Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT04588259
Sponsor trial ID:	NN1218-4357
Official title of study:	Efficacy and Safety of Fast-acting Insulin Aspart Compared to NovoRapid® both in Combination with Insulin Degludec with or without Metformin in Adults with Diabetes
Document date:	30 November 2020

* Document date refers to the date on which the document was most recently updated.
Note: The date in the header of page 2 is the date of compilation of the documents and not of an update to content.

9.1.1 Protocol and protocol amendments

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Protocol version 5.0 including:

Protocol Amendment No 3 to final protocol version 4.0, dated 3rd April 2020

Trial ID: NN1218-4357

Efficacy and Safety of Fast-acting Insulin Aspart Compared to NovoRapid® both in Combination with Insulin Degludec with or without Metformin in Adults with Diabetes

Trial phase: 3a

China trial

Protocol amendment summary of changes table

DOCUMENT HISTORY		
Document version	Date	Applicable in country(-ies) and/or site(s)
Protocol version 4.0	03 April 2020	China
Protocol version 3.0	01 July 2019	China
Protocol version 2.0	01 December 2017	China
Original protocol version 1.0	24 October 2017	China

Overall rationale for preparing protocol, version 5.0

The overall primary rationale for updating the protocol was due to an error discovered in the Titration Guideline a1. In addition, minor updates to the protocol were implemented as outlined below.

Section # and name	Description of change	Brief rationale
Section 2 Flowchart	Deleted X for 4 point profile at visit 2	The subjects will receive blood glucose meter at visit 2 and hence will not be able to perform 4 point profile prior to visit 2.
Section 2 Flowchart	Deleted X for Medication Error at V27 and P28	Medication Error should not be reported because the trial treatment has ended.
Section 2 Flowchart	Added footnote (*f*) for V10 ECG	Updated to align with timelines for ECG similar to visit 26.
Section 2 Flowchart	Deleted X for Drug Accountability at visit 9	Visit 9 this is not a dispensing visit and the subjects are not supposed to bring their trial product to the site at this visit, unless they do not continue in the trial.
Section 2 Flowchart	Footer description for footer f updated.	Text deleted to also cover visit 10 ECG.
Section 8.4.2 Hypoglycaemic episodes	Deleted text regarding reporting of hypoglycaemic episodes between visit 27 and phone visit 28.	Data on hypoglycaemic episodes between follow-up visit 1 (visit 27) and follow-up visit 2 (phone visit 28) is not collected since the subjects are using commercially obtained medication for which hypoglycaemic episodes should not be reported in the trial.
Section 8.4.4 Electrocardiogram (ECG)	Inserted visit 10	Updated to align with timelines for ECG similar to visit 26.
Section 8.5.2 Laboratory assessments for safety	Updated abbreviation of AST from Aspartate phosphatase to Aspartate aminotransferase.	Updated to be aligned throughout the protocol.

Appendix A1: Insulin Titration Guideline for T1DM subjects, Table 3	Updated table 3 as follows: Calculate the total daily dose of insulin. Adjust the basal-to-bolus ratio to be between 40:60 and 60:40. Use table 2 to find the total number of bolus insulin units and divide this value into three even or uneven doses of NovoRapid® to be taken with breakfast, lunch and dinner. ~~Calculate the daily bolus units from the bolus component of the total daily dose. Divide the calculated number into three even or uneven doses of NovoRapid® to be taken with breakfast, lunch and dinner.~~	Updated to correct bolus insulin dose calculation.

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Appendix A:
A1: Insulin Titration Guideline for T1DM subjects
A2: Insulin Titration Guideline for T2DM subjects

Attachment I: Country list of key staff and relevant departments and suppliers

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List of abbreviations

ADA	American Diabetes Association	IEC	independent ethics committee
AE	adverse event	IMP	investigational medicinal product
ALT	alanine aminotransferase	IRB	institutional review board
AST	aspartate aminotransferase	IWRS	interactive web response system
BG	blood glucose	LDL	low-density lipoprotein
CDS	Chinese Diabetes Society	LSFV	last subject first visit
CFDA	China Food and Drug administration	LSLV	last subject last visit
CRO	contract research organisation	NYHA	New York Heart Association
CTR	clinical trial report	OAD	oral antidiabetic drug
DUN	dispensing unit number	PCD	primary completion date
ECG	electrocardiogram	PG	plasma glucose
eCRF	electronic case report form	PPG	post prandial glucose
EASD	European Association for the Study of Diabetes	SAE	serious adverse event
EMA	European Medicines Agency	s.c.	subcutaneous(ly)
FAS	full analysis set	SD	Standard deviation
FDA	U.S. Food and Drug Administration	SmPC	summary of product characteristics
FPG	fasting plasma glucose	SMPG	self-measured plasma glucose
FSFV	first subject first visit	SUSAR	suspected unexpected serious adverse reaction
GCP	Good Clinical Practice	T1DM	Type 1 diabetes mellitus
HbA_{1c}	glycosylated haemoglobin	T2DM	Type 2 diabetes mellitus
hCG	human chorionic gonadotrophin	TEAE	treatment emergent adverse event
HDL	high-density lipoprotein	TMM	Trial Materials Manual
IB	Investigators Brochure	UTN	Universal Trial Number
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use		
ICMJE	International Committee of Medical Journal Editors		

1 Summary

Objectives and endpoints:

Primary objective:
To confirm the effect in terms of glycaemic control of treatment with fast-acting insulin aspart compared to NovoRapid® both in combination with insulin degludec with or without metformin in Chinese adults with type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM) inadequately treated with a basal-bolus or a premix regimen, using a non-inferiority approach.

Secondary objective:
To compare the safety of fast-acting insulin aspart to NovoRapid® both in combination with insulin degludec with or without metformin in Chinese adults with T1DM or T2DM inadequately treated with a basal-bolus or a premix regimen.

Primary endpoint:
Change from baseline (week 0) in glycosylated haemoglobin (HbA_{1c}) to 16 weeks after randomisation.

Secondary endpoints:

Supportive secondary efficacy endpoints:
- Change from baseline in 30- minutes, 1- hour, 2- hour and 3- hour post prandial glucose (PPG) increment to 16 weeks after randomisation (meal test)
- Change from baseline in 30- minutes, 1- hour, 2- hour and 3- hour PPG to 16 weeks after randomisation (meal test)
- Change from baseline in fasting plasma glucose (FPG) to 16 weeks after randomisation
- If a subject achieves HbA_{1c} target 16 weeks after randomisation:
  - $HbA_{1c} < 7.0\%$
  - $HbA_{1c} < 7.0\%$ without severe hypoglycaemia
- Change from baseline in 7-9-7-point self-measured plasma glucose (SMPG) to 16 weeks after randomisation:
  - Mean of the 7-9-7-point profile
  - 1-hour PPG and PPG increment (mean, breakfast, lunch, main evening meal)
  - Fluctuation in 7-9-7-point profile
- If a subject achieves PPG target (overall mean of daily PPG measurements in SMPG) 16 weeks after randomisation:
  - Overall PPG (1-hour) ≤7.8 mmol/L
  - Overall PPG (1-hour) ≤7.8 mmol/L without severe hypoglycaemia
- Insulin dose (Units/day and Units/kg/day; total basal, total bolus and individual meal insulin dose) 16 weeks after randomisation

Supportive secondary safety endpoints:

- Number of treatment emergent adverse events during the 16 weeks after randomisation
- Number of treatment emergent injection site reactions during the 16 weeks after randomisation
- Number of treatment emergent hypoglycaemic episodes classified both according to the American Diabetes Association (ADA) definition and Novo Nordisk definition during the 16 weeks after randomisation
  - Overall
  - Daytime and nocturnal hypoglycaemic episodes (00:01-05:59 – both inclusive)
  - Hypoglycaemic episodes from start of meal until 30 minutes, 1, 2, 4 hours and from 2 hours (exclusive) to 4 hours (inclusive) after start of meal

Trial design:

This is a phase 3a, 16-week, multicentre, 1:1 randomised, double-blind, active controlled, treat-to-target, two-arm parallel group trial with an 8-week run-in period comparing the effect and safety of fast-acting insulin aspart to NovoRapid® both in combination with insulin degludec with or without metformin in subjects with T1DM or T2DM inadequately treated with a basal-bolus or a premix regimen. The trial includes two blinded dosing arms – mealtime fast-acting insulin aspart and mealtime NovoRapid®.

Trial population:

A total of 505 subjects are planned to be screened and 300 subjects are planned to be randomised.

Key inclusion criteria:

- Male or female, age above or equal to18 years at the time of signing informed consent
- Diagnosed with T1DM ≥ 1 year prior to screening or diagnosed with T2DM ≥ 5 years prior to of screening
- Treated with a basal-bolus insulin regimen or a premix insulin regimen ≥ 1 year prior to screening. Insulin regimen must be unchanged within 60 days prior to screening. A basal-bolus insulin regimen is defined as basal insulin once or twice daily and bolus insulin taken with meals at least thrice daily. A premix insulin regimen is defined as premix insulin twice or thrice daily
- For subjects with T1DM: not treated with any oral anti-diabetes drugs (OADs) for at least 90 days prior to screening
  For subjects with T2DM: not treated with any OADs or treated with 1-2 OADs within 90 days prior to screening. Allowed OADs are metformin, alpha-glucosidase inhibitor, SGLT2i and DPP4i. Change in OAD and dose prior to screening is allowed.
- HbA_{1c} 7.5-9.5% (both inclusive) as assessed by central laboratory at screening

Key exclusion criteria:

- Any of the following: myocardial infarction, stroke, hospitalisation for unstable angina pectoris or transient ischaemic attack within the past 180 days prior to the day of screening
- Subjects presently classified as being in New York Heart Association (NYHA) Class IV
- Planned coronary, carotid or peripheral artery revascularisation known on the day of screening
- Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria within the past 90 days prior to the day of screening
- Anticipated initiation or change in concomitant medications (for more than 14 consecutive days) known to affect weight or glucose metabolism (e.g. treatment with orlistat, thyroid hormones, or corticosteroids)

Randomisation criterion:

- $HbA_{1c} \leq 9.0\%$ measured by the central laboratory at visit 9 (week -1)

Assessments:

- HbA_{1c}
- PPG and PPG increment (meal test)
- PPG and PPG increment (7-9-7-point SMPG)
- Hypoglycaemic episodes
- Adverse events (AEs)

Trial products:

Investigational medicinal products (IMPs):

- Test products:
  - Fast-acting insulin aspart, 100 U/mL solution for s.c. injection, 3 mL PDS290 pen-injector (blinded)
  - Insulin degludec (Tresiba®), 100 U/mL solution for s.c. injection, 3 mL PDS290 pen-injector
- Reference therapy:
  - Insulin aspart (NovoRapid®), 100 U/mL solution for s.c. injection, 3 mL PDS290 pen-injector (blinded)

