis for the non-inferiority analysis.

17.4 Secondary endpoints

17.4.1 Supportive secondary endpoints

For all supportive secondary endpoints, meal-time faster-acting insulin aspart will be compared to meal-time NovoRapid®, and post-meal faster-acting insulin aspart will be compared to meal-time NovoRapid®.

17.4.1.1 Change from baseline refers to the change from randomisation to 26 weeks after randomisation.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 only be presented using the on treatment observation period.

The following endpoints will be assessed 26 weeks after randomisation:

Change from baseline in 8-point profiles.

PPG increments based on the 8-point 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. PPG will be recorded by the Subject as part of two 8-point profiles prior to the visits. PPG increment for each meal (breakfast, lunch, main evening meal) will be derived from the 8-point profile as the difference between PPG values and the PG value before meal in each separate profile. The mean of the derived increments will then be calculated separately for each meal. Mean PPG increment over all meals will be derived as the mean of all corresponding mean meal increments.

- Change from baseline in mean PPG and PPG increment over all three meals

Mean PPG and PPG increment will be analysed separately using a model similar to 1), except with the corresponding baseline value as covariate.

- Change from baseline in individual meal (breakfast, lunch and main evening meal) PPG and PPG increment from 8-point profile

PPG and PPG increment endpoints for the individual meals (breakfast, lunch, main evening meal) will be analysed separately using a model similar to 1) except with the corresponding baseline value as covariate.

- Change from baseline in mean of the 8-point profile

The mean of the 8-point profile is defined as the area under the profile divided by the measurement time, and is calculated using the trapezoidal method. Mean of the 8-point profile will be analysed using a model similar to 1) except with the corresponding baseline value as covariate.

- Change from baseline in fluctuation in 8-point profile

The fluctuation in the 8-point profile is defined as

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

where T, PG(t) and $\overline{PG}$ denotes the length of the profile, the PG value at time t and the mean of the profile, respectively. Fluctuation in the 8-point profile will be logarithmically transformed and analysed in the same way as mean of the profile is analysed except with the corresponding log-transformed baseline values as covariate. Estimated treatment means and the estimated treatment difference with corresponding 95% CI will be back-transformed to the original scale, resulting in estimated geometric means, a treatment ratio and a 95% CI for the treatment ratio.

- Change from baseline in FPG
  Change from baseline in FPG will be analysed using a model similar to 1) except with baseline FPG as covariate.

- Change from baseline in 1,5-anhydroglucitol
  Change from baseline in 1,5-anhydroglucitol will be using a model similar to 1) except with baseline 1,5-anhydroglucitol as covariate.

- Percentage of Subjects reaching HbA_{1c} target (HbA_{1c} <7.5%) according to ISPAD guidelines[7]
  This dichotome (responder/non-responder) endpoint will be defined based on whether a Subject has met the ISPAD HbA_{1c} target (HbA_{1c} < 7.5%) 26 weeks after randomisation. This responder endpoint will be analysed based on a logistic regression model using treatment, region and strata as factors, and baseline HbA_{1c} as covariate. In the in trial observation period analysis subjects withdrawn from trial is included as non-responders. In the on treatment observation period analysis both subjects who prematurely discontinue faster-acting insulin aspart/NovoRapid® or withdraw from trial are included as non-responders. Subjects without HbA_{1c} at week 26 will be treated as non-responders.

- Percentage of Subjects reaching HbA_{1c} target (HbA_{1c} <7.5%) according to ISPAD guidelines, without severe hypoglycaemia[7].
  This dichotome (responder/non-responder) endpoint will be defined based on whether a Subject has met the ISPAD HbA_{1c} target (HbA_{1c} < 7.5%) 26 weeks after randomisation without treatment emergent severe hypoglycaemic episodes[7].
  This responder endpoint will be analysed based on a logistic regression model using treatment, region and strata as factors, and baseline HbA_{1c} as covariate. In the in trial observation period analysis subjects withdrawn from trial is included as non-responders. In the on treatment observation period analysis both subjects who prematurely discontinue

faster-acting insulin aspart/NovoRapid® or withdraw from trial are included as non-responders. Subjects without HbA_{1c} at week 26, will be treated as non-responders.

- Insulin dose (total basal, total bolus and individual meals insulin dose).
  Bolus insulin doses will be recorded together with time of administration. The insulin doses will be summarised descriptively by treatment week according to regimen, both by meal type and as total daily dose in units and units/kg (total daily and separately for each meal time dose). Insulin doses will be summarised using the on treatment observation period and using the SAS.

Supportive secondary CGM related efficacy endpoints

The following endpoints will be assessed 26 weeks after randomisation:

- Change from baseline of time spent in low IG (IG ≤ 3.9 mmol/L [70 mg/dL])

The time spent in low IG is defined for each Subject at each CGM period as the accumulated time in hours spent below or equal to 3.9 mmol/L from the first valid sensor value divided by the actual duration of the entire profile. To report the endpoint in minutes per 24 hours the ratio is multiplied by 1440. The endpoint will be analysed using an analysis of variance model including treatment, region and strata as factors and the baseline value of time in low IG as covariate.

- Incidence of episodes and percentage of time spent with IG ≤2.5, 3.0, 3.9 mmol/l [45, 54, 70 mg/dL]) and IG >10.0, 12.0 mmol/l [180, 216 mg/dL])

- Percentage of time spent within IG target range 4.0-10.0 mmol/L (71-180 mg/dL)

IG measurements during meal test will be excluded.

All CGM endpoints will be summarised descriptively by treatment.

Supportive secondary CGM and meal-characteristics efficacy endpoints

The following endpoints will be assessed 26 weeks after randomisation:

Change from baseline in meal characteristics of IG profile (4 hours after start of each meal), measured as:

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

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

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

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

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

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

These endpoints will also be derived for each main meal separately (breakfast, lunch and main evening meal). IG measurements during meal test will be excluded. The endpoints will be analysed separately, using an analysis of variance model including treatment, region and strata as factors and the corresponding baseline value as covariate.

All CGM endpoints will be summarised descriptively by treatment.

Supportive secondary meal test related efficacy endpoints

The following endpoints will be assessed 26 weeks after randomisation:

- Change from baseline in 30-min PPG and PPG increment
- Change from baseline in 1-hour PPG and PPG increment
- Change from baseline in 2-hour PPG and PPG increment

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

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

All PPG endpoints will be summarised descriptively by treatment.

Supportive secondary CGM and meal test related efficacy endpoints

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

The following endpoints will be assessed 26 weeks after randomisation:

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

$AUC_{IG,0\text{-}15\ min}$, $AUC_{IG,0\text{-}30\ min}$, $AUC_{IG,0\text{-}1h}$, $AUC_{IG,0\text{-}2h}$, and $AUC_{IG,0\text{-}4h}$ will be calculated as the area under the IG curve using the trapezoidal method. Each endpoint will be analysed using an analysis of variance model including treatment, region and strata as factors and the corresponding baseline value as covariate.

IG peak and time to IG peak 26 weeks after randomisation will be compared separately between treatments using an analysis of variance model including treatment, region and strata as factors and with the corresponding baseline value as covariate. An additive model will be used to estimate the treatment means and treatment differences with a 95% confidence interval.

All CGM endpoints will be summarised descriptively by treatment.

17.4.1.2 Safety endpoints

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

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

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 treatment with IMP after randomisation, and no later than 1 day after the last day on IMP.

Nocturnal hypoglycaemic episodes: are episodes occurring between 23:00 and 07.00 both inclusive.

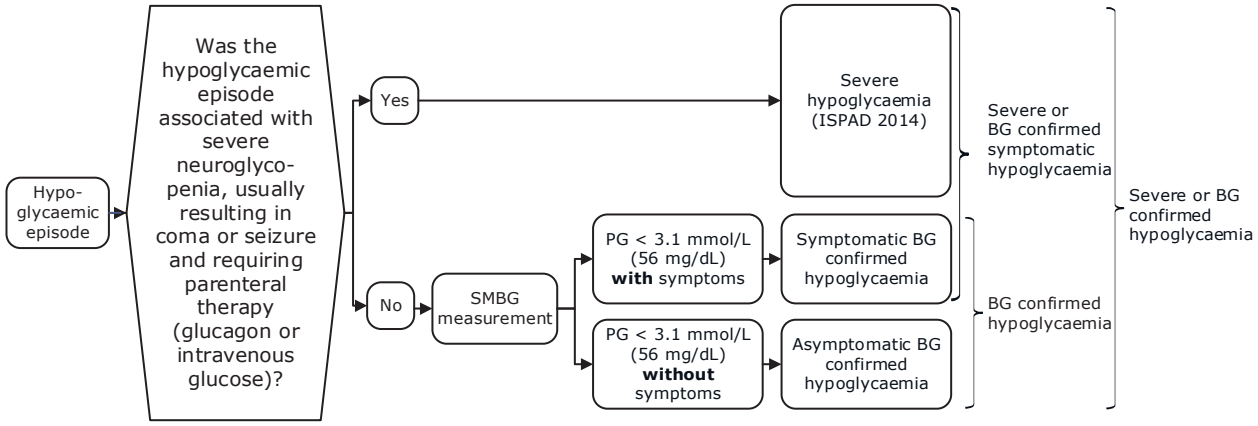
Hypoglycaemic episodes are classified according to ISPAD's definition of severe hypoglycaemia[34], as well as Novo Nordisk classification of hypoglycaemia (see Figure 17–1) and the ADA classification of hypoglycaemia[35] (see Figure 17–2).

Novo Nordisk classification of hypoglycaemia in paediatrics

In normal physiology, symptoms of hypoglycaemia occur below a PG level of 3.1 mmol/L (56 mg/dL)[46]. 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 ISPAD classification[34]: Was the hypoglycaemic episode associated with severe neuroglycopenia, usually resulting in coma or seizure and requiring parenteral therapy (glucagon or intravenous glucose)?
- Symptomatic BG confirmed hypoglycaemia: An episode that is BG confirmed by PG value < 3.1 mmol/L (56 mg/dL) **with** symptoms consistent with hypoglycaemia.
- Asymptomatic BG confirmed hypoglycaemia: An episode that is BG confirmed by PG value < 3.1 mmol/L (56 mg/dL) **without** symptoms consistent with hypoglycaemia.
- Severe or BG confirmed symptomatic hypoglycaemia: An episode that is severe according to the ISPAD classification[34] or BG confirmed by a PG value <3.1 mmol/L (56 mg/dL) **with** symptoms consistent with hypoglycaemia.
- BG confirmed hypoglycaemia: An episode that is BG confirmed by a PG value < 3.1 mmol/L (56 mg/dL) **with** or **without** symptoms consistent with hypoglycaemia.
- Severe or BG confirmed hypoglycaemia: An episode that is severe according to the ISPAD classification[34] or BG confirmed by a PG value <3.1 mmol/L (56 mg/dL) **with** or **without** symptoms consistent with hypoglycaemia.

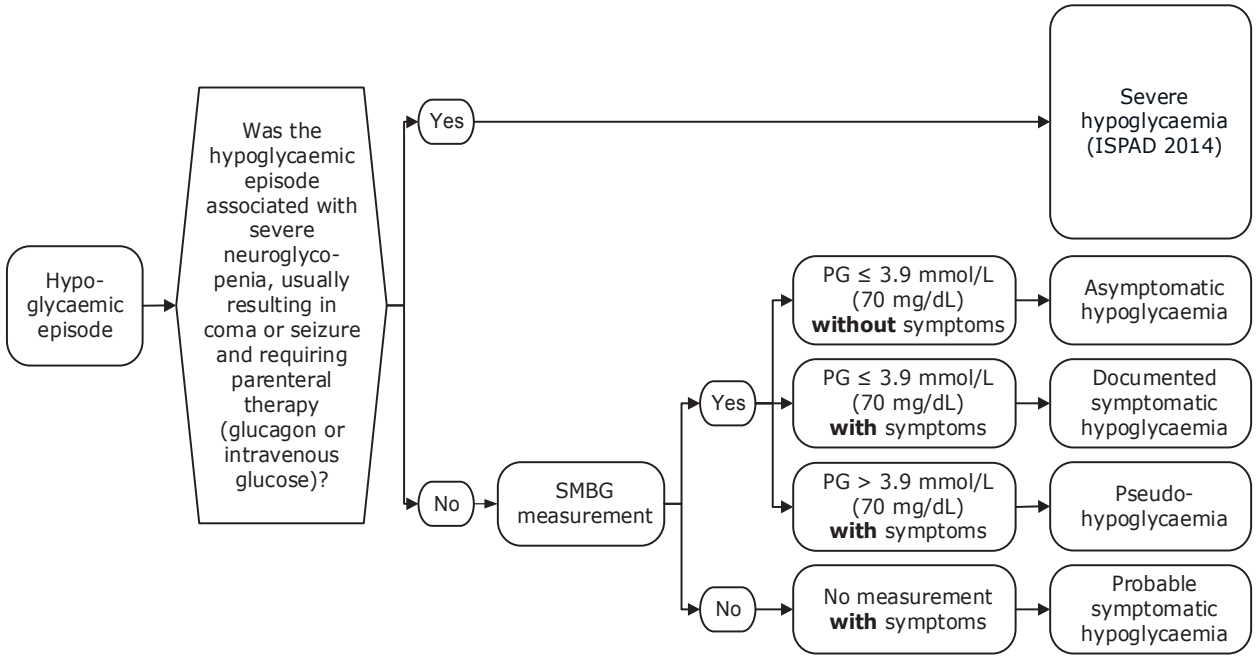


Note: Glucose measurements are performed with capillary blood calibrated to plasma equivalent glucose values

Figure 17–1 Novo Nordisk classification of hypoglycaemia in paediatrics

ADA[35]/ISPAD classification of hypoglycaemia in paediatrics

- Severe hypoglycaemia according to the ISPAD classification[34]: Was the hypoglycaemic episode associated with severe neuroglycopenia, usually resulting in coma or seizure and requiring parenteral therapy (glucagon or intravenous glucose)?
- Asymptomatic hypoglycaemia: An episode not accompanied by typical symptoms of hypoglycaemia, but with a measured PG concentration ≤ 3.9 mmol/L (70 mg/dL).
- Documented symptomatic hypoglycaemia: An episode during which typical symptoms of hypoglycaemia are accompanied by a measured PG concentration ≤ 3.9 mmol/L (70 mg/dL).
- Pseudo-hypoglycaemia: An episode during which the person with diabetes reports any of the typical symptoms of hypoglycaemia with a measured PG concentration > 3.9 mmol/L (70 mg/dL) but approaching that level.
- Probable symptomatic hypoglycaemia: An episode during which symptoms of hypoglycaemia are not accompanied by a PG determination but that was presumably caused by a PG concentration ≤ 3.9 mmol/L (70 mg/dL).



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

Figure 17–2 ADA/ISPAD classification of hypoglycaemia in paediatrics

The following safety endpoints will be assessed:

- Number of treatment emergent hypoglycaemic episodes
  - According to ADA/ISPAD classification
  - According to Novo Nordisk/ISPAD classification

- Number of treatment emergent hypoglycaemic episodes subdivided into daytime and nocturnal (23:00-7:00, both included)
  - According to ADA/ISPAD classification
  - According to Novo Nordisk/ISPAD classification

- Number of treatment emergent meal related (from start of meal until 1, 2, and 4 hours after start of meal and from 2-4 hours after start of meal, respectively) hypoglycaemic episodes
  - According to ADA/ISPAD classification
  - According to Novo Nordisk/ISPAD classification

Data on treatment emergent hypoglycaemic episodes are presented in terms of the number of Subjects with at least one event (N), the percentage of Subjects with at least one event (%), the

number of events (E) and the event rate per 100 years of exposure (R). Separate summaries are made by severity (the ISPAD criterion for severe hypoglycaemia[34]) considering all episodes, nocturnal and daytime episodes using Novo Nordisk and ADA classified episodes. Episodes will also be summarised overall and by category in relation to time since start of meal, as occurring during first 1, 2, and 4 hours after start of meal and from 2-4 hours after start of meal. Non-treatment emergent hypoglycaemic episodes will be listed.

The number of treatment emergent hypoglycaemic episodes (all, daytime, nocturnal) will be analysed using a negative binomial regression model with a log-link function and the logarithm of the time period for which a hypoglycaemic episode is considered treatment emergent as offset. The model will include treatment, region and strata as factors, and will be based on the FAS. To the extent where data allow, separate analyses will be performed for severe episodes (all).

- Number of treatment emergent adverse events (AEs)

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

A Treatment Emergent Adverse Event (TEAE) is defined as an event that has an onset date on or after the first day of exposure to randomised treatment, and no later than 7 days after the last day of randomised treatment.

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

Furthermore summary tables based on system organ class and preferred term are made for

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

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

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

- Number of treatment emergent injection site reactions

Injection site reactions occurring during the trial, related to either basal and/or bolus insulin will be summarised and listed. No formal statistical analysis will be made.

- Change from baseline in clinical evaluations
    - Physical examination (head, ears, eyes, nose, throat, neck, respiratory system, cardiovascular system, gastrointestinal system incl. mouth, musculoskeletal system, central and peripheral nervous system, skin, Tanner stage)
      The physical examination parameters, and their change from baseline, will be summarised descriptively in shift tables. All findings will be listed.
    - Vital signs (blood pressure, pulse)
      Vital signs include diastolic blood pressure, systolic blood pressure and pulse. The measurements and their change from baseline will be summarised descriptively.
- Change from baseline in body weight, height, body mass index (BMI) and SD-score of body weight and BMI (z-score)
  SD-scores are defined to be able to normalise the body weight in the various age groups. To estimate the growth of children, standardised weight is calculated for each year of age and for each sex. Thus, a child with a weight equal to the mean value for its age and sex has an SD score of 0, while a child with a weight 2 SDs above the mean value for its age and sex has an SD score of +2. The SD scores are derived from the age and sex of the Subjects and the body weight together with growth curves defined for reference population of each country. SD scores for BMI will be determined in a similar way as SD scores for weight based on reference populations for each country, based on age and sex. For countries with no accessible reference values, the reference values for the US will be used.
  The measurements and their change from baseline will be summarised descriptively. In addition, the endpoints will be analysed separately using a statistical model using multiple imputation similar to 1) including treatment, region and strata as factors and the corresponding baseline measurement as covariate.

- Change from baseline in laboratory assessments
    - Haematology (haemoglobin, haematocrit, erythrocytes, thrombocytes, and leucocytes)
    - Biochemistry (creatinine, ALT, AST, AP, sodium, potassium, albumin, and total bilirubin)
    - Lipid profile (total cholesterol, HDL, low density lipoproteins LDL)

Individual laboratory values will be compared to their relevant reference range (when existing) and flagged as being below or above the range. The measurements and their change from baseline will

be summarised descriptively. Change from baseline will be summarised descriptively using both the actual values and the low/normal/high categorisation in shift tables.

Lipid endpoints (LDL, HDL, and total cholesterol) will be log-transformed and analysed separately using a statistical model using multiple imputation similar to 1) including treatment, region and strata as factors and the corresponding log-transformed baseline measurement as covariate.The treatment difference and associated 95% confidence intervals will be back-transformed providing results in terms of ratios of geometric means on the original scale. NovoRapid® will be used as reference.

- Change from baseline in anti-insulin aspart (specific and cross-reacting with human insulin) antibody development

The measurements and their change from baseline will be summarised descriptively. The correlation to other relevant variables such as insulin dose and HbA_{1c} are illustrated using graphs.

18 Ethics

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

18.1 Clinical benefits and risk assessments

All Subjects included in the trial will be treated with insulin degludec as basal insulin in addition to either NovoRapid® or faster-acting insulin aspart. Insulin degludec will be titrated weekly by the Investigator during the initial 12-week run-in period. The bolus insulin will be adjusted daily or weekly during the treatment period of the trial depending on the methods used by the Subject to adjust their bolus dose.

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

Subjects randomised in the trial will be transferred to a treatment regimen anticipated to be either better than or equal to the treatment they received at the time they entered the trial. However, Subjects will have to use extra time, as additional visits to the clinic are required and some of the assessments performed during the trial are done outside normal practice.

When treatment with trial products ends, the Subject and Investigator will decide on the best available treatment on the market. It will not be possible for the Subjects to continue using faster-acting insulin aspart or insulin degludec trial products.

Summary of clinical pharmacology

Results from clinical pharmacology trials in adults comparing pharmacokinetic and pharmacodynamic properties of faster-acting insulin aspart and NovoRapid® have shown that faster-acting insulin aspart elicited an earlier onset of appearance and a greater early exposure to insulin aspart than NovoRapid® in Subjects with T1DM, with the largest difference found within the first 15 minutes after injection. Faster-acting insulin aspart also elicited a greater early glucose-lowering effect than NovoRapid®, but no statistically significant difference between faster-acting insulin aspart and NovoRapid® in total glucose-lowering effect[17].

Results from a clinical pharmacology trial comparing the pharmacokinetic and pharmacodynamic properties of faster-acting insulin aspart and NovoRapid® during a meal test in children (6-11 years), adolescents (12-17 years) and adults (18-64 years) with T1DM have shown that faster-acting insulin aspart elicited an earlier onset of exposure and a higher early insulin exposure whilst maintaining a similar total exposure and maximum concentration compared to NovoRapid® across all age groups. Faster-acting insulin aspart had a larger glucose-lowering effect compared to

NovoRapid® during the meal-test in children. In adolescents, a larger glucose-lowering effect for faster-acting insulin aspart was not demonstrated during the meal-test, despite a greater early insulin exposure. In adults, the glucose-lowering effect tended to be larger for faster-acting insulin aspart than for NovoRapid® during a meal-test. Overall, the glucose-lowering effect was comparable between age groups[17].

No safety concerns were raised during any of the trials[17].

Clinical benefits and risk considerations for the trial

The current trial will compare the efficacy and safety of meal-time and post-meal faster-acting insulin aspart as meal-time insulin as well as post-meal injected insulin versus NovoRapid® in a basal-bolus regimen in combination with insulin degludec in children and adolescents.

In a recent study in a population aged 1 to less than 18 years, insulin degludec was shown to be safe and to effectively improve long-term glycaemic control in all Subjects[19]. At the time of this protocol issuance, insulin degludec is approved in more than 60 countries, including USA, all of the EU countries, and marketed in 26 countries. Insulin degludec was recently approved for use in children and adolescents aged 1 to less than 18 years old in the EU.

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

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

In a subgroup, the trial will also assess glucose excursions during blinded CGM, further contributing to obtaining improved HbA_{1c} results, as these excursions are revealed to the Investigator when the data is uploaded.

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

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.

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

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

Subjects in this trial will be using bolus and basal insulin administered via two differently coloured durable 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. Special attention is required when changing the insulin cartridges and the Subject will be trained in handling the devices safely. It is expected that the risk of mixing up basal and bolus insulin in this trial is similar to in normal clinical practice.

No maximum dose of insulin is specified as doses are titrated individually. All Subjects will record 4-point profiles on the three days prior to a scheduled site visit/phone contact every week throughout the trial for safety purposes and for the purpose of insulin titration.

Insulin aspart is marketed as NovoRapid® (marketed as NovoLog® in the US) and approved in children down to 2 years. No studies have been performed in children below the age of 2 years. In line with current praxis NovoRapid® will only be used in this age group under careful medical supervision. See the local labelling for a description of risks and benefits[15,16].

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

Conclusion

Subjects in this trial will benefit from an intensified insulin treatment in a basal-bolus regimen in a treat-to-target setting under close supervision.

The safety profile of insulin aspart is well established from the market use of NovoRapid®. The data available for faster-acting insulin aspart in non-clinical and clinical studies taken together with review of the additional excipients in the faster-acting insulin aspart formulation have not revealed any safety issues that would prohibit the administration of faster-acting insulin aspart formulations in accordance with this trial.

It is therefore concluded that the clinical benefits from the trial as well as the contribution to the development of a new faster-acting insulin aspart outweigh the potential risks of participating in this trial.

18.2 Informed consent

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

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

The Subject and LAR(s) 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 and LAR(s) 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 and LAR(s) before any trial-related activity commence.

If the minor reaches legal age during the conduct of the trial, the Subject has to re-consents to the standard (adult) SI/IC. This is done by using the SI/IC signature sheet for Subject turning legal age included in the standard (adult) SI/IC form.

The responsibility for seeking informed consent must remain with the Investigator, but the task may be delegated by the Investigator to a medically qualified person, in accordance with local requirements. The 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 and LAR(s) in a timely manner, and revised written Subject information must be provided and a new informed consent must be obtained.

18.2.1 Child Assent Form

A minor’s choice to participate in a clinical trial is called “assent” as a child is not legally capable of giving consent. An assent means a child’s affirmative agreement to participate in research. The form that documents this agreement is called an “assent form”.

If required by local requirements, assent from the child (17 years of age and below) must be obtained in addition to parental consent/consent from the LAR(s). A Child Assent Form must be used to document the child’s affirmative agreement.

18.3 Data handling

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

- Data already collected and data collected at the end-of-trial visit will be retained by Novo Nordisk, entered into the database and used for the trial report.
- Safety events will be reported to Novo Nordisk and regulatory authorities according to local/national requirements.