2 Flowchart

NN1218-4357	Protocol section	Screening	8-week run-in period					Randomisation	16-week treatment period Blinded trial product									End of treatment	Premature discontinuation	Follow-up 1	Follow-up 2	Premature discontinuation
Visit (V) Phone contact (P)		V1	V2	P3 P4 P5	V6	P7 P8	V9	V10	P11	V12	P13	V14	P15 P16 P17	V18	P19 P20 P21	V22	P23 P24 P25	V26	V26A	V27	P28	V26B
Time of visit (weeks)		-10	-8	-7 -6 -5	-4	-3 -2	-1	0	1	2	3	4	5 6 7	8	9 10 11	12	13 14 15	16	At treat. discont.	+7 days	+30 days	16
Visit window (days)		+10	±3	±3	±3	±3	±3	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		+5	+5	±3
SUBJECT RELATED INFO/ASSESSMENTS																						
Informed consent	18.2	X																				
In-/exclusion criteria	6.2, 6.3	X	X																			
Run-in period exclusion criteria	6.4			X	X	X	X	X														
Randomisation criterion	6.5							X														
Randomisation	8.1.3							X														
Criteria for premature discontinuation of trial products	6.6								X	X	X	X	X	X	X	X	X					
Demography	8.2.1	X																				
Tobacco use	8.2.8	X																				
Diabetes history	8.2.2	X																				
Hypoglycaemia unawareness	8.2.3	X																				

NN1218-4357	Protocol section	Screening	8-week run-in period					Randomisation	16-week treatment period Blinded trial product									End of treatment	Premature discontinuation	Follow-up 1	Follow-up 2	Premature discontinuation
Visit (V) **Phone contact (P)**		V1	V2	P3 P4 P5	V6	P7 P8	V9	V10	P11	V12	P13	V14	P15 P16 P17	V18	P19 P20 P21	V22	P23 P24 P25	V26	V26A	V27	P28	V26B
Time of visit (weeks)		-10	-8	-7 -6 -5	-4	-3 -2	-1	0	1	2	3	4	5 6 7	8	9 10 11	12	13 14 15	16	At treat. discont.	+7 days	+30 days	16
Visit window (days)		+10	±3	±3	±3	±3	±3	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		+5	+5	±3
Concomitant illness and medical history	8.2.4	X																				
Concomitant medication	8.2.5 8.2.6	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Childbearing potential	8.2.7	X																				
EFFICACY																						
Meal test	8.3.1							X										X	X			
Fasting plasma glucose	8.5.1							X						X				X	X			
HbA_{1c}	8.5.1	X			X		X	X				X		X		X		X	X			X
4-point profile[a]	8.3.2			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
7-9-7-point profile[b]	8.3.2							X						X				X	X			
Lipids	8.5.1							X						X				X	X			
SAFETY																						
Adverse event	8.4.1,12	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[c]
Hypoglycaemic episodes	8.4.2		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Injection site reactions	8.4.1.2		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

NN1218-4357	Protocol section	Screening	8-week run-in period					Randomisation	16-week treatment period Blinded trial product									End of treatment	Premature discontinuation	Follow-up 1	Follow-up 2	Premature discontinuation
Visit (V) **Phone contact (P)**		V1	V2	P3 P4 P5	V6	P7 P8	V9	V10	P11	V12	P13	V14	P15 P16 P17	V18	P19 P20 P21	V22	P23 P24 P25	V26	V26A	V27	P28	V26B
Time of visit (weeks)		-10	-8	-7 -6 -5	-4	-3 -2	-1	0	1	2	3	4	5 6 7	8	9 10 11	12	13 14 15	16	At treat. discont.	+7 days	+30 days	16
Visit window (days)		+10	±3	±3	±3	±3	±3	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		+5	+5	±3
Technical complaint	12.1.6		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Medication error	12.1.4		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Body height	8.4.5	X																				
Body weight	8.4.5	X						X						X				X	X			
Physical examination	8.4.6	X						X										X				
Vital signs	8.4.7	X						X										X				
Eye examination	8.4.3	X[d]						X[e]										X[f]				
ECG	8.4.4	X[g]						X[f]										X[f]				
Biochemistry	8.5.2	X						X						X				X	X			
Haematology	8.5.2	X						X						X				X	X			
Pregnancy test[h]	8.5.2	X						X										X	X			
TRIAL MATERIAL																						
Dispensing visit	9.4		X		X			X		X		X		X		X						
New (prescribed) dose of trial insulin	8.3.3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					

NN1218-4357	Protocol section	Screening	8-week run-in period					Randomisation	16-week treatment period Blinded trial product									End of treatment	Premature discontinuation	Follow-up 1	Follow-up 2	Premature discontinuation
Visit (V) Phone contact (P)		V1	V2	P3 P4 P5	V6	P7 P8	V9	V10	P11	V12	P13	V14	P15 P16 P17	V18	P19 P20 P21	V22	P23 P24 P25	V26	V26A	V27	P28	V26B
Time of visit (weeks)		-10	-8	-7 -6 -5	-4	-3 -2	-1	0	1	2	3	4	5 6 7	8	9 10 11	12	13 14 15	16	At treat. discont.	+7 days	+30 days	16
Visit window (days)		+10	±3	±3	±3	±3	±3	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		+5	+5	±3
Dosing (start/stop date of trial insulin)[i]	8.3.3		X					X										X	X			
Dose of basal & bolus insulin[k]	8.3.3		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			
IWRS session	10	X	X		X		X	X		X		X		X		X		X	X			
REMINDERS																						
Attend visit fasting[j]	8.1.5							X						X				X	X			
Hand out ID card	8.1.1	X																				
Confirmation of unchanged metformin	8.2.6		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Hand out directions for use	9.2		X																			
Training in trial product, pen-handling	8.6.1		X		X			X				X		X								
Training in pen differentiation	8.6.1		X					X				X		X								
Hand out pen differentiation guide	9.2		X					X														
Hand out and instruct in diary	8.6.2	X	X		X		X	X		X		X		X		X		X	X	X		

NN1218-4357	Protocol section	Screening	8-week run-in period					Randomisation	16-week treatment period Blinded trial product									End of treatment	Premature discontinuation	Follow-up 1	Follow-up 2	Premature discontinuation
Visit (V) **Phone contact (P)**		V1	V2	P3 P4 P5	V6	P7 P8	V9	V10	P11	V12	P13	V14	P15 P16 P17	V18	P19 P20 P21	V22	P23 P24 P25	V26	V26A	V27	P28	V26B
Time of visit (weeks)		-10	-8	-7 -6 -5	-4	-3 -2	-1	0	1	2	3	4	5 6 7	8	9 10 11	12	13 14 15	16	At treat. discont.	+7 days	+30 days	16
Visit window (days)		+10	±3	±3	±3	±3	±3	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		+5	+5	±3
Collect and review diary data	8.6.2		X		X		X	X		X		X		X		X		X	X	X		X
Hand out and instruct in BG-meter	8.3.2		X																			
End of treatment	8.1.7									,								X	X			
End of trial																					X	X

Footer	Description
a	A 4-point SMPG profile should be performed on the three days prior to the visit/phone contact during the run-in and treatment period of the trial for titration purposes. The 4-point SMPG profiles can be part of the 7-9-7 point SMPG profile as appropriate.
b	The 7-9-7 point profiles should be measured on 3 consecutive days prior to the scheduled site visit.
c	SAEs only.
d	If an eye examination has been performed within the past 90 days prior to screening or in the period between screening and V2, and if the results are available at V2 then the procedure does not need to be repeated.
e	An eye examination must be performed at the randomisation visit (V10) or within 14 days prior to V10 (the results do not need to be available for randomisation).
f	ECG and eye examination obtained within 3 weeks prior to the visit is acceptable if the result is available at the visit.
g	ECG obtained less than 3 weeks prior to V1 as part of routine practice can replace the screening assessment if the results are available at V1.
h	Serum-HCG pregnancy testing should be performed on females with childbearing potential at visit indicated in the flowchart (analysed by central laboratory). If pregnancy is suspected between visits, a urine pregnancy test should be done locally. If test shows positive, then a confirmatory serum-HCG test should be sent to the central laboratory.
i	Start/stop date of trial product depending on when the subject discontinues/completes treatment.
j	Fasting is defined as at least 8 hours without drink or food intake (only water is allowed). If the subject attends the clinic in a non-fasting condition then the visit should be re-scheduled within the visit window. Diabetic medication should be withheld on the day of the visit until all blood samples have been taken.
k	On the last three days prior to visit/phone contact

3 Background information and rationale for the trial

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

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

3.1 Background information

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

Basal-bolus insulin therapy aims at mimicking the physiological insulin response in the healthy state to the largest possible extent. For that purpose, rapid-acting insulin analogues were developed to more effectively control the PPG excursions compared to subcutaneously injected human regular insulin, primarily through offering a faster onset and shorter duration of action. However, unmet needs exist within prandial insulin therapy for people with diabetes. The current insulin analogues are not able to match the speed of the normal physiological post meal insulin secretion, leading to suboptimal control of blood glucose, and an exogenous insulin with a faster glucose lowering effect is needed for tighter PPG control. In addition, a faster glucose lowering effect is also likely to offer greater flexibility in the time of dosing around meals thus increasing convenience for the patients and may allow the patients to better match the insulin taken to the meal.[7]

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

3.1.1 Therapeutic area

T1DM is a chronic disorder characterised by insulin deficiency and progressive complications due to hyperglycaemia. In T1DM a common treatment regimen is a basal-bolus therapy which was confirmed to be effective in reducing the incidence of late diabetic complications in the Diabetes Control and Complication Trial (DCCT).[2] The ADA recommends an HbA_{1c} target of less than 7.0% (<53 mmol/mol), without substantial hypoglycaemia.[8]

Due to the progressive nature of T2DM, many patients are likely to be candidates for intensified insulin therapy. Prandial insulin supplementation is recommended by European Association for the Study of Diabetes (EASD)/ADA guidelines[9] for treatment intensification in patients with T2DM who do not reach an HbA_{1c} target below 7.0% on oral antidiabetic drugs (OADs) and basal insulin

alone. The recommendation is a stepwise addition of bolus insulin when significant PPG excursions occur. A trial investigating step-wise addition of bolus insulin (basal-plus regimen) showed that around 75% of patients enrolled in the trial needed three boluses after 36 weeks of treatment in order to achieve an HbA_{1c} below 7.0%.[10] Results from the PREFER[11] trial indicated that one-third of the total prandial insulin dose is delivered with each meal in the majority of patients achieving HbA_{1c} ≤7.0%. When used as part of a basal-bolus regimen in patients with T2DM who had previously received other insulin and/or OAD regimens, insulin aspart in combination with insulin degludec was a safe, well tolerated and effective treatment associated with clinically relevant reductions in hyperglycaemia.[12]

3.1.2 NovoRapid® (Insulin aspart)

Insulin aspart has been marketed in China since 2002, is marketed worldwide as NovoRapid® (US: NovoLog®) and is a rapid-acting insulin analogue indicated for the treatment of diabetes. In the remainder of this protocol, NovoRapid® will be applied as the trade name for insulin aspart in the marketed formulation.