If data is used, it will always be in accordance with local regulations and IRBs/IECs.

18.4 Information to Subject during trial

The site will be offered a communication package to the Subject during the conduct of the trial. The package content is issued by Novo Nordisk. The communication package will contain the letters intended for distribution to the Subjects. The letters will be translated and adjusted to local requirements and distributed to the Subject by discretion of the Investigator. The Subject may receive a "welcome to the trial letter" and a "thank for your participation letter" at the end of the trial. Further the Subject may receive trial letters during the trial period.

All written information to the Subjects will be submitted to the health authorities and IRBs/IECs for approval/favourable opinion and to the regulatory authorities for approval or notification according to local regulations.

18.5 Premature termination of the trial and/or trial site

Novo Nordisk, the Investigator, the IRBs/IECs or a regulatory authority may decide to stop the trial, part of the trial or a trial site at any time, but agreement on procedures to be followed must be obtained.

If a trial is suspended or prematurely terminated, the Investigator must inform the Subjects promptly and ensure appropriate therapy and follow-up. The Investigator and/or Novo Nordisk must also promptly inform the regulatory authorities and IRBs/IECs and provide a detailed written explanation. The relevant regulatory authorities must be informed.

If, after the termination of the trial, the risk/benefit analysis changes, the new evaluation must be provided to the IRBs/IECs in case it has an impact on the planned follow-up of Subjects who have participated in the trial. If it has an impact, the actions needed to inform and protect the Subjects should be described.

19 Protocol compliance

19.1 Protocol 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 clinical database.

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

19.2 Prevention of missing data

A significant proportion of missing data can be a potential source of bias when analysing data in clinical trials leading to a risk of misinterpretation of the trial results. Missing data may affect both estimation of treatment effect and the confidence interval that surrounds it as well as the representativeness of the sample size in relation to the target population.

The run-in period in this trial will reduce the likelihood of drop-outs as only those who adhere to the protocol requirements will undergo randomisation. 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 withdrawal post randomisation. In addition, only absolutely necessary criteria for premature discontinuation of trial product primarily focusing on Subjects safety are included and thereby reducing the number of withdrawals and securing maximum amount of data.

Close surveillance of retention rate will be performed throughout the trial by Novo Nordisk with focus on reasons for premature discontinuation of trial product or withdrawal from trial (e.g. adverse events, Subject withdrawing consent or due to any of the criteria for premature discontinuation of trial product). In case of decreasing retention rate at a site, the site will be re-trained in the importance of emphasising to the Subject the importance of continuing in the trial and adhering to trial procedures.

Investigators must make every effort to ensure all assessments are performed and data are collected. If missing data does occur the reason will be collected via the protocol deviation process (see section 19.1) and trends will be monitored on an on-going basis throughout the trial followed by appropriate actions (e.g. training of Subjects and site staff).

It should be noted that there is no universal best statistical method for handling missing data. The assumptions that go into the primary statistical analysis will be investigated by further sensitivity analysis. Considerably consistent results from sensitivity analyses and from the primary analysis will provide assurance of the overall trial conclusions. In the final clinical trial report, results for all pre-specified analyses and any substantial differences between the analyses will be the Subject of explicit discussion.

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

20 Audits and inspections

Any aspect of the clinical trial may be Subject to audits conducted by Novo Nordisk or inspections from domestic or foreign regulatory authorities or from IRBs/IECs. Audits and inspections may take place during or after the trial. The Investigator and the site staff as well as Novo Nordisk staff have an obligation to cooperate and assist in audits and inspections. This includes giving auditors and inspectors direct access to all source documents and other documents at the trial site relevant to the clinical trial. This includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are relevant to the evaluation of the trial.

21 Critical documents

Before a trial site is allowed to start screening Subjects, the following documents must be available to Novo Nordisk:

- Regulatory approval and/or acknowledgement of notification as required
- Approval/favourable opinion from IRBs/IECs clearly identifying the documents reviewed as follows: protocol, any protocol amendments, Subject information/informed consent form, any other written information to be provided to the Subject and Subject recruitment materials
- List of IRB/IEC members and/or constitution
- Curricula vitae of Investigator and Sub-Investigator(s) (current, dated and signed - must include documented GCP training or a certificate)
- Signed receipt of IB and SmPC as appropriate
- Signed and dated agreement on the final protocol
- Signed and dated agreement on protocol amendment, if applicable
- Financial agreement(s)
- Source document agreement
- Central laboratory certification and normal ranges
- Insurance statement, if applicable
- Signed and dated Investigator Agreement
- 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 each Investigator

FDA form 1572:

For US sites:

- Intended for US sites
- Conducted under the IND
- All US Investigators, as described above, will sign FDA Form 1572

For sites outside the US:

- Intended for participating sites outside of the US
- Not conducted under the IND
- All Investigators outside of the US will not sign FDA form 1572

Novo Nordisk will analyse and report data from all sites together.

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

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

22 Responsibilities

All staff involved in the trial (Novo Nordisk, site, laboratory, CRO etc.) will conduct the trial in compliance with ICH GCP[1], applicable regulatory requirements and the Declaration of Helsinki[2].

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

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

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

The Investigator will follow instructions from Novo Nordisk when processing data.

The Investigator is responsible for filing essential documents (i.e., those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced) in the Investigator's trial file. The documents should be kept in a secure locked facility, so no unauthorized persons can get access to the data. The Subject identification code list must be kept securely and separate from the personal 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 Principal Investigator will be appointed 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 ICMJE for research publications[47].

23.1 Communication of results

No permission to publish shall be granted to any clinical research organisation involved in the trial. Novo Nordisk commits to communicating, and otherwise making available for public disclosure, results of trials regardless of outcome. Public disclosure includes publication of a paper in a scientific journal, abstract submission with a poster or oral presentation at a scientific meeting, or disclosure by other means.

The results of this trial will be Subject to public disclosure on external web sites according to international and national regulations, as reflected in the Novo Nordisk Code of Conduct for Clinical Trial Disclosure.

Novo Nordisk reserves the right to defer the release of data until specified milestones are reached, for example when the 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 principal Investigator from each trial site will be named in an acknowledgement or in the supplementary material, as specified by the journal.

Novo Nordisk maintains the right to be informed of plans by any Investigator to publish and to review any scientific paper, presentation, communication or other information concerning the investigation described in this protocol. Any such communication must be submitted in writing to Novo Nordisk before submission for comments. Comments will be given within four weeks from receipt of the planned communication.

23.1.1 Authorship

Authorship of publications should be in accordance with the Uniform Requirements of the International Committee of Medical Journal Editors [47] (sometimes referred to as the Vancouver Criteria).

The Investigator(s) offered authorship will be asked to comment and approve the publication.

23.1.2 Site-specific publications by Investigators

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 and human biospecimens

24.1 Retention of clinical trial documentation

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

The Investigator must agree to archive the documentation (this includes both electronic and paper-based records) pertaining to the trial in an archive after completion or discontinuation of the trial if not otherwise notified. The Investigator should not destroy any documents without prior permission from Novo Nordisk. If the Investigator cannot archive the documents at the trial site, Novo Nordisk can refer the Investigator to an independent archive provider that has a system in place to allow only the Investigator to access the files.

The Investigator must be able to access his/her trial documents without involving Novo Nordisk in any way. Site-specific CRFs and other Subject data (in an electronic readable format or as paper copies or prints) will be provided to the Investigator before access is revoked to the systems and/or electronic devices supplied by Novo Nordisk. These data must be retained by the trial site. If the Novo Nordisk provided data (e.g. the CD-ROM) is not readable during the entire storage period, the Investigator can request a new copy. A copy of all data will be stored by Novo Nordisk.

Novo Nordisk will maintain Novo Nordisk documentation pertaining to the trial for as long as the product is on the market plus 20 years.

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

24.2 Retention of human biospecimens

Blood samples will be collected to measure insulin antibodies. The total volume of blood that will be obtained from a Subject during the trial for antibody analysis is approximately 4.5 mL. The blood samples will be stored at a central archive for later analysis and will be destroyed after marketing approval.

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

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 the 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 risk/benefit 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's trial 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.

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Appendix A

Faster-acting insulin aspart titration guideline

Trial ID: NN1218-4101

Efficacy and Safety of Faster-acting Insulin Aspart compared to NovoRapid® both in Combination with Insulin Degludec in Children and Adolescents with Type 1 Diabetes

onset®7

Trial Phase: 3b

Author

[redacted]
[redacted] Insulin & Diabetes Outcomes

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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 [1-10].

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 and/or the Subjects' legally acceptable representative(s) (LAR(s)) 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 once daily (OD) and NovoRapid® / faster-acting insulin aspart in a basal-bolus regimen in connection with meal.

At the run-in (Visit 2), eligible Subjects will be transferred from their previous basal insulin to insulin degludec OD (section 3.1). During the following 12 weeks the basal insulin will be titrated by the Investigator on a weekly basis to the pre-breakfast glycaemic target (section 3.2). In addition, the Subjects will be transferred to NovoRapid® as bolus insulin at the run-in (Visit 2). NovoRapid® will not be titrated during the run-in period unless the Investigator finds it necessary for safety reasons.

At randomisation (Visit 14), Subjects will be randomised to continue using meal time NovoRapid® or to receive meal time/post-meal faster-acting insulin aspart.

In the 26-week treatment period, the Investigator should focus on optimising bolus insulin on a weekly basis to the pre-meal targets. Adjustment of basal insulin dose should be minimized during the treatment phase. However, if necessary, basal insulin dose may be adjusted at the Investigator's discretion. (section 3.4).

No maximum or minimum insulin dose is specified.

2.1 Injection area

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

Faster-acting insulin aspart and 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.

Meal time faster-acting insulin aspart or NovoRapid® should be given 0-2 minutes before meals.

Post-meal dosing is defined as injecting 20 minutes after the start of the meal.

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

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

3.1 Initiation of insulin degludec

When changing basal insulin to insulin degludec, dose reduction of basal and bolus insulin needs to be considered on an individual basis in order to minimise the risk of hypoglycaemia.

At the beginning of run-in (Visit 2), the Investigator should aim at adjusting the basal-bolus ratio to be between 50:50 to 30:70. The desired total daily bolus and basal doses can be found in Table 3-1. When Subjects switch from their previous insulin regimen to the trial insulin regimen at Visit 2, the total daily dosage should be calculated, and the dose of insulin degludec will be estimated according to Table 3-1. e.g. if the total daily insulin dose is 28U, the Subject should receive a total of 8U of insulin degludec at the ratio of 30:70, or a total of 14U of insulin degludec at the ratio of 50:50.

Table 3-1 Start doses of total basal and bolus insulin

Total daily insulin dose (U)	**Basal: bolus ratio 50:50**		**Basal: bolus ratio 30:70**		**Total daily insulin dose (U)**	**Basal: bolus ratio 50:50**		**Basal: bolus ratio 30:70**	
	Total Basal (U)	Total Bolus (U)	Total Basal (U)	Total Bolus (U)		Total Basal (U)	Total Bolus (U)	Total Basal (U)	Total Bolus (U)
4	2	2	1	3	**46**	23	23	14	32
6	3	3	2	4	**48**	24	24	14	34
8	4	4	2	6	**50**	25	25	15	35
10	5	5	3	7	**52**	26	26	16	36
12	6	6	4	8	**54**	27	27	16	38
14	7	7	4	10	**56**	28	28	17	39
16	8	8	5	11	**58**	29	29	17	41
18	9	9	5	13	**60**	30	30	18	42
20	10	10	6	14	**62**	31	31	19	43
22	11	11	7	15	**64**	32	32	19	45
24	12	12	7	17	**66**	33	33	20	46
26	13	13	8	18	**68**	34	34	20	48
28	14	14	8	20	**70**	35	35	21	49
30	15	15	9	21	**72**	36	36	22	50
32	16	16	10	22	**74**	37	37	22	52
34	17	17	10	24	**76**	38	38	23	53
36	18	18	11	25	**78**	39	39	23	55
38	19	19	11	27	**80**	40	40	24	56
40	20	20	12	28	**82**	41	41	25	57
42	21	21	13	29	**84**	42	42	25	59
44	22	22	13	31	**86**	43	43	26	60

3.2 Titration of insulin degludec during run-in

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

Insulin degludec should be titrated based on the lowest of three pre-breakfast SMPG values measured on the three days prior to the contact in accordance with Table 3-2. The fasting SMPG will be targeted at 4.0 – 8.0 mmol/L (71 – 145 mg/dL).

Table 3-2 Titration of insulin degludec

Current dose		**≤ 15U**	**>15U**
Lowest of three pre-breakfast SMPGs		**Adjustment**	
mmol/L	mg/dL		
≤ 3.9	≤ 70	-1	-2
4.0 – 8.0	71 - 145	0	0
8.1 – 10.0	146 - 180	+1	+2
10.1 – 15.0	181 – 270	+2	+4
> 15.1	> 270	+3	+6

3.3 Initiation of NovoRapid®

At the beginning of run-in (Visit 2), the Investigator should aim at adjusting the basal-bolus ratio to be between 50:50 to 30:70. The desired total daily bolus and basal doses can be found in Table 3-1. When Subjects switch from their previous insulin regimen to the trial insulin regimen at Visit 2, the total daily insulin dosage will be calculated, and the dose of NovoRapid® will be estimated according to Table 3-1 e.g. if the total daily insulin dose is 28U, the Subject should receive a total of 20U of NovoRapid® at the ratio of 30:70, or a total of 14U of NovoRapid® at the ratio of 50:50.

3.4 Titration of bolus insulin from randomisation

Titration of bolus insulin will be performed from randomisation (Visit 14) and onwards while the adjustments of basal insulin dose(s) can be performed according to the Investigators' discretion.

For the purpose of insulin titration the Subjects will be instructed to perform 4-point profiles on the three days prior to a scheduled site visit/phone contact every week during the conduct of the trial.

Faster-acting insulin aspart/NovoRapid® titration will be done once weekly based on the lowest pre-meal and bedtime SMPG measured on the three days prior to the scheduled site visit/phone contact in accordance with Table 3-3 and Table 3-4 respectively, or using principles of flexible bolus

dosing based on the carbohydrate content of a meal 3.4.2. It is recommended that the Subjects use the method that they are most familiar with.

3.4.1 Bolus dosing according to the algorithm

The pre-meal SMPG will be targeted at 4.0 – 8.0 mmol/L (71 – 145 mg/dL), while the bed-time SMPG will be targeted at 6.7–10 mmol/L (120–180 mg/dL)[10].

3.4.1.1 Pre-breakfast and pre-lunch bolus insulin titration

- Pre-breakfast faster-acting insulin aspart/NovoRapid® will be adjusted according to the lowest pre-lunch SMPG value measured on the three days prior to the site visit/phone contact Table 3-3
- Pre-lunch faster-acting insulin aspart/NovoRapid® will be adjusted according to the lowest pre-main evening meal SMPG value measured on the three days prior to the site visit/phone contact Table 3-3

Table 3-3 Titration of pre-breakfast and pre-lunch faster-acting insulin aspart/NovoRapid®

Current dose		**< 5U**	**≥ 5U**
Lowest pre-meal SMPG value measured on the three days prior to the site visit/phone contact		**Adjustment**	
mmol/L	mg/dL		
≤ 3.9	≤ 70	-1	-2
4.0 – 8.0	71 – 145	0	0
≥ 8.1[a]	≥ 146	+½	+1

a. It is at the Investigator's discretion to use a higher dose increment.

3.4.1.2 Pre-dinner bolus insulin titration

- Before main evening meal faster-acting insulin aspart/NovoRapid® will be adjusted according to the lowest bedtime SMPG value measured on the three days prior to the site visit/phone contact Table 3-4

Table 3-4 Titration of pre-dinner faster-acting insulin aspart/NovoRapid®

Current dose		**< 5U**	**≥ 5U**
Lowest bed-time SMPG value measured on the three days prior to the site visit/phone contact		**Adjustment**	
mmol/L	mg/dL		
≤ 6.7	≤ 120	-1	-2
6.7 – 10.0	120 – 180	0	0
≥ 10.0 [a]	≥ 180	+½	+1

a. It is at the Investigator's discretion to use a higher dose increment.

3.4.2 Subjects following principles of flexible bolus insulin dosing

NovoRapid® and faster-acting insulin aspart may be titrated in accordance with principles of flexible bolus dosing whereby the meal carbohydrate content and pre-prandial plasma glucose value are used to determine the bolus insulin dose. This method is applicable to Subjects and/or LAR(s) who have demonstrated prior hands-on experience with using this method of determining bolus insulin doses. At visit 2, it is the responsibility of the Investigator to ensure that the Subject and/or LAR(s) are adequately trained and comfortable using this method. If more training is needed this should be carried out according to local practise.

Using this method, bolus insulin dose adjustment is conducted several times daily in accordance with the Insulin:Carbohydrate (I:Carb) ratio and the plasma glucose correction factor (sensitivity factor). Bolus insulin dose consists of meal bolus to cover for carbohydrates consumed in the meal and, if required, a correction dose (to supplement or reduce the dose based on the difference between the SMPG and the target).

The I:Carb ratio expresses the amount of carbohydrate (in grams) for which 1U of bolus insulin would effectively minimise postprandial plasma glucose excursions. The plasma glucose correction factor (sensitivity factor) expresses the expected reduction in plasma glucose per 1U of bolus insulin. The I:Carb ratio and the correction factor (sensitivity factor) per type of meal should be recorded at Visit 2 and should, if needed, be adjusted at the discretion of the Investigator during the weekly contacts based on the reviewed SMPGs.

The target pre-prandial plasma glucose ranges are 4.0 – 8.0 mmol/L (71 – 145 mg/dL) for breakfast and lunch and 6.7 – 10.0 mmol/L (120-180 mg/dL) for bedtime.

In the following, an example on how to cover a Subject's prandial insulin dose is provided. In case of hypoglycaemic episodes, the dose will be reduced at the Investigator's discretion.
Example 1 – Carbohydrate coverage of a meal and plasma glucose correction dose:

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

The meal coverage dose is calculated as follows:

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

The plasma glucose correction factor (sensitivity factor) has been estimated to be 2 mmol/L (36 mg/dL) per 1U. The pre-prandial plasma glucose target range is 4.0 – 8.0 mmol/L (71 – 145 mg/dL) for breakfast and lunch. The Subject was advised to correct to the target plasma glucose of 8.0 mmol/L (145 mg/dL) at this meal.

The correction dose can be calculated as follows: (Pre-prandial plasma glucose – target plasma glucose) ÷ plasma glucose correction factor = bolus insulin unit

(10.0 mmol/L – 8.0 mmol/L) ÷ 2.0 mmol/L/U = 1U or

(180 mg/dL – 145 mg/dL) ÷ 36 mg/dL/U = 1U

Thus this Subject needs 7U of bolus insulin to cover for the meal and correct for hyperglycaemia before the meal.

Examples for initial plasma glucose correction factors and I:Carb ratios according to age group are presented in Table 5.

Table 5 Plasma glucose correction factors and I:Carb ratios

Age group	Plasma glucose correction Factor	I:Carb ratio
Infant/Toddler	1U:15 mmol/L (270 mg/dL)	1U:60g
Pre-Pubertal	1U:10 mmol/L (180 mg/dL)	1U:45g
Early Puberty	1U:5 mmol/L (90 mg/dL)	1U:15 g
Older Adolescent	1U:2.5 mmol/L (45 mg/dL)	1U:10g

3.5 Deviations from the algorithm

It is recommended that the algorithms described in the present guideline will be followed. However, it is also important that the decision to adjust the insulin doses are based on all relevant information as described in section 1. A reason for deviating from the algorithm should be entered into the eCRF.

4 Data collection

In this trial the Subjects will be provided with a diary where the Subjects should record the 4-point profiles and insulin doses on the three days prior to a site visit/phone contact and all hypoglycaemic episodes. The data used for titration (4-point profiles and insulin doses) should be transcribed into the eCRF by the Investigator within 24 hours on work days after each site visit/phone contact.

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 titration data 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.

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Appendix B

Continuous Glucose Monitoring (CGM) and Meal Test

Trial ID: NN1218-4101

Efficacy and Safety of Faster-acting Insulin Aspart compared to NovoRapid® both in Combination with Insulin Degludec in Children and Adolescents with Type 1 Diabetes

onset®7

Trial phase: 3b

Author

[redacted]

[redacted] Insulin, GH & Devices

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1 List of abbreviations

CGM	continuous glucose monitoring
eCRF	electronic case report form
i.v.	intravenous
I:carb	insulin:carbohydrate ratio
IG	interstitial glucose
IV/WRS	interactive voice/web response system
LAR	legally acceptable representative
PG	plasma glucose
PPG	postprandial glucose
SMPG	self-measured plasma glucose

2 Investigators to whom this protocol appendix applies

This protocol appendix only applies to Investigators at selected sites providing trial Subjects to the Continuous Glucose Monitoring (CGM) and meal test subgroup as part of the NN1218-4101 trial.

The sites that will participate in the CGM and meal test subgroup will be selected by Novo Nordisk based on their qualifications and experience with performing CGM and standardised meal tests. The site selection will also be based on the country specific approval status of the CGM device.

Once the required number of 150 randomised Subjects (approximately 50 Subjects in each treatment arm) is met in the CGM and meal test subgroup globally, no more Subjects will be asked to participate in the CGM and meal test assessment.

2.1 Rationale for protocol appendix

As only selected countries and sites will participate in the CGM and meal test assessment, this appendix has been prepared for these selected sites. The appendix will be available to all Investigators, Regulatory Authorities and Institutional Review Boards/Independent Ethics Committees.

3 Flow chart

In addition to the trial design and flow chart described in the NN1218-4101 protocol section 2, the below flow chart describes the procedures which should be carried out for Subjects participating in the CGM and meal test assessment.

Table 1 Flow chart – CGM and meal test procedures

Trial NN1218-4101	**Appendix section**	**Screening**	**Run-in**		**Randomisation**	**Treatment period[d]**			**Premature Discontinuation**	
Visit (V) / Phone contact(P)		**V1**	**V12**	**P13**	**V14**	**V38**	**P39**	**V40**		**V40A**
Time of visit (weeks)[a]		-14	-2	-1	0	24	25	26		
Visit window (days)			±3	±3		±3	±3	±3		
CGM Assessment			**CGM Fitting**	**CGM Fitting**	**CGM Removal**	**CGM Fitting**	**CGM Fitting**	**CGM Removal**	**CGM Fitting**	**CGM Removal**
Meal test Assessment					**Meal test**			**Meal test**		**Meal test**
Subgroup informed consent	4.3	x								
Fitting & supply of the CGM devices[b]	5.2 & 5.3		x	x		x	x		x	
Instruct Subjects in CGM calibration procedure (beginning 2 hours after the device is fitted and every 12 hours during the CGM period)	5.4		x	x		x	x		x	
Instruct Subjects in CGM procedures in general	5.4		x	x		x	x		x	
Meal test[c]	6				x			x		x
Attend visit fasting	6.1				x			x		x
Removal of CGM device	5.3			x	x		x	x		x
Upload of CGM data	5.5			x	x		x	x		x
Weight & age check	4.3	x								

[a] The time of the visit is defined from the randomisation visit (V14)
[b] The fitting of the CGM devices must be scheduled to ensure the meal test is not performed on the 1st or 7th day when Subject is wearing a CGM sensor. In case of premature discontinuation of trial product or withdrawal from trial please see section 7 and 8
[c] The meal test must be performed after a minimum of 11 days of wearing a CGM sensor
[d] The assessments is not applicable for premature discontinued Subjects, see section 7

4 Rationale for the CGM and meal test assessment

4.1 Rationale for the CGM assessment

The rationale for the CGM assessment is to get a thorough evaluation of the glycaemic control achieved with the different treatments in this trial. The glucose profiles will be recorded by the CGM device during 11 to 13 consecutive days also covering the meal test.

The CGM assessment will be performed in two periods during the trial:

- At baseline: 11 to 13 consecutive days before randomisation and before randomised treatment
- During treatment: 11 to 13 consecutive days before the end of the 26-week treatment period

4.2 Rationale for the meal test assessment

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

4.3 CGM and meal test subgroup population

A total of 150 randomised Subjects are planned to enter the CGM and meal test subgroup. To ensure capability of the Subjects to comply with the CGM and meal test procedures only Subjects ≥ 8 years of age and with a weight of ≥ 20.0 kg (44.0 lbs) at screening (due to blood sampling volume restrictions) are allowed to participate in the CGM and meal test subgroup. Subjects participating in the subgroup will be selected by the Investigator based on the Subject's interest in participating and the Investigator's judgement of the Subject's capability of fulfilling the requirements for the CGM and meal test assessment. The Subjects must not wear their own real time CGM during the run-in and treatment periods.

For the Subjects who wish to take part in the CGM and meal test subgroup an additional Informed Consent Form and Child Assent Form must be signed according to local requirements before any trial-related procedures commence. See protocol section 18.2 and 18.2.1 for detailed information.