NovoRapid® is homologous to human insulin, with the exception of the substitution of proline with aspartic acid at position B28. The rapid action of NovoRapid® is related to a weakened tendency of the insulin molecules to self-associate due to this modification and thereby is related to faster absorption as compared with regular human insulin. Compared with human insulin, NovoRapid® has a faster onset and a shorter duration of action, resulting in superior postmeal glucose control by means of lowering total glucose excursion following a meal, both in subjects with T1DM[13, 14] and in subjects with T2DM.[15-17] This also allows NovoRapid® to be injected immediately before a meal, in contrast to regular human insulin which should be injected 30 minutes prior to the meal. For further details, please refer to the current version of the NovoRapid® local labelling.[18, 19]

3.1.3 Fast-acting insulin aspart

Fast-acting insulin aspart (hereafter referred to as faster aspart, marketed as Fiasp®) is an innovative formulation of insulin aspart with two additional excipients which results in an increased early absorption of insulin aspart following subcutaneous injection. This leads to a greater early glucose-lowering effect compared to NovoRapid®.[20] Faster aspart aims at approaching the physiological prandial insulin secretion pattern better than currently available treatment and thereby more effectively controlling the PPG excursions and achieving a better PPG control and increased flexibility in the time of dosing around meals compared with NovoRapid®. Results from clinical pharmacology trials in adults comparing pharmacokinetic and pharmacodynamic properties of faster aspart and NovoRapid® have shown that faster aspart resulted in an earlier onset of appearance and a greater early exposure to insulin aspart than NovoRapid® in subjects with T1DM, with the largest difference found within the first 15 minutes after injection. Faster aspart also

resulted in a greater early glucose-lowering effect than NovoRapid®, but no statistically significant difference was found between faster aspart and NovoRapid® in total glucose-lowering effect.

In the global phase 3a programme, treatment with mealtime faster aspart effectively improved HbA_{1c} in both subjects with T1DM and subjects with T2DM confirming non-inferiority between faster aspart and NovoRapid®. [21, 22] In a therapeutic confirmatory basal-bolus trial in adult subjects with T1DM, mealtime faster aspart in combination with insulin detemir effectively improved glycaemic control and the reduction in HbA_{1c} was statistically significantly greater than with NovoRapid®. Mealtime faster aspart provided superior PPG control compared to NovoRapid® based on 2-hour PPG increment during a meal test. A statistically significant difference was also demonstrated for 1-hour PPG increment (meal test) in favour of mealtime faster aspart. No statistically significant difference was seen in overall rate of severe or blood glucose (BG) confirmed hypoglycaemic episodes between mealtime faster aspart and NovoRapid®. The rate during the first one hour after start of a meal, constituting a smaller fraction of all severe or BG confirmed hypoglycaemic episodes was statistically significantly higher for faster aspart compared to NovoRapid®. The overall safety profile for faster aspart and NovoRapid® was similar and as expected for insulin aspart.

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

Across the global phase 3a trials, faster aspart was well tolerated with similar safety profile as compared to NovoRapid®, with the most common adverse event being hypoglycaemia, similar to the levels observed with NovoRapid®.[21, 23] The insulin aspart molecule has a well-known safety profile based on more than 19 years of clinical experience. Compared to NovoRapid® faster aspart contains excipients which results in a faster initial absorption of insulin aspart following subcutaneous injection. The added excipients are included in the U.S. Food and Drug Administration's (FDA) list for approved drug products for injections, and no toxicological concerns have been predicted from subcutaneous use in humans at the proposed concentrations. For further details, please refer to the current edition of the Investigator's Brochure (IB)[24] and any updates hereof.

At the time of this protocol issuance, faster aspart is approved in more than 40 countries including USA, the European Union, Australia, Canada, Switzerland, South Korea and India. Submission and approval processes are currently ongoing in multiple countries worldwide.

3.1.4 Insulin Degludec

Insulin degludec (marketed as Tresiba®) was approved in China in September 2017, and is a basal insulin with an ultra-long duration of action for once-daily subcutaneous administration at any time of the day, preferably at the same time every day. After subcutaneous injection, soluble and stable multi-hexamers are formed creating a depot of insulin in the subcutaneous tissue. Insulin degludec monomers gradually separate from the multihexamers thus resulting in a slow and continuous delivery of insulin degludec into the circulation, leading to the observed ultra-long pharmacokinetic and pharmacodynamic profiles and thereby a flat and stable glucose-lowering effect. The duration of action of insulin degludec is beyond 42 hours within the therapeutic dose range.

For further details please refer to the current version of the Tresiba® local labelling. [25, 26]

At the time of this protocol issuance, insulin degludec is approved in more than 90 countries including US, all EU countries and Japan.

3.2 Rationale for the trial

The purpose of this trial is to confirm the effect and evaluate the safety of faster aspart compared to NovoRapid® both in combination with insulin degludec with or without metformin in Chinese subjects with T1DM or T2DM.

In the European Medicines Agency (EMA), U.S. Food and Drug Administration (FDA) and China Food and Drug administration (CFDA) 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.[27-29]

The results from this trial will be used in the registration file in China to document the efficacy and safety of faster aspart as meal time insulin in combination with basal insulin (basal-bolus regimen) in Chinese subjects with T1DM or T2DM.

The trial is intended to confirm the effect of faster aspart by demonstrating non-inferiority (at 0.4 % level) of faster aspart compared to NovoRapid® in terms of glycaemic control and testing for superiority of faster aspart in terms of glycaemic control in Chinese subjects with T1DM or T2DM.

4 Objectives and endpoints

4.1 Objectives

4.1.1 Primary objective

To confirm the effect in terms of glycaemic control of treatment with faster aspart compared to NovoRapid® both in combination with insulin degludec with or without metformin in Chinese adults with T1DM or T2DM inadequately treated with a basal-bolus or a premix regimen, using a non-inferiority approach.

4.1.2 Secondary objective

To compare the safety of faster aspart to NovoRapid® both in combination with insulin degludec with or without metformin in Chinese adults with T1DM or T2DM inadequately treated with a basal-bolus or a premix regimen.

4.1.3 Primary estimand

The primary estimand is defined as the treatment difference in change from baseline in HbA_{1c} 16 weeks after randomisation between treatment with faster aspart and treatment with NovoRapid® both in combination with insulin degludec with or without metformin in adult subjects with T1DM or T2DM on basal-bolus regimen with a basal optimisation if all had adhered to randomised treatment. This estimand aims to reflect the treatment effect for subjects that are actually able to take the drug during the intended treatment period.

4.2 Endpoints

Baseline is defined as randomisation (V10, week 0).

4.2.1 Primary endpoint

- Change from baseline (week 0) in HbA_{1c} to 16 weeks after randomisation

4.2.2 Secondary endpoints

4.2.2.1 Supportive secondary efficacy endpoints

- Change from baseline in 30-minutes, 1-hour, 2-hour and 3-hour PPG increment to 16 weeks after randomisation (meal test)
- Change from baseline in 30-minutes, 1-hour, 2-hour and 3-hour PPG to 16 weeks after randomisation (meal test)
- Change from baseline in FPG to 16 weeks after randomisation
- If a subject achieves HbA_{1c} target 16 weeks after randomisation:
  - $HbA_{1c} < 7.0\%$

- HbA_{1c} < 7.0% without severe hypoglycaemia

- Change from baseline in 7-9-7-point SMPG to 16 weeks after randomisation:
  - Mean of the 7-9-7-point profile
  - 1-hour PPG and PPG increment (mean, breakfast, lunch, main evening meal)
  - Fluctuation in 7-9-7-point profile
- If a subject achieves PPG target (overall mean of daily PPG measurements in SMPG) 16 weeks after randomisation:
  - Overall PPG (1-hour) ≤7.8 mmol/L
  - Overall PPG (1-hour) ≤7.8 mmol/L without severe hypoglycaemia
- Insulin dose (Units/day and Units/kg/day; total basal, total bolus and individual meal insulin dose) 16 weeks after randomisation

4.2.2.2 Supportive secondary safety endpoints

- Number of treatment emergent adverse events during the 16 weeks after randomisation
- Number of treatment emergent injection site reactions during the 16 weeks after randomisation
- Number of treatment emergent hypoglycaemic episodes classified both according to the ADA definition and Novo Nordisk definition during the 16 weeks after randomisation
  - Overall
  - Daytime and nocturnal hypoglycaemic episodes (00:01-05:59 – both inclusive)
  - Hypoglycaemic episodes from start of meal until 30 minutes, 1, 2, 4 hours and from 2 hours (exclusive) to 4 hours (inclusive) after start of meal

5 Trial design

5.1 Type of trial

This is a phase 3a, 16-week, multicentre, 1:1 randomised, double-blind, active controlled, treat-to-target, two-arm parallel group, non-inferiority trial with an 8-week run-in period comparing the effect and safety of faster aspart to NovoRapid® both in combination with insulin degludec with or without metformin in subjects with T1DM or T2DM inadequately treated with a basal-bolus or a premix regimen.

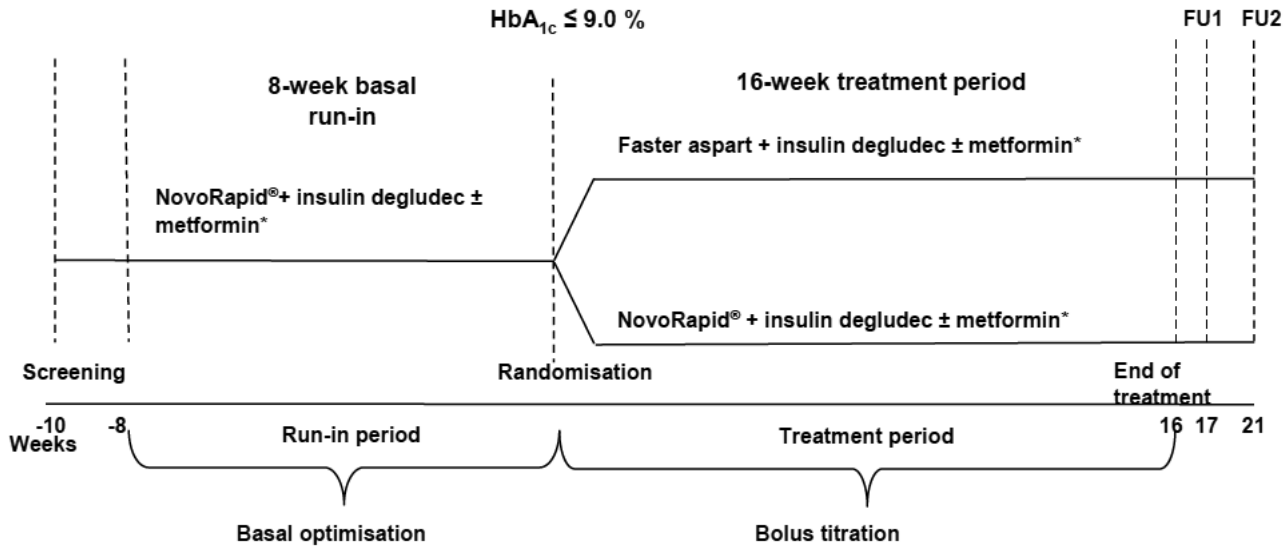


Figure 5–1 Trial design

*Treatment with metformin is only applicable for subjects with T2DM treated with metformin prior to the trial.