5 Continuous glucose monitoring

As indicated in the flow chart (section 3) and described in section 4.1, Subjects will have CGM profiles generated for a period of 11 to 13 consecutive days, twice during this trial. The profiles will be generated by a Food and Drug Administration approved and European Union CE labelled CGM device, developed for continuous monitoring of glucose levels in persons with diabetes mellitus.

The CGM device will be blinded to the Subject during the CGM period. Upon upload of CGM data at site the Investigator or delegated site staff should review the CGM data capture and CGM trends and document this according to section 5.5.1. The unblinded CGM trend reports must remain blinded to the Subject and the legally acceptable representatives(s) (LAR(s)) prior to End of Treatment visit (Visit 40).

The unblinded CGM trend reports generated must not be used for insulin dose titration or for hypoglycaemic episodes reporting; only when supported by self-measured plasma glucose (SMPG) measurements.

Please refer to the CGM manufacturer's user guide for how to use the CGM device.

5.1 CGM receiver setting and test upload

The CGM receiver must be set up before use. The set up includes: date and time setting, entry of CGM transmitter ID and blinding of the CGM receiver. Upon set up of the CGM receiver a test upload must be performed to verify correct installation of CGM software and correct set up of the CGM receiver.

Upon the test upload a CGM device status report will be available in the CGM Software system. The CGM device status report shows the CGM receiver serial number, the CGM transmitter ID, the blinded status, the clock accuracy and verification that no data exists on the CGM receiver prior to use.

The CGM device status report should be printed out, dated and signed and filed as source document.

5.2 Eligibility for baseline CGM and meal test subgroup

At the fitting visit the Investigator must ensure that Subjects are eligible to continue in the trial, i.e. assess the withdrawal criteria for the trial before the CGM device is fitted. If the Subject is not eligible to be randomised based on the randomisation criteria listed in protocol section 6.5 and 6.5.1, a site visit must be scheduled in order to stop the CGM sensor measurement and have the CGM device removed and the Subject is considered a run-in failure.

5.3 Fitting and removal of the CGM device

During the fitting visit the Investigator will insert a glucose sensor under the Subject's skin in the belly or the upper buttocks, measuring the concentration of glucose in the interstitial fluid every 5 minutes. The sensor is attached to a transmitter and both are worn by the Subject. The transmitter transfers the interstitial glucose (IG) data wirelessly to the receiver where data is stored.

The CGM sensor has an in-use period of 7 days (168 hours). The CGM device will automatically stop recording data exactly 7 days after sensor insertion; therefore a second sensor will have to be fitted to the Subjects before or when reaching the 168 hours after first insertion in order to obtain 11 to 13 days data. This should be taken into account when scheduling the Subject visits.

The CGM device should be worn for at least 11 days (264 hours) by each Subject in each of the two CGM periods.

The CGM device should be fitted to the Subject at the site as indicated in the flowchart (see section 3).

The first fitting visit in the first CGM period (during the run-in period) has to be planned from 11 to 13 days prior to the randomisation visit in order to register baseline CGM data while the meal test is performed at Visit 14. The first fitting visit in the second CGM period (during treatment) has to be planned from 11 to 13 days prior to Visit 40 in order to register treatment CGM data while the meal test is performed at Visit 40.

An overview of the scheduled CGM sensor fitting and removal days relative to the meal test is outlined in Table 2.

Table 2 Overview of scheduled CGM sensor fitting and removal days relative to meal test at either Visit 14 or Visit 40

Visit(V) / Phone contact(P)	V12/V38 (±3 days)							P13/P39 (±3 days)[a]										V14/V40
Days prior to V14/V40	-17	-16	-15	-14	-13	-12	-11	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	0
CGM based on two sensor periods					Schedule Fitting 1							Schedule Removal 1 and Fitting 2						Meal test and Removal 2

[a] Removal of the first sensor and fitting of the second sensor can be performed at home by the Subject and LAR(s), if the Subject and LAR(s) have been trained and are able to perform it correctly, according to the Investigator's judgement. Otherwise Phone Contact 13 and Phone Contact 39 can be changed to a site visit.

Additional fitting of sensors can be planned if the meal test assessment has to be rescheduled more than 7 days after the second fitting visit, which means the Subject can be on CGM for more than 13 days. If the sensor is dislodged and needs to be replaced or visit windows must be accommodated additional fitting of sensors can be planned as well. In case the sensor dislodges, the Subject and LAR(s) must contact site in order to schedule a new fitting at site or if capable at home according to the Investigator's judgement.

The meal test must not be scheduled on the 1st or 7th day after having fitted the second sensor. Hence the fitting of the sensors must be scheduled accordingly and as a minimum one day before the meal test visit. The rationale for this is firstly; the sensor will not start measuring IG until after the 2 hour start-up calibration on the 1st day, and the Subject will have to wait 2 hours after the sensor insertion before the meal test can start. Secondly the risk of the CGM device stopping before or during the meal test is possible as the CGM device will automatically stop the recording of data exact 7 days after sensor insertion.

Removal of the first sensor and fitting of the second sensor can be performed at home by the Subject and LAR(s), if they have been trained and are able to perform it correctly, according to the Investigator's judgement.

In order to ensure that the CGM device is measuring correctly the insulin injection site must be in a distance of at least 7.6 cm (3 inches) from where the CGM sensor has been inserted. This will also ensure that local skin reactions, if any, may be related to the correct trial product and/or device.

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

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

The second sensor should not be removed until after the meal test has been completed (after 240 minutes) at Visit 14 and Visit 40 respectively.

It is not considered an unscheduled visit, if the Subjects attend the site for a CGM fitting between visits. Instead this needs to be documented in the Subject's medical record.

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

5.4 Wearing and calibration of the CGM device

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

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

The accuracy of the CGM system is dependent on calibration values from the Subject. It is therefore essential that the Subject, the LAR(s) and site staff are fully trained in the use of the CGM device according to the CGM manufacturer's user guide and quick user guide.

- Start-up calibration should be performed 2 hours after fitting the device; two SMPG measurements are needed for start-up calibration.
- While wearing the device the Subjects will continue to enter at least two SMPG values into the CGM receiver per day for calibration purposes according to the CGM manufacturer's user guide.
- The SMPG value for calibration should be entered directly into the CGM receiver within 5 minutes from performing the SMPG measurement.
- One calibration must be entered every 12 hour. The device will give an alert if calibration values are missing after 12 hours.
- Two SMPG values from the 4-point profile can be used for the calibration.
- Any SMPG values ≤ 3.9 mmol/L (70 mg/dL) used for calibrations must also be recorded as a hypoglycaemic episodes by the Subject, according to the protocol section 8.5.1.1.
- Some additional measurement may be required for calibration if the SMPG value entered in the device is very different from the sensor glucose reading.

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

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

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

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

- Date, actual clock time and carb content of meals (breakfast, lunch, main evening meal and other meals)
- Date, actual clock time and dose of bolus and basal injections
- For extra insulin boluses: Date, actual clock time, dose (units), time and type of previous meal and reason for the extra bolus

The receiver battery will need to be charged by the Subject during the 11 to 13 days, this should be done taking into account the transmission range of 6 meters (20 feet) from the transmitter to the receiver.

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

5.5 Uploading of CGM data

Each CGM period is made up of two sensor periods. Uploading data after the first sensor period is optional, but data from both sensor periods must be uploaded no later than 3 days after Visit 14 and Visit 40, respectively.

A CGM Software program will be provided by the CGM manufacturer to allow upload of the CGM data. Following information must be entered in the CGM Software program when uploading CGM data:

- Trial ID
- Subject ID
- Visit ID

The following information must also be recorded and transferred into the trial database:

- Confirmation of CGM assessment
- Serial number of the CGM receiver

5.5.1 CGM reports

Upon each data upload the CGM data capture report and the unblinded CGM trend reports will be available in the CGM Software system. Both the CGM data capture report and the unblinded CGM trend reports should be printed out, dated and signed and filed as source documents.

5.5.1.1 CGM data capture report

The CGM data capture report shows the CGM data capture in percentage and the daily SMPG calibration values entered into the CGM receiver for each CGM period.

- The CGM data capture in percentage shows whether the Subject has kept the CGM receiver within the required transmission range of 6 meters (20 feet) from the CGM transmitter and that the wireless communication between the transmitter and receiver has worked well. Deviation from this requirement should lead to re-training of the Subject or technical troubleshooting
- The daily SMPG calibration values shows whether the Subject has entered their SMPG value twice per day (every 12 hour) into the CGM receiver. Deviation from this requirement should lead to re-training of the Subject

5.5.1.2 Unblinded CGM trend reports

The unblinded CGM trend reports show the CGM profiles generated by the CGM device during each CGM period.

- The CGM profiles show trends or patterns which could lead to consideration whether additional plasma glucose measurements may be needed

The unblinded CGM trend reports must not be shared with the Subject and the LAR(s) prior to End of Treatment visit (Visit 40).

5.6 CGM data

During the data recording period the CGM device, in which the data is “born”, is regarded as an intermediate media, as the data cannot be accessed until uploaded to an electronic system at the trial site. Data will be transferred from the CGM device to an electronic system, and then to the trial database. During each CGM period the Subject will be blinded to the CGM data. The Investigator will be able to review the CGM data capture and CGM trends upon data upload at site but the unblinded CGM trend reports must remain blinded to the Subject and the LAR(s) prior to End of Treatment visit (Visit 40). After finalisation of the trial, the CGM source data for each Subject will be provided to the Investigator. The CGM source data is then stored and archived on site.

6 Meal test

The Subjects will have two standardised meal tests performed; one at Visit 14 and one at Visit 40, as outlined in Table 1.

The meal test has to be performed in the morning as the Subject needs to be fasting on the day of the visit.

The CGM sensor used at Visit 14 and Visit 40 must not be removed until after the meal test has been completed (after 240 minutes).

The total duration of the meal test is expected to be approximately 5 hours and will include consumption of a standardised liquid meal, i.v. cannulation, and four blood samples obtained in total during 120 minutes. One blood sample will be obtained prior to consumption of the liquid meal and three blood samples will be obtained after consumption of the liquid meal according to the schedule in Table 3.

6.1 Meal test procedure

The Subject should achieve an SMPG value within a range of 4.0-8.8 mmol/L [71-160 mg/dL] before beginning the meal test. The time and value of this SMPG measurement should be recorded in the diary before starting the meal test. If the Subject does not attend the meal test visit fasting and/or the SMPG value is outside the range, then the entire visit should be rescheduled within the visit window.

The Subject should be instructed to:

- Follow normal routine regarding eating and exercise habits 24 hours prior to the meal test
- Bring their trial bolus insulin to the meal test visits
- Attend the meal test visits in a fasting condition. For definition of fasting please refer to protocol section 8.1.7
- Withhold Insulin injections (including basal insulin if this is usually taken in the morning) and medication which should be taken during or after a meal until the meal test has been performed

The Subject's body weight must be measured and a blood sample for assessment of plasma glucose (PG) must be drawn 2 minutes before intake of the standardised liquid meal.

Meal test at Visit 14:

- The Subjects should consume 1.5 g of carbohydrates per kg body weight, but no more than 80 g of carbohydrates in total.
  The volume of the standardised liquid meal to be consumed should be measured out by the Investigator.
  The carbohydrate content of the standardised liquid meal may differ from country to country.

- The bolus insulin dose for the meal test should be calculated by the Investigator by dividing the carbohydrate content of the standardised liquid meal by the Subject's current I:carb ratio. The calculated dose should be rounded to the nearest half unit.

- The bolus insulin should be injected 0-2 minutes before the start of consuming the liquid meal. The bolus insulin injection should be injected subcutaneously in the abdomen.

Meal test at Visit 40:

- The Subjects must consume same amount of carbohydrates and use same bolus insulin dose as they did for Visit 14, i.e. calculations of the volume of the liquid meal and the bolus dose should not be repeated.

- The bolus insulin injection should be injected subcutaneously in the abdomen depending on the Subject's randomisation, as described below:

    - Meal-time dosing: Injecting 0 - 2 minutes before the start of consuming the standardised liquid meal
    - Post-meal dosing: Injecting 20 minutes after the start of consuming the standardised liquid meal

The Subject must consume the standardised liquid meal as quickly as possible and preferably within 12 minutes. The Investigator should confirm that the Subject consumed the required volume of the standardised liquid meal in the electronic case report form (eCRF). Please refer to section 10.2 for details regarding supply of the standardised liquid meal.

Time point 0 is defined as the time when the Subject starts the consumption of the standardised liquid meal. Blood samples should be taken at -2, 30, 60 and 120 minutes after the start of the meal test as outlined in Table 3.