The trial design is summarised in Figure 5–1.

The total duration of the trial is approximately 30 weeks divided into the following periods:

- An approximately 2-week screening period
- An 8-week run-in period primarily for optimisation of the basal insulin treatment
- A 16-week treatment period
- A 30-day follow-up period: FU1; 7 days after end of treatment and FU2; 30 days after end of treatment

The trial includes a screening visit to assess subject's eligibility and additional weekly visits/phone contacts during the trial. After screening, all eligible subjects will be enrolled in an 8-week run-in

period. All subjects eligible for the trial will receive the basal insulin degludec once daily. After the run-in period, subjects eligible for randomisation ($HbA_{1c} \leq 9.0\%$ measured at visit 9) will be randomised (1:1) to receive double blinded treatment with either faster aspart or NovoRapid® both in combination with once daily insulin degludec with or without metformin. To aim for an even distribution of treatment groups within T1DM and T2DM, the randomisation will be stratified according to the type of diabetes.

All subjects will have a standardised meal test at baseline (V10 before randomisation) and at end of treatment (V26/V26A). The meal test will be described in more details in Section 8.3.1.

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

5.2 Rationale for trial design

The 8-week run-in period has been included to ensure the subjects are being trained in the trial procedures and that the basal insulin titration is optimised. A 16-week treatment period is needed to obtain valid and adequate efficacy and safety data.

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

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

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

5.2.1 Rationale for choice of non-inferiority margin

In a recently finalised faster aspart trial (NN1218-4049, data on file) with a bolus insulin naïve T2DM adult population comparing a basal insulin treatment in addition to metformin to a full basal-bolus insulin treatment in addition to metformin the estimated treatment effect in change from baseline HbA_{1c} was - 0.94% [-1.17; -0.72]. In this trial the addition of three times daily faster aspart led to a reduction in HbA_{1c} of 1.16% after 18 weeks of treatment. In a similar phase 4 trial[30] investigating the stepwise addition of NovoRapid® to a full basal-bolus regimen in bolus naïve T2DM adults the observed reduction in HbA_{1c} after 21 weeks of treatment was 1.15% (data ANA-3786, data on file) with 3 times daily NovoRapid® added to basal insulin. This gives some indication that the effect of NovoRapid® versus placebo would be close to the 0.94% observed in trial NN1218-4049. Thus using a non-inferiority margin of 0.4%, one of the suggested margins in the FDA guidance[28], an improvement of approximately 0.54% would have been preserved using the 0.4% non-inferiority margin. In a faster aspart trial (NN1218-3852) with a T1DM adult population, the HbA_{1c} reduction from baseline to end of trial was larger with mealtime faster aspart when

compared to mealtime NovoRapid®. Therefore using a non-inferiority margin of 0.4% in a population with both T1DM and T2DM subjects, the improvement would be expected to be preserved.

5.3 Treatment of subjects

At V2, eligible subjects will be enrolled in a run-in period where all subjects will be switched from their pre-trial insulin treatment to basal insulin degludec once daily and bolus insulin NovoRapid® thrice daily as described in the titration guideline (Appendix A1 and A2) with or without metformin.

Subjects with T2DM treated with metformin prior to the trial should continue with their pre-trial dose of metformin. The dose and dosing frequency of metformin should not be changed at any time during the trial, unless due to safety concerns. For T2DM subjects treated with alpha-glucosidase inhibitor, SGLT2i and DPP4i prior to the trial, the OAD(s) must be stopped at the run-in visit (V2). Initiation of any other diabetes treatment is not allowed during the screening, run-in or treatment period and must be reported (see Section 8.2.5). This includes metformin for subjects with T2DM not treated with metformin prior to the trial. During the run-in period, the investigator will focus on optimising the basal insulin treatment using a treat-to-target approach following the titration guideline (Appendix A1 and A2). The bolus insulin will not be titrated during the run-in period unless the investigator finds it necessary to adjust the bolus insulin for safety reasons.

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

In the treatment period, eligible subjects will receive double blinded treatment with either faster aspart or NovoRapid® both in combination with once daily insulin degludec with or without metformin. The investigator should focus on optimising the bolus insulin treatment following the bolus dosing algorithm as described in the titration guideline (Appendix A1 and A2). Surveillance of insulin titration will be performed by Novo Nordisk.

Throughout the trial the bolus insulin (faster aspart or NovoRapid®) should be administered 0-2 minutes prior to the three main meals (i.e. breakfast, lunch and main evening meal). Additional bolus dosing is allowed at the discretion of the investigator.

The maximum duration of treatment will be 24 weeks including the run-in period. No maximum dose is specified. Doses are adjusted according to SMPG values (Appendix A1 and A2).

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

5.4 Treatment after discontinuation of trial product

When discontinuing trial products (either prematurely or at end of treatment), the subject should be switched to a suitable marketed product at the discretion of the investigator. Doses of subsequent anti-diabetic treatment should be carefully titrated based on BG measurements.

5.5 Rationale for treatment

Based on the currently available pharmacokinetic data on faster aspart, it is anticipated that treatment with faster aspart as a mealtime insulin will enable insulin therapy to more closely approach a physiologic insulin secretory pattern. Consequently, the PPG excursions may be more effectively controlled. For further details, please refer to the current version of the faster aspart IB.[24]

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

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

Combination of insulin treatment with metformin in T2DM subjects is associated with better glycaemic control, fewer hypoglycaemic events, and less weight gain than treatment with insulin alone, therefore metformin should be continued when T2DM subjects are on insulin therapy.

6 Trial population

6.1 Number of subjects

Number of subjects planned to be screened: 505

Number of subjects planned to be included in the run-in period: 353

Number of subjects planned to be randomised: 300

At least 20% of the subjects randomised are expected to be subjects with T1DM.

A screening failure rate of approximately 30% and a run-in failure rate of approximately 15% are anticipated for this trial.

6.2 Inclusion criteria

For an eligible subject, all inclusion criteria must be answered “yes”.

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial
2. Male or female, age above or equal to 18 years at the time of signing informed consent
3. Diagnosed with T1DM ≥ 1 year prior to screening (V1) or diagnosed with T2DM ≥ 5 years prior to screening (V1)
4. Treated with a basal-bolus insulin regimen or a premix insulin regimen ≥ 1 year prior to the day of screening (V1). Insulin regimen must be unchanged within 60 days prior to screening. A basal-bolus insulin regimen is defined as basal insulin once or twice daily and bolus insulin taken with meals at least thrice daily. A premix insulin regimen is defined as premix insulin twice or thrice-daily
5. For subjects with T1DM: not treated with any OADs for at least 90 days prior to screening (V1).
   For subjects with T2DM: not treated with any OADs or treated with 1-2 OADs within 90 days prior to screening (V1). Allowed OADs are metformin, alpha-glucosidase inhibitor, SGLT2i and DPP4i. Change in OAD and dose is allowed prior to screening
6. HbA_{1c} 7.5-9.5% (both inclusive) as assessed by central laboratory at screening (V1)
7. Able and willing to adhere to the protocol including performance of SMPG profiles and meal tests
8. Able and willing to consume 3 main meals (breakfast, lunch and dinner) daily throughout the trial

The criteria will be assessed at the investigator’s discretion unless otherwise stated.

6.3 Exclusion criteria

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

1. Known or suspected hypersensitivity to trial product(s) or related products
2. Previous participation in this trial. Participation is defined as signed informed consent
3. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using an adequate contraceptive method. Adequate contraceptive measures in China are defined as sterilisation, intrauterine device (IUD), oral contraceptives or barrier methods
4. Participation in any clinical trial of an approved or non-approved investigational medicinal product within 30 days before screening (V1). Clinical trials do not include non-interventional studies
5. Any disorder, except for conditions associated with diabetes, which in the investigator's opinion might jeopardise subject's safety or compliance with the protocol
6. Anticipated change in lifestyle (such as eating, exercise or sleeping pattern) during the trial
7. Any of the following: myocardial infarction, stroke, hospitalisation for unstable angina pectoris or transient ischaemic attack within the past 180 days prior to the day of screening (V1)
8. Subjects presently classified as being in New York Heart Association (NYHA) Class IV
9. Planned coronary, carotid or peripheral artery revascularisation known on the day of screening (V1)
10. Inadequately treated blood pressure defined as Grade 3 hypertension or higher (systolic ≥180 mmHg or diastolic ≥110 mmHg) at screening (V1)
11. Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria within the past 90 days prior to the day of screening (V1)
12. Anticipated initiation or change in concomitant medications (for more than 14 consecutive days) known to affect weight or glucose metabolism (e.g. treatment with orlistat, thyroid hormones, or corticosteroids)
13. Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a fundus examination performed within the past 90 days prior to screening or in the period between screening and run-in (V2). Pharmacological pupil-dilation is a requirement unless using a digital fundus photography camera specified for non-dilated examination
14. Presence or history of malignant neoplasms within the past 5 years prior to the day of screening. Basal and squamous cell skin cancer and any carcinoma in-situ are allowed
15. Any episodes of diabetic ketoacidosis within the past 90 days prior to the day of screening (V1)
16. Renal impairment measured as estimated Glomerular Filtration Rate (eGFR) value of eGFR < 30 mL/min/1.73 m^2 as defined by KDIGO 2012
17. Impaired liver function, defined as Alanine Aminotransferase (ALT) ≥ 2.5 times or Bilirubin >1.5 times upper normal limit at screening (V1)

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

The criteria will be assessed at the investigator's discretion unless otherwise stated.