Table 3 Meal test schedule

Time point (minutes)	Blood sample (PG)	SMPG measurement	Standardised liquid meal	Visit 14 Bolus insulin injection	Visit 40 Bolus insulin injection
Before start of meal test		X (within target range 4.0-8.8 mmol/L [71-160 mg/dL])			
-2	X	X (as appropriate to ensure Subject's safety)			
0			X	X Bolus insulin injection 0 – 2 minutes before the start of the standardised liquid meal	X **Meal-time dosing:** Bolus insulin injection 0 – 2 minutes before the start of the standardised liquid meal
20					X **Post-meal dosing:** Bolus insulin injection 20 minutes after the start of the standardised liquid meal
30	X				
60	X				
120	X				
240 End of meal test		X (for Subject's safety)			

The Subject should stay at the clinic during the meal test to have the blood samples drawn after 30, 60 and 120 minutes from the start of the standardised liquid meal, as indicated in Table 3.

For the meal test at Visit 14 at time point 0 the Subjects must receive the trial product that was also used in the run-in period.

For the meal test at visit 40 the Subjects should receive the trial product they are randomised to and have used throughout the treatment period. Depending on the randomisation to either meal-time or post-meal dosing, the Subjects must be dosed at time point 0 or at time point 20 accordingly.

During the meal test the Subject should be resting in a chair. Water consumption should, to the extent possible, be avoided during the first two hours of the meal test. Food intake should not take place until at least 4 hours after meal test bolus insulin injection, as the Subject's glucose values will be measured by the CGM device until end of the meal test.

If SMPG values ≤ 3.9 mmol/L, (70 mg/dL) are measured then the hypoglycaemia should be treated according to local practice and the meal test should continue according to the Investigator's discretion. The hypoglycaemia must be reported according to protocol section 8.5.1.1.

After the end of the meal test the Investigator should confirm that the Subject is safe to leave the site by performing an additional SMPG measurement. The Subject needs to stay at the site for at least 4 hours after the bolus insulin injection time due to safety concerns.

6.1.1 Handling of blood samples

For convenience and for safety reasons, the Subjects may have i.v. catheters inserted for the collection of blood samples during the meal test according to Table 3 and in the event of hypoglycaemic episodes requiring immediate i.v. glucose administration.

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

6.2 Data collection and data management

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

- Fasting status
- Body weight
- Time and value of SMPG measurement prior to the meal test confirming that the Subject is within the target of 4.0-8.8 mmol/L (71-160 mg/dL)
- Time of blood samples
- Time and dose of insulin injection
- I:carb ratio used for bolus dose calculation (to be recorded at Visit 14 only)
- Start and end-time of standardised liquid meal
- Volume and carb content of standardised liquid meal calculated for consumption (calculated amounts for Visit 14 must also be used at Visit 40)
- Confirmation that the Subject consumed the required volume of the standardised liquid meal
- Volume of standardised liquid meal consumed
- Batch no. of standardised liquid meal consumed
- Hypoglycaemic episode number, time of intervention and amount of glucose rescue treatment if relevant

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 end of trial.

7 Premature discontinuation of trial product

If a Subject is prematurely discontinued from trial product after randomisation (Visit 14), the Investigator must ensure every possible effort is made to undertake the CGM and meal test procedures at Visit 40A, similar to the CGM and meal test procedures for Visit 38, Phone contact 39 and Visit 40, as soon as possible after decision of ending treatment.

The CGM and meal test procedure at the premature discontinuation Visit 40A must be performed with the exception that the CGM period can be less than 11 days. The meal test must not be scheduled on the 1st or 7th day after having fitted the sensor. The meal test at Visit 40A should be performed with trial product according to randomisation unless this is not feasible for safety reasons as judged by the Investigator. Confirmation that the meal test was taken with trial product will be recorded in the eCRF.

The CGM and meal test procedure should not be repeated at Visit 40.

Please refer to protocol section 8.2 for further procedures related to premature discontinuation of trial product.

8 Withdrawal from trial

If a Subject withdraws consent from the trial after randomisation (Visit 14), the Investigator must ensure every possible effort is made to undertake procedures similar to those for Visit 40, including the CGM and meal test procedures as soon as possible after decision of ending trial. The meal test should be performed with trial product according to randomisation unless this is not feasible due to safety reasons as judged by the Investigator.

Please refer to protocol section 8.3 for further procedures related to withdrawal from trial.

9 Interactive voice/web response system

The Interactive voice/web response system (IV/WRS) will be used to register that a Subject will take part in the CGM and meal test subgroup and to ensure the required number of Subjects in the CGM and meal test subgroup has been met.

During the Screening Visit the Subject will be registered as a CGM and meal test Subject. At Visit 14 the Subject will be asked to confirm that he/she has performed the subgroup assessment. This confirmation is used for tracking the recruitment of the subgroup.

9.1 IV/WRS data change session

If a CGM and meal test Subject changes his/her mind with regards to consenting/participate in the CGM and meal test subgroup an IV/WRS data change session must be performed prior to randomisation (Visit 14). If a Subject who has not consented to the CGM and meal test subgroup would like to participate, the data change session must be performed prior to Visit 12 in order to have the CGM device fitted in due time.

10 Trial Supplies

10.1 CGM supplies

Novo Nordisk will provide the following:

- CGM devices (receiver and transmitter)
- CGM user manual and quick guides (for site use)
- Instructions for Subjects and the LAR(s)

CGM devices should be returned to Novo Nordisk at end of trial.

The CGM manufacturer will provide the following:

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

10.1.1 Site PC

Please ensure that a PC with internet connection is available at site (same PC as used for electronic data capture can be utilised). For further instruction and requirements please see CGM manufacturer's user guide.

10.1.2 Storage of CGM sensors

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

10.2 Meal test supplies

The meal test will be provided by Novo Nordisk. More details on composition and ordering of the product are described in the laboratory flowchart.

11 Monitoring procedures

11.1 CGM procedures

During the course of the trial, the monitor will verify that the CGM procedures described in this appendix have been adhered to, that all issues have been recorded and that monitoring and source data verification has taken place.

The monitor will have to verify that:

- CGM data has been recorded and uploaded in accordance with the CGM manufacturer's user guide

11.1.1 CGM Source data verification

In addition to protocol section 14 and 14.1 the following should be monitored from the diary data:

- Date, actual clock time and carb content of meals (breakfast, lunch, main evening meal and other meals)
- Date, actual clock time and dose of bolus and basal injections
- For extra insulin boluses: Date, actual clock time, dose (units), time and type of previous meal and reason for the extra bolus

The following should be monitored from the CGM reports:

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

11.2 Meal test procedures

During the course of the trial, the Monitor will verify that the meal test procedures described in this appendix have been adhered to, that all issues have been recorded and that monitoring and source data verification have taken place.

The Monitor will have to verify that:

- Meal test procedures have been followed
- Blood samples have been drawn and recorded in accordance with the time schedule
- All blood samples have been sent to the central laboratory

11.2.1 Meal test source data verification

In addition to protocol section 14 and 14.1 the following should be source data verifiable:

- Fasting status
- Body weight
- Time and value of SMPG measurement prior to meal test confirming that the Subject is within the target of 4.0-8.8 mmol/L (71-160 mg/dL)
- Time of blood samples
- Time and dose of insulin injection
- I:carb ratio used for bolus dose calculation (to be recorded at Visit 14 only)
- Start and end-time of standardised liquid meal
- Volume and carb content of standardised liquid meal calculated for consumption (calculated amounts for Visit 14 must also be used at Visit 40)
- Confirmation that the Subject consumed the required volume of the standardised liquid meal
- Volume of standardised liquid meal consumed
- Batch no. of standardised liquid meal consumed
- Hypoglycaemic episode number, time of intervention and amount of glucose rescue treatment if relevant

Protocol Amendment

no 1
to Protocol, final version 2.0
dated 10 November 2015

Trial ID: NN1218-4101

Efficacy and Safety of Faster-acting Insulin Aspart compared to NovoRapid® both in Combination with Insulin Degludec in Children and Adolescents with Type 1 Diabetes

onset®7

Trial phase: 3b

Applicable to all countries

Amendment originator:

[redacted]

Insulin, GH & Devices

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1 Introduction including rationale for the protocol amendment

A minor discrepancy have been identified in the presentation of the non-inferiority concept in the statistical section "General considerations" compared to what is presented in detail in the section "Primary analysis". The primary analysis remains unchanged.

In this protocol amendment:

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

2 Changes

17 Statistical considerations

General considerations

The primary objective, confirming the effect of treatment with meal-time faster-acting insulin aspart in children and adolescents with type 1 diabetes will be assessed using a non-inferiority approach comparing the change from baseline HbA_{1c} to meal-time NovoRapid®, where both treatments are combined with insulin degludec. More specifically the upper limit of the 95% confidence interval should be compared to a non-inferiority margin of 0.4. If it is below *or equal to* 0.4 non-inferiority will be considered established and the effect demonstrated.

Protocol Amendment

no 2
to Protocol, final version 3.0
dated 16 February 2016

Trial ID:NN1218-4101

Efficacy and Safety of Faster-acting Insulin Aspart compared to NovoRapid® both in Combination with Insulin Degludec in Children and Adolescents with Type 1 Diabetes

Trial phase: 3b

Applicable to all countries

Amendment originator:

[redacted]

Insulin, GH & Devices

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Table of Tables

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1 Introduction including rationale for the protocol amendment

The main reason for preparing this protocol amendment is to address a mistake identified in the blood sampling volume at visit 14 and visit 40 for the subjects participating in the CGM and meal test subgroup. Consequently the required minimum weight for participation in the CGM and meal test subgroup has increased to ensure the blood volume collected at visit 14 and visit 40 does not exceed 1% of the subjects total blood volume.

Additional changes are described below:

Exclusion criterion #3 has been updated to clarify adequate contraceptive measures for Bulgaria, Czech Republic, Lithuania, Latvia, Poland, Estonia and Finland.

The requirements for reporting of hyperglycaemic episodes have been updated to reflect that subjects have to have high SMPG values, feeling/looking ill and have elevated ketones before reporting the hyperglycaemic episode in the eCRF.

It has been clarified that fasting plasma glucose results measured at central laboratory ≤3.9 mmol/L (70 mg/dL) has to be reported as a clinical laboratory adverse event instead of an adverse event.

The tables for titration of insulin degludec and pre-dinner bolus insulin in appendix A have been corrected so there is no overlap between the SMPG values used for titration.

Minor mistakes and inconsistencies have been corrected.

In this protocol amendment:

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

2 Changes to the protocol

2.1 Table of Contents

2.2 List of abbreviations

CLAE	*clinical laboratory adverse event*
EU	*European Union*

2.3 Section 2 Flow chart

For 'Informed consent' the following footnote is added:
[n] *Informed consent for participation in the CGM and meal test subgroup can be obtained up to visit 12 (including visit 12)*

Footnote b:
b) Visit 2 can take place as soon as the Subject has been found eligible and must take place no later than 1~~3~~7 days after the screening visit (Visit 1). The results of all the screening assessments must be available (including central laboratory results) and must have been reviewed by the Investigator before the Subject can enter the run-in period

For both 'Hypoglycaemic episodes' and for 'Hyperglycaemic episodes' the 'x' at V2 is deleted.

2.4 Section 5.2.2 Rationale for choice of non-inferiority margin

….

In a similar phase 4 trial[27~~26~~] investigating the stepwise addition of insulin aspart 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 on file) with 3 times daily insulin aspart 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. Using a non-inferiority margin of 0.4, one of the suggested margins in the FDA guidance[26~~27~~], an improvement of approximately 0.54% would have been preserved using the 0.4% non-inferiority margin.

2.5 Section 6.2.1 Additional inclusion criteria for the CGM and meal test subgroup

….

11. Weight ≥ ~~20.0~~ *22.5* kg (~~44.0~~ *49.5* lbs) measured at the time of screening (Visit 1)

2.6 Section 6.3 Exclusion criteria

….

3. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using adequate contraceptive methods (adequate contraceptive measures as required by local regulation or practice)
For EU only: Adequate contraceptive measures are implants, injectable, combined oral contraceptives, hormonal IUD, sexual abstinence or vasectomised partner.
For Bulgaria, Czech Republic, Lithuania, Latvia, Poland, Estonia and Finland only: Adequate contraceptive measures also include double barrier method (condom or diaphragm with spermicide) in addition to the measures listed under EU.

2.7 Section 8.2 Premature discontinuation of trial product

….

In addition, Subjects prematurely discontinued from trial product should continue with the per protocol planned visits after 12 weeks (Visit 26) and 26 weeks (Visit 40) from randomisation depending on when the Subject discontinues trial product. The following ~~assessments~~ are not applicable for prematurely discontinued Subjects at *V26 and* V40: 4-point profile, technical complaints, CGM and meal test, IV/WRS call~~.~~*, drug accountability and training in trial product and pen handling.*

2.8 Section 8.5.1.1 Hypoglycaemic episodes

….