6.4 Run-in period exclusion criteria

The subject must be withdrawn from the trial during the run-in period if the following applies after the screening visit (V1), and before or at randomisation (V10):

1. Included in the trial in violation of the inclusion and/or exclusion criteria
2. Pregnancy
3. Intention of becoming pregnant
4. Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product
5. Any disorder which in the investigator's opinion might jeopardise subject's safety or compliance with the protocol
6. Inability or lack of willingness to adhere to the protocol, based on the investigator's judgement

6.5 Randomisation criterion

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

1. $HbA_{1c} \leq 9.0\%$ measured by the central laboratory at V9 - one week before randomisation

6.6 Criteria for premature discontinuation of trial products

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

The subject may be prematurely discontinued from trial products at the discretion of the investigator due to a safety concern and must be prematurely discontinued from trial products if the following applies after randomisation:

1. Included in the trial in violation of the inclusion and/or exclusion criteria and/or randomised in violation of the randomisation criterion
2. Pregnancy
3. Intention of becoming pregnant

4. Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product anytime during the treatment period

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

6.7 Withdrawal from trial

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

A subject is considered withdrawn from trial if the following applies before V26:

1. Subject is lost to follow up (see Section 8.1.10.1)
2. Subject withdraws consent
3. Death

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

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

6.8 Subject replacement

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

6.9 Rationale for trial population

The trial population consists of adult subjects with T1DM or T2DM who have been treated with a basal-bolus insulin or a premix insulin regimen for at least 1 year, but are not optimally controlled as demonstrated by an $HbA_{1c} \geq 7.5\%$ at screening, and may benefit from intensified insulin treatment using a treat-to-target approach. The treatment strategy e.g. basal-bolus insulin regimen and glycaemic target are similar for both groups, as recommended by EASD/ADA and Chinese Diabetes Society (CDS) guidelines for diabetes.[9, 31, 32] The basal-bolus treatment has been confirmed to be effective in both T1DM subjects and advanced T2DM subjects. For subjects with T2DM, the clinical diagnosis should be at least 5 years prior to screening to ensure more progressed disease requiring a full basal-bolus insulin supplementation. The subjects need to be on a basal-bolus insulin regimen or a premix insulin regimen for at least 1 year in order to ensure that they have been adequately educated and are familiar with using the intensive regimen required in this trial. This will also help to avoid including newly diagnosed patients that could enter in the metabolic remission period.

Subjects with an $HbA_{1c} > 9.5\%$ are not included in this trial. This is because the trial protocol requires strict adherence and good subject compliance and a likely cause of elevated $HbA_{1c} > 9.5\%$

in a diabetic subject is poor compliance with treatment regimens or an atypical course of the disease. The upper HbA_{1c} limit is also expected to select a population that can achieve adequate basal insulin coverage in the 8-week run-in basal insulin titration period. Subjects in relative good glycaemic control defined as HbA_{1c} <7.5 % may not significantly benefit from this trial and hence the lower cut-off value has been chosen.

7 Milestones

Planned duration of recruitment period (i.e. First Subject First Visit (FSFV) to Last Subject First Visit (LSFV)) is 18 months.

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

Recruitment:
The screening and randomisation rate will be followed closely via the interactive web response system (IWRS) in order to estimate when to stop screening. The ratio of randomised subjects with T1DM (minimum 20%) and subjects with T2DM (maximum 80%) will be controlled by the IWRS. All investigators will be notified immediately when the recruitment period ends or when the maximum number of subjects with T2DM has been reached, after which no further subjects may be screened and the IWRS will be closed for further screening. Subjects screened and found eligible can be randomised.

Trial registration:
Information of the trial will be disclosed at clinicaltrials.gov, chinadrugtrials.org.cn and novonordisk-trials.com. According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure[33], it will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE)[34], the Food and Drug Administration Amendment Act (FDAAA)[35] European Commission Requirements[36, 37] and other relevant recommendations or regulations including requirements by the China Food and Drug administration (CFDA). If a subject requests to be included in the trial via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the subject. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

The Primary Completion Date (PCD) is the last assessment of the primary endpoint, and is for this trial Last Subject First Treatment + 16 weeks corresponding to V26. If the last subject is withdrawn/dropout early the PCD is considered the date when the last subject would have completed V26. The PCD determines the deadline for the results disclosure at clinicaltrials.gov according to FDAAA.

8 Methods and assessments

The following sections describe the assessments and procedures. These are also included in the flow chart (see Section 2) along with their timing.

8.1 Visit procedures

8.1.1 Screening (V1)

Informed consent must be obtained before any trial related activity, see Section 18.2.
All subjects must be provided with a copy of their own signed and dated informed consent form.

Subjects will continue on their current diabetes treatment until start of the run-in period (V2) and they will not be supplied with any trial products until then.

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.

A screening session must be performed in the IWRS, see Section 10. Each subject will be assigned a unique 6-digit subject number which will remain the same throughout the trial. The investigator must keep a subject screening log, a subject identification code list and a subject enrolment log. Only subjects who have signed the informed consent form should be included on the logs. The subject screening log and subject enrolment log may be combined in one log.

Inclusion or exclusion criteria should not be answered “Yes” or “No” in the electronic case report form (eCRF) before source data is available. For central laboratory results, ECG and eye examination evaluations “Result pending” can be answered. Answers to these criteria should be changed to “Yes” or “No” when results and/or evaluations are available.

The investigator is required to make a reasonable effort to obtain necessary additional information from external sources e.g. primary physician and other hospitals/departments to document the subjects’ eligibility. Unless otherwise mentioned, all concomitant illness and medical history related to the inclusion and exclusion criteria are based on source documents such as the subject's medical record. It is the responsibility of the investigator to have sufficient evidence to ensure eligibility.

Screening failures
For screening failures, the end of trial form in the eCRF must be completed with the reason for not continuing in the trial. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet requirements from regulatory authorities. Minimal information includes date of informed consent, demography, screen failure details, eligibility criteria, and any SAE (serious adverse events). SAEs from screening failures

must be transcribed by the investigator into the eCRF. Follow-up on SAEs must be carried out according to Section 12.
A screening failure session must be made in the IWRS and the case book must be signed.

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

8.1.2 Run-in (V2)

If the subject is found eligible to continue in the trial the subject will enter an 8-week run-in period. V2 can take place as soon as the subject has been found eligible and must take place no later than 17 days after V1.

At start of the run-in period (V2), the subject will receive the trial products; basal insulin (insulin-degludec) and bolus insulin (NovoRapid®) (Section 9). The subject must be trained in how to handle the insulin pen-injectors (Section 8.6.1). Training may be repeated during the trial. Date of first trial products must be recorded in the eCRF.

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

The BG meter, BG meter test strips and a diary must be provided to the subject at V2. Subjects must be trained in use of the BG meter and completion of the diary.

Run-in failures
Subjects fulfilling any of the run-in period exclusion criteria, not fulfilling the randomisation criterion or withdrawing from trial during the run-in period are considered as run-in failures. Consequently, a run-in failure session must be made in the IWRS and a run-in failure form must be completed in the eCRF together with the reason for not continuing in the trial. The last date of trial product must be captured in the eCRF. No follow-up visit should take place and no additional assessments are needed.

SAEs and non-serious AEs from run-in failures must be recorded by the investigator in the eCRF. Follow-up of AEs must be carried out according to Section 12.3.

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

8.1.3 Randomisation (V10)

If the subject meets the randomisation criterion as measured at V9, the subject will at V10 be randomised into one of the two treatment arms using an IWRS randomisation session. A drug accountability session confirming dispensing of allocated trial products should also be performed.

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

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

8.1.4 Phone contacts

Before any phone contact, both the investigator and subject should agree on the timing and direction of the call. The investigator remains responsible for ensuring that the phone contacts occur even if it is agreed that the subject should call the site. A phone contact may be converted to a site visit if needed.

8.1.5 Fasting visits

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

Insulin dosing (including basal insulin) and medication which should be taken with or after a meal should be withheld until blood sampling has been performed. If a subject attends the visit non-fasting, then the subject's blood samples, meal test and body weight measurement should be re-scheduled within the visit window and at V10 before randomisation to trial product.

8.1.6 Rescheduled visits

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

8.1.7 End of treatment (V26)

At end of treatment (V26) trial products must be discontinued and an IWRS completion session must be performed. Last date on the basal and bolus trial insulins must be recorded in eCRF.

The subject should be switched to a suitable marketed product(s) at the discretion of the investigator.

8.1.8 Follow-up period

The follow-up visit 1 (V27) is a site visit and should take place 7-12 days after the end of treatment visit. Follow-up contact 2 (P28) is a phone contact and should take place 30-35 days after the end of treatment visit.

Follow-up visit 1
The following data will be collected:

- AEs
- Concomitant medication
- Current diabetes medication
- Hypoglycaemic episodes
- Additional information on injection site reactions (see Section 8.4.1.2)

Follow-up contact 2
The following data will be collected:

- AEs
- Concomitant medication
- Current diabetes medication

8.1.9 Premature discontinuation of trial products

If a subject prematurely discontinues trial products after randomisation (V10), the investigator must undertake procedures as included for V26A as soon as possible (see flowchart Section 2). Subjects who prematurely discontinue trial products during the run-in period before randomisation are considered run-in failures.

Subjects should perform a 7-9-7 point SMPG profile before discontinuing trial products.

Subjects should attend V26A in a fasting state and should undergo the meal test before discontinuing trial products. The meal test should be performed with bolus trial insulin. If it is not feasible due to safety reasons including pregnancy as judged by the investigator the meal test should be performed with the marketed bolus analogue the subject is switched to. The meal test should not be performed if the subject is switched to premix insulin treatment or basal-bolus treatment using regular human insulin as bolus insulin.

In addition, a blood sample for measuring HbA_{1c} must be collected.

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

The subject should be switched to a suitable marketed product at the discretion of the investigator.

The subject should also complete the follow-up visits (FU1 and FU2) 7 days (+5 days) and 30 days (+ 5 days) after discontinuation of trial product.

Finally, subjects prematurely discontinued from trial products should attend V26B at the time corresponding to 16 weeks after randomisation, where the following assessments will be done:

- Blood sample to measure HbA_{1c}
- SAEs
- Concomitant medication (diabetes)

A subject that permanently discontinues trial product before the End of Treatment visit (V26), will be considered to be a treatment non-completer.

8.1.10 Withdrawal from trial

If a subject withdraws consent, and the subject agrees, the investigator must aim to undertake procedures similar to those for V26A as soon as possible (see flowchart Section 2). The investigator should encourage the subject to undergo the meal test at V26A, which should be done in a fasting state and before trial product is discontinued. The meal test should be performed with bolus trial insulin. If it is not feasible due to safety reasons including pregnancy as judged by the investigator the meal test should be performed with the marketed bolus analogue the subject is switched to. The meal test should not be performed if subject is switched to premix insulin treatment or basal-bolus treatment using regular human insulin as bolus insulin.

If the subject agrees, the follow up visits (FU1 (V27) and FU2 (P28)) must be performed 7 (+5 days) and 30 days (+5 days) after discontinuation of trial product.

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

Although a subject is not obliged to give his/her reason(s) for withdrawing consent, the investigator must make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights. Where the reasons are obtained, the primary reason for withdrawing consent must be specified in the end of-trial-form in the eCRF.

A subject that is withdrawn from trial before the End of Treatment Visit (V26), will be considered to be a treatment non-completer and a trial non-completer.

8.1.10.1 Lost to follow-up

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

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible
- The site must re-train the subject in the importance of maintaining the scheduled visits

In cases in which the subject is deemed lost to follow-up the investigator must make every effort to regain contact with the subject (e.g. via e-mail or certified letter to the subject as applicable). These contact attempts must be documented in the subject's medical records. Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the trial with the primary reason being "lost to follow-up".