If the hypoglycaemic episode fulfils the criteria for an SAE then an AE form and a safety information form must also be filled in, as described in section 1.. *One AE form and safety*

information form can cover several hypoglycaemic episode forms if the subject has not recovered between the episodes.

2.9 Section 8.5.1.2 Hyperglycaemic episodes

....

The Investigator must review the diary data at each contact for correct reporting of hyperglycaemic episodes. ~~High SMPG values and/or ketones not having a hyperglycaemic episode form completed within 7 days since the SMPG and/or ketone measurement should be reported on a hyperglycaemic episode form with as much information as possible (as a minimum the date and SMPG value); hyperglycaemic episodes will not be queried for additional information retrospectively due to decreased validity of such data~~ *High SMPG values where subject looked/felt ill, and had elevated ketones but not having a hyperglycaemic episode form completed in the eCRF within 7 days since the SMPG measurement should be reported on a hyperglycaemic episode form in the eCRF with as much information as possible. Novo Nordisk will not query for additional data except for the date, SMPG value, ketone value and looking/feeling ill due to decreased validity of such data* [36,37].

2.10 Section 8.6.1 Blood volumes for blood sampling

Table 2–1 Table 8-2 Approximate blood volumes collected during the trial

	Age ~~**2**~~ **< ~~Age 2~~ (mL)**	**2 ≤ Age ~~<~~ ≤ 6 years (mL)**	**6 ~~≤~~ < Age < 18 (mL)**	**Age ≥ 8 and in CGM and meal test subgroup (mL)**
Visit 1	3.0	5.0	6.5[a]	6.5[a]
Visit 12	0.5	1.2	2.0	2.0
Visit 14	5.8	8.4	10.0[a]	*18.0*~~10.0~~[a]/[b]
Visit 26	5.8	8.4	10.0	10.0
Visit 40[c]	5.8	8.4	10.0[a]	*18.0*~~10.0~~[a]/[b]
Total blood volume collected	20.9	31.4	38.5	*54.5*~~38.5~~

[a] Including blood volume for performing hCG pregnancy test for females of childbearing potential only (females having had menarche).

[b] including four PG blood samples collected during the meal test

[c] Same blood volume applicable for Visit 40A

....

If the Subject's weight is less than ~~20.0~~ *22.5* kg (~~44.0~~ *49.5* lbs) at screening (Visit 1) the Subject is not eligible for the CGM and meal test subgroup.

2.11 Section 8.6.4 Fasting plasma glucose

….

FPG results ≤ 3.9 mmol/L (70 mg/dL) should not be reported as hypoglycaemic episodes in the eCRF but as ~~an AE related to the procedure (e.g. if the FPG result is 2.9 mmol/L (52 mg/dL), please report as 'low plasma glucose of 2.9 mmol/L (52 mg/dL)').~~ *a clinical laboratory adverse event (CLAE) at the discretion of the investigator (see Section 12.1.1).*

2.12 Section 9.2 Labelling

….

The Investigator must document that direction for use is given to the Subject orally and in writing at ~~each~~ *the first* dispensing visit *(Visit 2).* ~~Direction for use must as a minimum be provided to the Subject in writing at the first dispensing visit (Visit 2).~~

2.13 Section 12.1.1 Adverse event

….

An AE includes:

- A clinically significant worsening of a concomitant illness.
  A clinical laboratory adverse event (*CLAE)*: a clinical laboratory abnormality which is clinically significant, i.e. an abnormality that suggests a disease and/or organ toxicity and is of a severity that requires active management.

2.14 Section 17.4.1 Supportive secondary endpoints

For all supportive secondary endpoints, meal-time faster-acting insulin aspart will be compared to meal-time NovoRapid®, and post-meal faster-acting insulin aspart will be compared to meal-time NovoRapid®. *Change from baseline refers to the change from randomisation to 26 weeks after randomisation.*

2.15 Section 17.4.1.1 ~~Change from baseline refers to the change from randomisation to 26 weeks after randomisation.~~Efficacy endpoints

3 Changes to Appendix A

Appendix A, version 3.0, dated 16 February 2016

3.1 Section 3.2 Titration of insulin degludec during run-in

Table 3–1 Table 3-2 Titration of insulin degludec

Current dose		**≤ 15U**	**>15U**
Lowest of three pre-breakfast SMPGs		**Adjustment**	
mmol/L	mg/dL		
≤ 3.9	≤ 70	-1	-2
4.0 – 8.0	71 - 145	0	0
8.1 – 10.0	146 - 180	+1	+2
10.1 – 15.0	181 – 270	+2	+4
~~>~~ ≥ 15.1	~~>~~ ≥ 27~~0~~*1*	+3	+6

3.2 Section 3.4.1.2 Pre-dinner bolus insulin titration

Table 3–2 Table 3-4 Titration of pre-dinner faster-acting insulin aspart/NovoRapid®

Current dose		**< 5U**	**≥ 5U**
Lowest bed-time SMPG value measured on the three days prior to the site visit/phone contact		**Adjustment**	
mmol/L	mg/dL		
≤ 6.~~7~~*6*	≤ 1~~20~~*19*	-1	-2
6.7 – 10.0	120 – 180	0	0
≥ 10.~~0~~*1* [a]	≥ 18~~0~~*1*	+½	+1

a. It is at the Investigator's discretion to use a higher dose increment.

4 Changes to Appendix B

Appendix B, version 3.0, dated 16 February 2016

4.1 Section 3 Flow chart

Table 4–1 Table 1 Flow chart – CGM and meal test procedures

Trial NN1218-4101	**Appendix section**	**Screening**	**Run-in**		**Randomisation**	**Treatment period[~~d~~4]**			**Premature Discontinuation**	
Visit (V) / Phone contact(P)		**V1**	**V12**	**P13**	**V14**	**V38**	**P39**	**V40**		**V40A**
Time of visit (weeks)[1]		-14	-2	-1	0	24	25	26		
Visit window (days)		*+10*	±3	±3		±3	±3	±3		
CGM Assessment			**CGM Fitting**	**CGM Fitting**	**CGM Removal**	**CGM Fitting**	**CGM Fitting**	**CGM Removal**	**CGM Fitting**	**CGM Removal**
Meal test Assessment					**Meal test**			**Meal test**		**Meal test**
Subgroup informed consent[5]	4.3	*(x)*	*(x)*							
Fitting & supply of the CGM devices[2]	5.2 & 5.3		X	x		x	x		x	
Instruct Subjects in CGM calibration procedure (beginning 2 hours after the device is fitted and every 12 hours during the CGM period)	5.4		X	x		x	x		x	
Instruct Subjects in CGM procedures in general	5.4		X	x		x	x		x	
Meal test[3]	6				x			x		x
Attend visit fasting	6.1				x			x		x
Removal of CGM device	5.3			x	x		x	x		x
Upload of CGM data	5.5			x	x		x	x		x

[1] The time of the visit is defined from the randomisation visit (V14)
[2] The fitting of the CGM devices must be scheduled to ensure the meal test is not performed on the 1st or 7th day when Subject is wearing a CGM sensor. In case of premature discontinuation of trial product or withdrawal from trial please see section 7 and 8
[3] The meal test must be performed after a minimum of 11 days of wearing a CGM sensor
[~~d~~4] The assessments is not applicable for premature*ly* discontinued Subjects, see section7
[5] *Informed consent for participation in the CGM and meal test subgroup can be obtained up to visit 12 (including visit 12)*

Trial NN1218-4101	Appendix section	Screening	Run-in		Randomisation	Treatment period[44]			Premature Discontinuation	
Visit (V) / Phone contact(P)		**V1**	**V12**	**P13**	**V14**	**V38**	**P39**	**V40**		**V40A**
Time of visit (weeks)[1]		-14	-2	-1	0	24	25	26		
Visit window (days)		*+10*	±3	±3		±3	±3	±3		
Weight & age check	4.3	x								

4.2 Section 4.3 CGM and meal test subgroup population

A total of 150 randomised Subjects are planned to enter the CGM and meal test subgroup. To ensure capability of the Subjects to comply with the CGM and meal test procedures only Subjects ≥ 8 years of age and with a weight of ≥ ~~20.0~~ *22.5* kg (~~44.0~~ *49.5* lbs) at screening (due to blood sampling volume restrictions) are allowed to participate in the CGM and meal test subgroup.

Protocol Amendment

no 3
to Protocol, final version 4.0
dated 01 April 2016

Trial ID:NN1218-4101

Efficacy and Safety of Faster-acting Insulin Aspart compared to NovoRapid® both in Combination with Insulin Degludec in Children and Adolescents with Type 1 Diabetes

onset®7

Trial phase: 3b

Applicable to Serbia only

Amendment originator:

[redacted]

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Page

1 Introduction including rationale for the protocol amendment

The reason for preparing this protocol amendment is to address the concerns received from Serbian Medicines and Medical Devices Agency for initial trial application. The Agency did not issue approval to run the trial in Serbia in population of children and adolescents between 1 year old and below 18 years old at the time of signing informed consent and below 18 years old at the time of randomisation.

The main rationale for rejecting the trial was lack of approval of comparator (Insulin Aspart – NovoRapid) and Insulin Degludec (Tresiba) in Serbia for diabetes treatment in children below 2 years old. Furthermore, the Serbian Medicines and Medical Devices Agency had concerns in relation to inability of children below 2 years old to properly recognize and acknowledge hypoglycaemia as well as high incidence of hypoglycaemic episodes in this population. Based on the above the Serbian Medicines and Medical Devices Agency judged the overall benefit-risk ratio for the trial subjects as unfavourable.

This protocol amendment changes the inclusion criterion number 2 for Serbia only in order to include subjects from 2 years old and below 18 years old at the time of signing informed consent and below 18 years old at the time of randomisation.

In this protocol amendment:

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

2 Changes

Section 1 Summary, Trial design

This is a 26-week randomised, partly double-blind, multicentre, multinational, active controlled, treat-to-target, three-armed parallel group trial with a 12-week run-in period comparing the effect and safety of meal-time faster-acting insulin aspart vs. meal-time NovoRapid® both in combination with insulin degludec once daily in a basal-bolus regimen in type 1 diabetes mellitus Subjects from ~~1~~*2* year*s* to less than 18 years of age. The trial will also include a 26-week open-label post-meal faster-acting insulin aspart dosing arm in combination with insulin degludec.

Section 1 Summary, Key inclusion criteria

- Male or female*,* ~~1~~*2* ≤ age < 18 years at the time of signing informed consent and < 18 years at the time of randomisation

Section 5.1 Type of trial

This is a 26-week randomised, partly double-blind, multicentre, multinational, active controlled, treat-to-target, parallel group trial with a 12-week run-in period comparing the efficacy and safety of meal-time faster-acting insulin aspart vs. meal-time NovoRapid® both in combination with insulin degludec once daily in a basal-bolus regimen in Subjects with T1DM from ~~1~~*2* year*s* to less than 18 years of age. The trial will also include a 26-week open-label post-meal faster-acting insulin aspart dosing arm in combination with insulin degludec.

Section 6.2 Inclusion criteria

2. Male or female, ~~1~~*2* ≤ age < 18 years at the time of signing informed consent and < 18 years at the time of randomisation

Section 6.9 Rationale for trial population

For children and adolescents diagnosed with T1DM, insulin therapy is indicated, and data from the The Diabetes Control and Complications Trial Research Group (DCCT) show that intensive treatment is beneficial in terms of the risk of developing long term complications[3]. As the disease usually presents in early childhood and adolescence, the assessment of safety and efficacy of new insulins is appropriate in all ages including childhood and adolescence.

The trial population consist of children and adolescents with T1DM, ~~1~~*2* ≤ age < 18 years with an HbA_{1c} ≤ 9.5 % (80 mmol/mol) at screening and at randomisation. Infants below the age of 1 year are not eligible for this trial since most cases of diabetes diagnosed at this very young age are cases

of neonatal diabetes. Neonatal diabetes is a distinct form of diabetes requiring specialized diagnosis and management beyond the scope of this trial.

In diabetes, a likely cause of elevated HbA_{1c} is poor compliance with treatment regimens or atypical course of the disease; consequently individuals with an HbA_{1c} greater than 9.5% (80 mmol/mol) are not included in this trial. The 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 where focus is not on bolus titration.

During the last 3 months prior to Visit 1 the Subjects must have been on an ongoing daily treatment with a basal-bolus insulin regimen using basal insulin analogue or NPH insulin in order to ensure a smooth switch from prior treatment to trial treatment, and to ensure that optimal adjustment of basal insulin can be done during the 12-week run-in period.