8.1.11 Review of results

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

If it is needed to clarify entries or discrepancies in the diary, the subject must be questioned and a conclusion made in the subject's medical record. Care must be taken not to bias the subject. Any discrepancies or missing data points available elsewhere related to a 7-9-7 point profile or hypoglycaemic episodes must be corrected or added.

For ECGs, physical examinations and eye examinations, the evaluations must follow the categories:
- Normal
- Abnormal
  - Was the result clinically significant? (yes/no)

The evaluation should be based on investigator's judgement.

For laboratory report values outside the reference range, the investigator must specify whether the value is clinically significant or not clinically significant. Review of laboratory reports must be documented either on the documents and/or in the subject's medical record.

8.2 Subject related information/assessments

8.2.1 Demography

Demography will be recorded at screening and consists of:
- Date of birth (according to local regulation)
- Sex
- Ethnicity (according to local regulation)
- Race (according to local regulation)

8.2.2 Diabetes history

Diabetes history will be recorded at screening and consists of:

- Date of diagnosis of T1DM or T2DM

8.2.3 Hypoglycaemia unawareness

Information on hypoglycaemia unawareness will be recorded at screening according to Clarke's questionnaire, question 8.[38]
The investigator must ask the subject whether he/she has ever experienced a hypoglycaemic episode? If the subject answers "yes", the investigator must ask the subject in the following way: "To what extent can you tell by your symptoms that your blood glucose is low?" The subject can answer never, rarely, sometimes, often or always.

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

8.2.4 Concomitant illness and medical history

A **concomitant illness** is any illness that is present at the start of the trial (V1) or found as a result of a screening procedure or other trial procedures performed before exposure to trial product.

Date of diagnosis of T1DM or T2DM should be reported separately in the Diabetes History Form in the eCRF.

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

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

Diabetes complications will be recorded at screening as part of the Concomitant illness and medical history and consists of;

Information regarding diabetes complications including date of onset:

- Diabetic retinopathy
- Diabetic neuropathy
- Diabetic nephropathy
- Macroangiopathy (including peripheral vascular disease)

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 (Section 12.2).

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

8.2.5 Concomitant medication

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

Details of any concomitant medication must be recorded at V1. Changes in concomitant medication must be recorded at each visit as they occur.

The information collected for each concomitant medication includes:
- trade name or generic name
- indication
- start date and stop date or continuation

If a change is due to an AE, then this must be reported according to Section 12. If the change influences the subject's eligibility to continue in the trial, the monitor must be informed.

8.2.6 Concomitant medication (diabetes)

Any diabetes medication, other than the trial product(s) which is taken during the trial, including the screening, run-in, treatment and follow-up periods must be recorded in a separate concomitant medication (diabetes) form in the eCRF, including:
- trade name or generic name
- total daily dose
- frequency
- start date and stop date or continuation

For subjects treated with metformin it is the start date and dose of last metformin dose which should be reported.

At the run-in visit (V2), pre-trial insulin(s) and OADs except for metformin for T2DM subjects must be discontinued and a stop date recorded. For T2DM subjects treated with metformin, investigator should at each weekly contact (visit or phone contact), confirm with the subject that dose and frequency of metformin has been unchanged. This should be documented in the medical records.

At the randomisation visit (V10) run-in bolus insulin (NovoRapid®) must be discontinued and a stop date recorded.

8.2.7 Childbearing potential

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

Pregnancy testing must be performed on female subjects of childbearing potential as described in Section 8.5.2. Female subjects of childbearing potential must be instructed to use adequate contraceptive methods (sterilisation, IUD, oral contraceptives or barrier methods) throughout the trial and until 1 week after end of treatment.

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

8.2.8 Tobacco use

Details of tobacco use must be recorded at V1. Smoking is defined as smoking at least one cigarette or equivalent daily.
Smoking status:
- Never smoked
- Previous smoker, smoking stop date
- Current smoker

8.3 Efficacy assessments

8.3.1 Meal test

The subject will undergo a standardised liquid meal test at two visits (V10 and V26/V26A) (see flowchart Section 2) and will have their -2, 30, 60, 120 and 180 minutes PPG measured. The total duration of the meal test is expected to be up to 5 hours including preparations. During that time blood samples will be drawn for plasma glucose, as specified in Table 8–1.

Before initiation of the meal test

The subject should be instructed to:

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

The meal test should be re-scheduled within the visit window and at V10 before randomisation to trial product in case:

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

At V10 (randomisation visit) the investigator must evaluate if the subject is eligible to continue in the trial before the meal test is performed. Only subjects eligible for randomisation should have the V10 meal test performed. Thus, this assessment should not be performed for run-in failure subjects. Randomisation should not take place before the meal test has ended.

Bolus insulin dose and meal test carbohydrate amount

The standardised liquid meal will be provided by Novo Nordisk and contains approximately 90 grams of carbohydrates. The volume of the liquid meal to be consumed should be measured out by the investigator to be the equivalent to approximately 90 grams of carbohydrates.

The bolus insulin dose should be calculated by the investigator based on the dose level of 0.2 unit/kg body weight. Body weight must be measured prior to the meal test. The calculated dose should be rounded to the nearest whole unit. The 0.2 unit/kg dose is chosen as an approximation of a clinically relevant bolus dose needed for the given size of a standardised meal.

The insulin should be administered subcutaneously in the abdomen in accordance with Table 8–1.

Initiation of meal test

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

For the meal test at V10 the subject must receive the bolus insulin (NovoRapid®) that was used in the run-in period.

For the meal test at V26 or V26A (for subjects who have prematurely discontinued trial products) the subject should receive the bolus trial insulin they were randomised to and have used throughout the treatment period.

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

Table 8–1 Meal test schedule

Time point (minutes)	Blood sample	SMPG values	Standardised meal	Bolus insulin injection
Before start of meal test		X (within target range 4.0-8.8 mmol/L [71-160 mg/dL])		
-2	X			
0		X (as appropriate to ensure subject's safety)	X	X Insulin injection at the start of the meal
15				
30	X			
60	X			
120	X			
180	X			
End of meal test		X (for subject's safety)		

Conduct of meal test

The subject should stay in the clinic to have the blood samples drawn after -2, 30, 60, 120 and 180 minutes from the start of the standardised meal, as detailed in Table 8–1. The samples will be analysed by the central laboratory.

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

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

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

When the meal test at V10 is completed, the subject will be instructed to discontinue NovoRapid® and start treatment with randomised trial product. When the meal test at V26/V26A is completed, the subjects will be switched to a marketed insulin product according to investigator's discretion as detailed in section 8.1.7 and 8.1.9.

Data collection

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

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

Laboratory results from meal test data will be loaded directly into the trial database by the central laboratory. The meal test results will not be provided to the investigator until after LPLV in order to keep the blinding of the subject and investigator.

8.3.2 Self-measured plasma glucose

At V2, subjects will be provided with a BG meter including auxiliaries as well as instructions for use. The subjects will be instructed in how to use the device.

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

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

Subjects must be instructed in how to transfer/record the results of the SMPG values into the diary. For each SMPG value date, time and value will be included.

4-point self-measured plasma glucose profile

For insulin titration purposes, the subjects will be instructed to perform 4-point profiles in the diary on the three days prior to a scheduled site visit/phone contact every week from V2 to V26, or V26A for subjects who discontinue prematurely. The measurements should be performed at the following time points:

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

For 4-point SMPG measurements date and value should be transferred to/recorded in the diary, where each measurement should be assigned to the corresponding time point.

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

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

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

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

Time point	Day -3 7-point profile	Day -2 9-point profile	Day -1 7-point profile
Before breakfast	X	√	√(X)[a]
60 minutes after the start of breakfast	X	√	X
Before lunch	X	√	X
60 minutes after the start of lunch	X	√	X
Before main evening meal	X	√	X
60 minutes after the start of main evening meal	X	√	X
At bedtime	X	√	X
At 4 am		√	

[a]The last SMPG in the 9-point profile and the first SMPG of the 7-point profile on day-1 are overlapping.

For 7-9-7 point SMPG measurements actual clock time, date and value should be transferred to/recorded in the diary, where each measurement should be assigned to the corresponding time point.

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

The measurements will be used to evaluate the glucose profile.

8.3.3 Insulin dose

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

- Date and dose of basal and bolus insulin on the three days prior to a visit/phone contact from V2 to V26
- Date, actual clock time, and dose for other (extra) bolus insulin administration as well as time of previous main meal and reason for the extra bolus from V2 to V26 on the three days prior to a visit/phone contact.

Dosing and dose adjustment (new dose)

The recommended insulin doses should be calculated based on the measured SMPG values as described in the Insulin Titration Guideline (see Appendix A1 and A2) for subjects with T1DM or

T2DM, respectively. At each visit/phone contact the investigator will titrate the subjects by making prescribed dose adjustments based on the recommendations described in Appendix A1 and A2 if applicable and provide the new prescribed dose to the subject.

Please refer to Appendix A for data to be collected. Information on the first and last date of trial products must be recorded in the eCRF.

8.4 Safety assessments

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

8.4.1 Adverse events

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

8.4.1.1 Medication error

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

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

For definition of medication errors, see Section 12.1.4.

8.4.1.2 Adverse events requiring additional data collection

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

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

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

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

8.4.2 Hypoglycaemic episodes

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

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

should be reported in the diary by the subject from V2 to V27 (FU1) In case a subject is not able to fill in the diary e.g. in case of a fatal event, then investigator will be allowed to report the hypoglycaemic episode in the eCRF.

Upon onset of a hypoglycaemic episode the subject is recommended to measure PG every 15 minutes until the SMPG value is >3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved in accordance to current guidelines.[39]

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

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

The record should include the following information:
- Start date and time of the hypoglycaemic episode
- The PG level before treating the episode (if available) and any follow up measurements
  The lowest value measured during the hypoglycaemic episode will be reported as the PG value for the episode, the remaining values will be kept as source data in the diary

- Whether the episode was symptomatic (Yes/No)
  A hypoglycaemic episode starting without symptoms should be updated to symptomatic if the subject experiences symptoms later during the episode. The subject is therefore to be questioned whether there are changes to symptoms for each low SMPG value within the 60 minutes period or until the subject has confirmed that the hypoglycaemic episode is symptomatic
- Whether the subject was able to treat him/herself
- If the severity of a hypoglycaemic episode aggravates, only one hypoglycaemic episode should be reported reflecting the most severe degree of hypoglycaemia. The subject is therefore to be questioned whether he/she is able to self-treat for each low SMPG value within the 60 minutes period or until the subject respond that he/she is not able to self-treat. Date, time and dose of last bolus insulin administration prior to the episode
- Date, time and dose of last basal insulin administration prior to the episode
- Date and time of last main meal (not including snacks) prior to the episode
- Whether the episode occurred in relation to physical activity
- Change in any concomitant illness
- Any sign of fever and/or other acute disease
- Whether the subject was asleep when the episode occurred
  - If yes, whether the symptoms of the episode woke up the subject

The answer to the question: "Was the subject able to treat him/herself?" must be answered "No" for an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. PG concentrations may not be available during an event, but neurological recovery following the return of PG to normal is considered sufficient evidence that the event was induced by a low PG concentration.[39]

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

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

- Who assisted in the treatment of the hypoglycaemic episode (i.e. medical person or non-medical person)?
- Where the treatment was administered (in clinic/emergency room/hospital or other. If the subject was treated in clinic/emergency room/hospital, whether they were transported in an ambulance or not)
- Type of treatment provided by another person (i.e. oral carbohydrates, glucagon, IV glucose or other)
- Were symptoms alleviated after administration of treatment?
- Factors contributing to the episode (i.e. physical activity, missed meal, diet change, medication error (i.e. overdose, mix-up between products, incorrect use of device), miscalculation of dose of antidiabetic medication, other factors not listed or unknown)

- Did the subject experience seizure?
- Was the subject unconscious/comatose?
- Did the subject experience any of the following symptoms[40] (layman term used in the diary is specified in brackets if different from the protocol term)?
  - Autonomic: sweating, trembling, hunger or palpitations (rapid or irregular heart beat)
  - Neuroglycopenic: confusion, drowsiness, speech difficulty, visual disturbances, odd behaviour, impaired balance or incoordination (reduced ability to coordinate movement)
  - General malaise: headache or malaise (feeling discomfort/unease)
- Other symptoms

The investigator must review the diary data for correct reporting of SMPGs and hypoglycaemic episodes. In case of incomplete or incorrect data in the diary, the subject must be questioned whether there have been any severe hypoglycaemic episodes since the last visit, i.e. any hypoglycaemic episodes where the subject was not able to self-treat. Any severe hypoglycaemic episodes must be reported.

Low SMPG values for non-severe hypoglycaemic episodes not having a hypoglycaemic episode form completed within 7 days since the SMPG measurement should be reported on a hypoglycaemic episode form with as much information as possible. Novo Nordisk will not query for additional data except for the start date, SMPG value and whether the subject was able to self-treat due to decreased validity of such data[41, 42].

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

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

8.4.3 Eye examination

Subjects with uncontrolled and potentially unstable diabetic retinopathy or maculopathy are not eligible as this indicates retinopathy that has recently progressed to a level that requires intervention or is approaching intervention, but has yet to be brought under control.

Results of an eye examination performed by an ophthalmologist, or equally qualified certified health care provider (e.g. optometrist) must be available and evaluated by the investigator before V2 to assess eligibility (see Section 8.1.11). The eye examination should be performed as a fundus photography (e.g. 2-field 60 degree or better, colour or red-free) or by slit-lamp biomicroscopy examination (e.g. using a pre-corneal or corneal contact lens examination) and performed with pharmacologically dilated pupils unless using a digital fundus photography camera specified for non-dilated examination.

If the subject had such an eye examination performed within 90 days prior to screening, the investigator may base their evaluation upon the results of that examination. The examination must be repeated before V2 if the subject has experienced worsening of visual function since the last examination. If the applicable eye examination was performed before the subject signed the informed consent form, it must be documented that the reason for performing the examination was not related to this trial.

After V2 an eye examination performed according to above must be performed as per the flowchart in Section 2. An eye examination must be performed at the randomisation visit (V10) or within 14 days prior to V10 (the results do not need to be available for randomisation). If the eye examination is performed at V10, it must be performed prior to administration of randomised treatment. Eye examination obtained within 3 weeks prior to V26 is acceptable if the result is available at the visit. The investigator should indicate the outcome of each eye examination. Relevant findings prior to randomisation must be recorded as concomitant illness/medical history. Relevant findings occurring after randomisation should be reported as an AE, if applicable according to section 8.4.

8.4.4 Electrocardiogram (ECG)

A 12-lead ECG must be performed as per flow-chart (see Section 2) and the assessment must be reviewed as described in Section 8.1.11.

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

If an ECG-12 lead has been performed within 3 weeks prior to screening (V1), and the results are available at V1, the ECG does not need to be repeated at V1. If performed before the subject consents to participate in the trial it must be stated in the subject's medical records that this procedure was not performed in relation to the trial.

ECG obtained within 3 weeks prior to V10 and V26 is acceptable if the result is available at the visit.

8.4.5 Body Measurements

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

Body weight should be measured in kilograms (kg) or pounds (lb) without shoes and wearing only light clothing. Body weight must be measured prior to the start of the meal test at V10 and V26/V26A.

Body weight will be recorded to one decimal place. The body weight should be assessed on the same weighing scale throughout the trial, if possible.

BMI will automatically be calculated by the eCRF.

8.4.6 Physical examination

Physical examination will include examination of:

- Respiratory system
- Cardiovascular system
- Central and peripheral nervous system
- Gastrointestinal system, including the mouth
- Skin

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

8.4.7 Vital signs

Diastolic blood pressure, systolic blood pressure and pulse should be measured while the subject is in a sitting position and after 5 minutes of rest.

At screening (V1) blood pressure needs to be measured three times and all values should be recorded in the eCRF. The mean value will be calculated by the eCRF, and must be used to assess the relevant exclusion criterion; please see Section 6.3.

8.5 Laboratory assessments

Except for urine pregnancy testing, which will be performed locally, all laboratory analyses will be performed by a central laboratory contracted by Novo Nordisk. The central laboratory will provide all laboratory supplies for the sampling and transportation of all blood samples taken during the trial.

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

Laboratory samples can be drawn on another day than on the day of the actual visit, as long as it is within the visit window, as stated in the flowchart in Section 2.

If laboratory samples need to be retaken due to missing result(s) (e.g. haemolysed, sample leaked during transit, sample not being conclusive, lost in transit, etc.), the subject should be called in for resampling. Please see the laboratory manual for further guidance.

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

The laboratory provides results to the trial sites on an ongoing basis. The results will be transferred to the trial database.

The laboratory equipment may provide analyses not requested in the protocol but produced automatically in connection with the requested analyses according to specifications in the laboratory standard operating procedures. Such data will not be transferred to the trial database, but abnormal values will be reported to the investigator. The investigator must review all laboratory results for concomitant illnesses and AEs and report these according to Section 8.2.4 and Section 12. Review of laboratory reports must be performed as described in Section 8.1.11.

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

Laboratory samples will be destroyed no later than the finalisation of the clinical trial report, or according to local regulations for the destruction of blood samples.

8.5.1 Laboratory assessments for efficacy

Glucose metabolism

PG will be measured during the meal test. See Section 8.3.1.

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

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

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

Lipids

Blood samples for lipids will be analysed to determine:

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

8.5.2 Laboratory assessments for safety

Biochemistry

Blood samples for biochemistry will be analysed to determine:

- alanine aminotransferase (ALT)
- aspartate aminotransferase (AST)
- albumin
- alkaline phosphatase
- creatinine
- creatinine clearance
- potassium
- sodium
- total bilirubin
- total protein
- eGFR at screening

eGFR will be calculated by the central laboratory based on the creatinine value using the CKD-EPI equation in order to access exclusion criteria 16.

Haematology

Blood samples for haematology will be analysed to determine:

- haemoglobin
- haematocrit
- erythrocytes
- leucocytes
- thrombocytes

Pregnancy testing

For females of childbearing potential (see Section 8.2.7), a blood human Chorion Gonadotropin (hCG) pregnancy test will be performed at the visits indicated in the flowchart in Section 2. In addition, urine pregnancy tests will be performed locally during the trial if pregnancy is suspected

or if required by local law. A positive urine test should be followed by a confirmatory serum-hCG (central laboratory).

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

8.6 Other assessments

8.6.1 Training in the pen-injector

The subjects must be trained in how to handle the pen-injector when handed out the first time. Training must be repeated during the trial at regular intervals in order to ensure correct use of the device.
The following should be emphasised:

- Always use a new needle for each injection as this will prevent contamination and blocked needles
- Remember to prime the pen to ensure product flow
- The needle should be kept in the skin while counting slowly to 6 after the dose counter has returned to zero after injection. If the needle is removed too early then the full dose may not have been delivered
- Always check that the correct pen is used (bolus or basal) e.g. by colour coding and label. Use the differentiation guide as a reference
- In-use time and storage conditions of pen-injectors (Section 9.3)

8.6.2 Diary

At visit 1 the subjects will be provided with a diary to capture health issues (adverse events and changes in concomitant medication) only. At the run-in visit (V2) the subjects will be provided with a diary to capture health issues (adverse events and changes in concomitant medication), hypoglycaemia, SMPGs and dose data. The investigator must carefully instruct the subject in how to use the diary. All data entered in the diary is considered source data, as described in sections 8.3.2, 8.3.3 and 8.4.2. The recordings must be reviewed as described in Section 8.1.11 and transcribed, as applicable. Entries in the diaries are only to be made by the subject, unless otherwise specified.

Selected titration data (e.g. certain SMPGs and dose data) will only be used during the trial for central titration surveillance, to ensure compliance with the titration guideline (Appendix A1 and A2), and will not be reported in the clinical trial report (CTR). All data will be stored by Novo Nordisk (Section 24).

8.7 Subject compliance

Throughout the trial, the investigator will remind the subjects to follow the trial procedures and requirements to ensure subject compliance.

Treatment compliance: During treatment with trial products, the investigator will at each weekly contact (visit or phone contact) assess the subject's compliance by evaluating the glycaemic control, adherence to treatment and completion of the subject's diary including the SMPG profiles, dose and hypoglycaemia reporting. In addition, subject compliance will be assessed by monitoring of drug accountability at specified visits, please refer to the flow chart (Section 2).

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.

9 Trial supplies

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

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

Trial products must not be used, if they do not appear clear and colourless.

9.1 Trial products

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

Table 9–1 Trial products (IMPs)

Trial product	Strength	Dosage form	Route of administration	Container/ delivery device
Faster aspart (test product, blinded)	100 U/mL	Solution for injection	Subcutaneously	3 mL PDS290 pen-injector
Insulin aspart (reference therapy, blinded)				
Insulin deglude (open label)	100 U/mL	Solution for injection	Subcutaneously	3 mL PDS290 pen-injector
Insulin aspart (open label for the run-in period)	100 U/mL	Solution for injection	Subcutaneously	3 mL PDS290 pen-injector

Metformin is a Non-Investigational Medicinal Product (NIMP) and will not be supplied by Novo Nordisk. However, metformin will be reimbursed if required according to local regulations.

In the treatment period the investigational medicinal products (IMPs) faster aspart and insulin aspart are visually identical.

9.2 Labelling

The trial products will be labelled in accordance with Annex 13[43], local regulations and trial requirements.

Each trial site will be supplied with sufficient trial products for the trial on an ongoing basis controlled by the IWRS. Trial products will be distributed to the trial sites according to enrolment and randomisation.

The investigator must document that direction for use (DFU) is given to the subject orally and in writing at the first dispensing visit (V2). Additionally, the pen differentiation guide must be provided to subjects at randomisation (V10). DFU and pen differentiation guide can be provided as needed at the following dispensing visits.