For safety reasons, Subjects with more than one episode of diabetic ketoacidosis requiring hospitalisation within the last 90 days prior to the screening visit are not eligible for this trial.

Protocol Amendment

no 4.0
to Protocol, final version 4.0
dated 01 April 2016

Trial ID: NN1218-4101

Efficacy and Safety of Faster-acting Insulin Aspart compared to NovoRapid® both in Combination with Insulin Degludec in Children and Adolescents with Type 1 Diabetes

onset®7

Trial phase: 3b

Applicable to all countries

Amendment originator:

[redacted]

Insulin & Devices

Table of Contents

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1 Introduction including rationale for the protocol amendment

The main reason for preparing this protocol amendment is to address an inaccuracy identified in the layman language for reporting hypoglycaemic episodes. This is to ensure adequate reporting of severe hypoglycaemia. The layman language is used in the Subject diaries and in EDC.

Additional changes are described below:

There was a need to clarify the run-in failure criteria, to provide more guidance on when to report a MESI, and that the FPG sample must be collected using the FPG home sampling kit no matter if the FPG sample is taken at home or at site.

The statistical section has been updated to clarify the analyses made for the primary and secondary estimand, the supportive secondary CGM and meal test related efficacy endpoints. A clarification has also been made to which treatment emergent hypoglycaemic episodes will be included in the analyses.

Appendix B has been updated to reflect the changes that have occurred due to the change in CGM supplier shortly before trial initiation.

Furthermore, minor mistakes and inconsistencies have been corrected.

In this protocol amendment:

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

2 Changes

2.1 Section 2 Flowchart

Changes to the flowchart:
For "Technical complaint" and for "Dosing" "x" is added at the premature discontinuation visit (V40A).

For "Hypoglycaemic episodes" and for "Hyperglycaemic episodes" "x" is added at V2.

For "Hypoglycaemic episodes" and "Hyperglycamic episodes" a foot note reference "o" is added.

Changes to the foot notes:
a) *Visit windows before Visit 14 is relative to Visit 2.* Visit windows *after Visit 14* are relative to ~~randomisation visit (~~Visit 14~~)~~, except for the follow-up visits which are relative to last day on trial product

o) Serious hypoglycaemic episodes and serious hyperglycaemic episodes must be reported from the first trial-related activity after the Subject has signed the informed consent

2.2 Section 6.4 Run-in failure criteria

The Subject may be withdrawn from the trial during the run-in period at the discretion of the Investigator due to a safety concern.

….

2.3 Section 6.7 Withdrawal from trial

The Subject may withdraw at will at any time either by the Subject or by the Subject's LAR(s). The Subject's request to ~~discontinue~~ *withdraw* must always be respected.

If the Subject considers withdrawing consent *after randomisation,* the Investigator must underline to the Subject the importance of continuing in the trial despite trial product discontinuation. If the Subject agrees to discontinue trial product but to stay in the trial, procedures similar to those described in section 8.2 must be followed.

….

A Subject *randomised* ~~included~~ in the trial in violation of the inclusion and/or exclusion criteria and/or randomised in violation of the randomisation criteria must discontinue treatment with trial product, but will not be withdrawn from the trial and will be followed as described in section 8.2

….

2.4 Section 7 Milestones

Planned duration of recruitment period (FSFV – LSFV): *51*~~38~~ weeks

….

2.5 Section 8.1.7 Fasting visits

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The Subjects included in the CGM and meal test subgroups must attend Visit 14 and Visit 40 fasting. *If the Subject prematurely discontinues trial product, Visit 40A must also be attended fasting.*

….

2.6 Section 8.2 Premature discontinuation of trial product

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Diary records after premature discontinuation of trial product:

….

- Was the hypoglycaemic episode associated with severe neuroglycopenia, usually resulting in coma or seizure and requiring parenteral therapy (glucagon or intravenous glucose)[34]? (Layman language used in the Subject diaries: Was the low blood glucose episode associated with symptoms severe enough to result in unconsciousness or a seizure *or*~~and~~ was glucagon (an injection) or IV glucose/sugar (drip) needed for your child to recover?)

….

2.7 Section 8.3 Withdrawal from trial

The Subject will become a run-in failure if the Subject withdraws consent prior to randomisation.

If a Subject withdraws consent after randomisation (Visit 14), the Investigator ~~should~~ *must* ensure every possible effort is made to undertake procedures similar to those for Visit 40, including the meal test for the Subjects included in the CGM and meal test subgroup, as soon as possible. The Subject *should*~~must~~ also complete the follow-up visits (Visit 41 and Phone Contact 42).

….

The End-of-Treatment/Trial form must be completed in the eCRF and final drug accountability must be performed even if the Subject is not able to come to the site. A "Treatment Discontinuation" session must be made in IV/WRS and reason for withdrawal must be specified on the End of Treatment/Trial form in the eCRF. ~~Final drug accountability must be performed even if the Subject is not able to come to the trial site.~~

….

2.8 Section 8.5.1.1 Hypoglycaemic episodes

….

The record should include the following information:

….

- Was the hypoglycaemic episode associated with severe neuroglycopenia, usually resulting in coma or seizure and requiring parenteral therapy (glucagon or intravenous glucose)[34]? (Layman language used in the Subject diaries: Was the low blood glucose episode associated with symptoms severe enough to result in unconsciousness or a seizure *or*~~and~~ was glucagon (an injection) or IV glucose/sugar (drip) needed for your child to recover?)

….

2.9 Section 8.5.1.3 Injection site reactions

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The injection site reaction form should only be used for events with an onset date *starting at* ~~between~~ Visit 2 and *up until* Visit 41 *(including Visit 41)*.

…..

2.10 Section 8.6.4 Fasting plasma glucose

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The Subject will receive a home blood sampling kit and instruction on how to use it. The Subject will bring the blood sample to the site visit and the sample will be handled by the site staff in accordance with the instructions described in the laboratory manual. If preferred, the FPG blood sampling can be performed at the site provided that the Subject is fasting for the site visit. *The home sampling kit must also be used if the FPG blood sampling is performed at the site.*

The FPG capillary blood sample must be taken while the Subject is fasting, in accordance with the fasting definition described in section 8.1.7 and before administration of insulin on that day. If these conditions cannot be met, collection of the FPG sample should be rescheduled within the permitted visit window, except f~~or the capillary FPG sample to be collected at the randomisation visit (Visit 14).~~ *at Visit 14(randomisation visit), where* ~~I~~if *conditions for* ~~no~~ FPG sampl~~e~~*ing is not met* ~~available at the randomisation visit~~ the *entire* randomisation visit should be rescheduled within the visit window.

….

2.11 Section 9.5.1 Auxiliaries supplied by Novo Nordisk ~~A/S~~

The following auxiliaries will be supplied by Novo Nordisk ~~A/S~~:

….

2.12 Section 12.1.4 Medical event of special interest

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

A medication error~~s~~ concerning trial products *is defined as:*

- Administration of wrong drug.
  Note: Use of wrong DUN is not considered a medication error unless it results in a confirmed administration of wrong drug.
- Wrong route of administration, such as intramuscular instead of s.c.
- 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~~.~~ *i.e. dose which may lead to significant health consequences, as judged by the Investigator, irrespective of whether the SAE criteria are fulfilled or not.* ~~That is a dose that deviates from the intended dose to an extent where clinical consequences for the trial Subject were likely to happen as judged by the Investigator, although not necessarily did happen.~~

2.13 Section 17.3 Primary endpoint

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Sensitivity analyses for the primary estimand:

2) The internal validity of the primary estimand will first be evaluated by repeating the primary analysis in 1), but excluding all factors ~~and covariates~~ except from treatment in the model. This analysis will explore the influence of the different factors and covariates. The analysis will use the in trial observation period.

….

b. Imputation will be done from the comparator arm (NovoRapid®). This will serve as a sensitivity analysis for the superiority analysis. It does not rely on the MAR assumption, but assumes that all Subjects that withdraw the trial in the faster-acting insulin aspart arms shift to NovoRapid®. The imputation will be done *conditional on observed information for Subjects that withdraw from the faster-acting insulin aspart arms* such that the treatment effect diminishes gradually after trial discontinuation (copy reference/*conditional imputation*). The analysis will use 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 assumes that all Subjects that withdraw the trial in the faster-acting insulin aspart arms shift to NovoRapid®. The imputation will be done *with no regard to observed information for Subjects that withdraw from the faster-acting insulin aspart arms* such that the treatment effect diminishes immediately after trial discontinuation (jump to reference/*unconditional imputation*). The analysis will use the in trial observation period.

….

Analyses for the secondary estimand

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6) A tipping point analysis will be implemented 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 trial product prematurely due to criteria 1, 2, 3, and 4) in the faster-acting insulin aspart groups will *not have a penalty added.* ~~have their imputations based on parameters estimated from the faster-acting insulin aspart groups (and not the NovoRapid® group).~~ These analyses are motivated by the fact that data from Subjects prematurely discontinuing trial product due to non-eligibility can reasonably be assumed to be missing completely at random. The analysis will use the on treatment observation period.

7) The same statistical model using multiple imputation as the primary analysis in 4), but using the PP analysis set and analysed using the on treatment observation period. This analysis will investigate the situation that Subjects deviate from the ideal treatment during the on treatment observation period and will serve as *a* sensitivity analysis for the non-inferiority analysis.

2.14 Section 17.4.1.1 Efficacy endpoints

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Supportive secondary CGM and meal test related efficacy endpoints

….

$AUC_{IG,0\text{-}15\ min}$, $AUC_{IG,0\text{-}30\ min}$, $AUC_{IG,0\text{-}1h}$, $AUC_{IG,0\text{-}2h}$, and $AUC_{IG,0\text{-}4h}$ will be calculated as the area under the IG curve using the trapezoidal method *and weighted by duration. The endpoint will also be calculated as increment where an average of the IG concentrations immediately before the meal is subtracted from the weighted AUC.* Each endpoint will be analysed using an analysis of variance

model including treatment, region and strata as factors and the corresponding baseline value as covariate.

….

2.15 Section 17.4.1.2 Safety endpoints

….

The number of treatment emergent *severe or BG confirmed* hypoglycaemic episodes (all, daytime, nocturnal) will be analysed using a negative binomial regression model with a log-link function and the logarithm of the time period for which a hypoglycaemic episode is considered treatment emergent as offset. The model will include treatment, region and strata as factors, and will be based on the FAS. To the extent where data allow, separate analyses will be performed for severe episodes (all).

….

3 Changes to Appendix A

Appendix A, version 4.0, dated 01 April 2016

3.1 Section 4 Data collection

In this trial the Subjects will be provided with a diary where the Subjects should record the 4-point profiles and insulin doses on the three days prior to a site visit/phone contact, ~~and~~ all hypoglycaemic episodes *and hyperglycaemic episodes within the definition of this protocol.* The data used for titration (4-point profiles and insulin doses) should be transcribed into the eCRF by the Investigator within 24 hours on work days after each site visit/phone contact.

4 Changes to Appendix B

Appendix B, version 4.0, dated 01 April 2016

4.1 Section 5.1 CGM receiver setting and test upload

The CGM receiver ~~must be set up before use~~ *has been setup when provided at site*. The set up includes: date and time setting, entry of CGM transmitter ID and blinding of the CGM receiver. ~~Upon set up of the CGM receiver a test upload must be performed to verify correct installation of CGM software and correct set up of the CGM receiver.~~ *Upon installation of the CGM Web uploader a 'Test of connectivity' should be performed to verify the connectivity from the CGM Web uploader to the server where CGM data will be uploaded to.*

~~Upon the test upload~~ *Upon the first upload for each subject* a CGM device status report will be available in the CGM Software system.
The CGM device status report shows the CGM receiver serial number, the CGM transmitter ID, the blinded status~~,~~ *and* the clock accuracy~~and verification that no data exists on the CGM receiver prior to use~~.

The CGM device status report should be printed out, dated and signed and filed as source document.

4.2 Section 6.2 Data collection and data management

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- *Lot*~~Batch~~ no. of standardised liquid meal consumed ….

4.3 Section 10.1 CGM supplies

Novo Nordisk will provide the following:

….

- *CGM Training (eLearning)*

CGM devices should be returned to Novo Nordisk at end of trial.

The CGM manufacturer will provide the following:

- ~~CGM Installation link to~~ CGM software
- CGM sensors (customs clearance ~~must~~ *may* be expected)
- ~~CGM Training (webinar or on-site)~~

4.4 Section 11.2.1 Meal test source data verification

….

- *Lot*~~Batch~~ no. of standardised liquid meal consumed ….

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