9.3 Storage

Table 9–2 Storage conditions

Trial product	Storage conditions (not-in-use)	In-use conditions	In-use time[a]
Faster aspart Insulin aspart (NovoRapid®)	Store in refrigerator (2°C - 8°C) Do not freeze Protect from light	Store below 30°C Do not refrigerate Do not freeze Protect from light	Use within 4 weeks
Insulin degludec	Store in refrigerator (2°C - 8°C) Do not freeze Protect from light	Store at 2°C- 30°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 that trial product is kept under proper storage conditions and record and evaluate the temperature. The investigator must inform Novo Nordisk **immediately** if any trial product has been stored outside specified conditions (e.g. outside temperature range). Additional details regarding handling of temperature deviations can be found in the TMM.

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

9.4 Drug accountability and destruction

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

Each trial product package is referred to as a dispensing unit (DU) and is uniquely numbered with a Dispensing Unit Number (DUN).

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

Investigator should instruct the subjects in what to be returned at the next visit.

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

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

9.5 Auxiliary supplies

The following will be provided by Novo Nordisk in accordance with the TMM:

- DFU for the prefilled pens
- Novo Nordisk needles for the pen devices
- BG meters and auxiliaries for the BG meters
- Standardised liquid meal (for the meal test)

Only needles provided by Novo Nordisk with a maximum length of 6 mm must be used for administration of trial product.

10 Interactive web response system

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

IWRS is used for:

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

IWRS user manuals will be provided to each trial site.

11 Randomisation procedure and breaking of blinded codes

At the randomisation visit (V10), eligible subjects will be randomised via the IWRS into two treatment arms in a 1:1 manner. See Section 5.1.

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

The randomisation will be stratified according to the type of diabetes in order to aim for an even distribution of treatments groups within T1DM and T2DM.

11.1 Breaking of blinded codes

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

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

When the code is broken, the treatment allocation will be accessible to the investigator and the Novo Nordisk Global Safety department. If IWRS is not accessible at the time of code break the IWRS helpdesk should be contacted. Contact details are listed in Attachment I.

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

12 Adverse events, and technical complaints and pregnancies

12.1 Definitions

12.1.1 Adverse event

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

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

An AE includes:

- A clinically significant worsening of a concomitant illness
- Any abnormal laboratory test results or safety assessments considered clinically significant in the medical and scientific judgement of the investigator, including events that have worsened from prior to the time point from which AEs are collected.
- Abuse: Persistent or sporadic, intentional excessive use of medical product, which is accompanied by harmful physical or psychological effects (e.g. overdose with the intention to cause harm).
- Misuse: Situation where the medicinal product is intentionally and appropriately used not in accordance with the protocol or the terms of the marketing authorization.

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

- Pre-existing conditions, including those found as a result of screening or other trial procedures performed before exposure to trial product (pre-existing conditions should be reported as medical history or concomitant illness)
- Medical or surgical procedures (e.g. endoscopy, appendectomy). The condition that leads to the procedure, should be reported as the AE.
- Non-serious hypoglycaemia is an AE, but is reported on a hypoglycaemic episode form instead of on an AE form, see Section 8.4.2

The following three definitions are used when assessing an AE:

- **Severity**
  - **Mild –** no or transient symptoms, no interference with the subject's daily activities
  - **Moderate** – marked symptoms, moderate interference with the subject's daily activities
  - **Severe** – considerable interference with the subject's daily activities; unacceptable
- **Causality**
  Relationship between an AE and the relevant trial product(s):
  - **Probable** - Good reason and sufficient documentation to assume a causal relationship

- **Possible** - A causal relationship is conceivable and cannot be dismissed
- **Unlikely** - The event is most likely related to aetiology other than the trial product

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

12.1.2 Serious adverse event

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

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

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

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

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

– Stays at the hospital for treatment or observation for more than 24 hours

Medical judgement must always be exercised, and when in doubt, the hospital contact should be regarded as a hospitalisation. Hospitalisations for administrative, trial related and social purposes do not constitute AEs and should therefore not be reported as AEs or SAEs. Hospital admissions for surgical procedures, planned before trial inclusion, are not considered AEs or SAEs.

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

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

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

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

12.1.3 Non-serious adverse event

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

12.1.4 Medication errors

A medication error concerning trial products is defined as:

- Administration of wrong drug
  Note: Use of wrong DUN is not considered a medication error.
- Wrong route of administration, such as intramuscular instead of subcutaneous
- 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

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

12.1.5 Adverse events requiring additional data collection

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

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

- Injection site reaction

For details, see Section 8.4.1.2.

12.1.6 Technical complaints

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

Examples of technical complaints:

- The physical or chemical appearance of trial products (e.g. discoloration, particles or contamination)
- All packaging material including labelling
- Problems related to devices (e.g. to the injection mechanism, dose setting mechanism, push button or interface between the pen and the needle)

12.2 Reporting of adverse events

All events meeting the definition of an AE must be collected and reported. This includes events from the first trial-related activity after the subject has signed the informed consent until the end of the post-treatment follow-up period (FU2). For subjects discontinuing trial product prematurely, only SAEs should be reported between FU2 and end of trial (V26B). The events must be recorded in the applicable eCRF forms in a timely manner, see timelines below and Figure 12–1.

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

All AEs, either observed by the investigator or subject, must be reported by the investigator and evaluated.

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

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

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

Timelines for initial reporting of AEs:

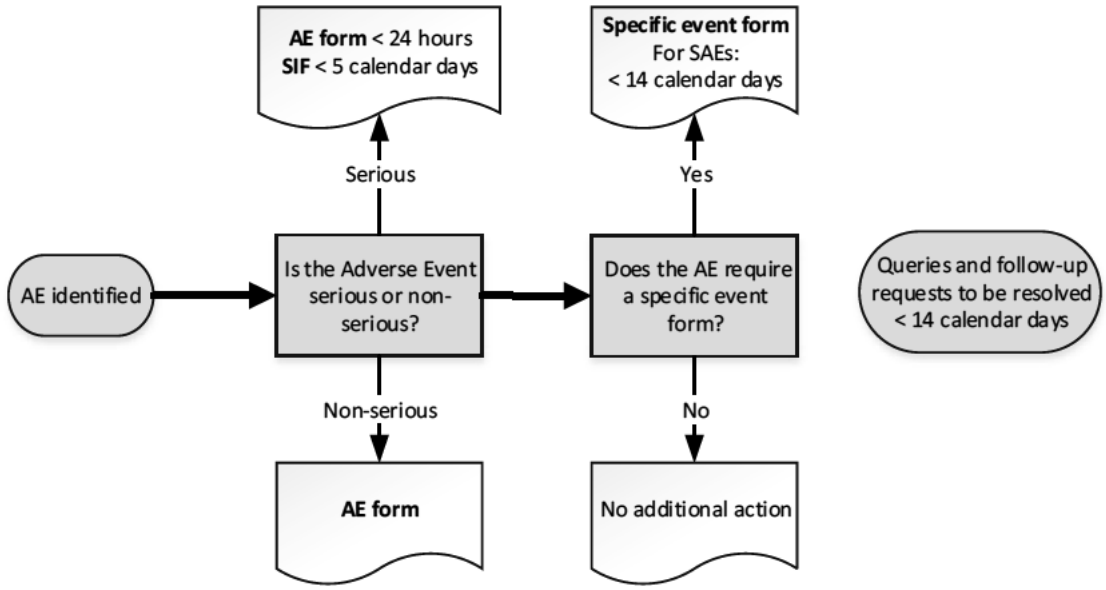
The investigator must complete the following forms in the eCRF within the specified timelines:

- **SAEs:** The AE form **within 24 hours** and the safety information form **within 5 calendar** days of the investigator's first knowledge of the SAE. Both forms must be signed within 7 calendar days from the date the information was entered in the eCRF.

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

If the eCRF is unavailable, the concerned AE information must be reported on a paper AE form and sent to Novo Nordisk by fax, encrypted e-mail or courier within the same timelines as stated above. When the eCRF becomes available again, the investigator must enter the information on the form into the eCRF.

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



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

AE: Adverse Event SIF: Safety Information form

Figure 12–1 Reporting of AEs

Reporting of trial product-related SUSARs by Novo Nordisk:

Novo Nordisk will notify the investigator of trial product-related suspected unexpected serious adverse reactions (SUSARs) in accordance with local requirements and ICH GCP[44]. In addition, the

investigator will be informed of any trial-related SAEs that may warrant a change in any trial procedure.

In accordance with regulatory requirements, Novo Nordisk will inform the regulatory authorities, including EMA, of trial product-related SUSARs. In addition, Novo Nordisk will inform the IRBs/IECs of trial product-related SUSARs in accordance with local requirement and ICH GCP[44], unless locally this is an obligation of the investigator.

Novo Nordisk products used as concomitant medication:

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

12.3 Follow-up of adverse events

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

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

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

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

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

of "recovering/resolving" when the subject has completed the follow-up period and is expected by the investigator to recover.

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

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

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

12.4 Technical complaints and technical complaint samples

12.4.1 Reporting of technical complaints

All technical complaints on any of the following products:

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

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

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

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

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

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

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

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

If the eCRF is unavailable or when reporting a technical complaint that is not subject related, the information must be provided on a paper form by fax, e-mail or courier to Customer Complaint Center, Novo Nordisk, within the same timelines as stated above. When the eCRF becomes available again, the investigator must enter the information on the technical complaint form in the eCRF. For reporting of technical complaints on the BG meter and auxiliaries, see Attachment I.

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

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

If the technical complaint sample is unobtainable, the investigator must specify on the technical complaint form why it is unobtainable.

Storage of the technical complaint sample must be done in accordance with the conditions prescribed for the product.

12.5 Pregnancies

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 new born infant is one month of age.

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

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

1. Reporting of pregnancy information

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

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

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

2. Reporting of AE information

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

Forms and timelines for reporting AEs:
Non-serious AEs:

- AE form[a]: Data must be recorded in the eCRF as soon as possible, preferably within 5 working days (see section 13.2)

SAEs:

- AE form[a] **within 24 hours** of the investigator's first knowledge of the SAE.
- Safety information form **within 5 calendar days** of the investigator's first knowledge of the SAE.
- **SAE follow-up information** to the AE form and/or safety information form **within 24 hours** of the investigator's first knowledge of the follow-up information.

[a] It must be clearly stated in the AE diagnosis field on the AE form if the event occurred in the subject, foetus or new born infant. If the AE occurred in the foetus or new born infant, the AE can only be reported on paper AE and safety information form.

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

12.6 Precautions and/or overdose

During treatment with insulin, there is a risk of hypoglycaemia (see Section 8.4.2). Symptoms of hypoglycaemia usually occur suddenly and may include cold sweat, nervousness or tremor, anxious feelings, unusual tiredness, confusion, difficulty in concentration, excessive hunger, temporary vision changes, headache, nausea, and palpitation. Prolonged or severe hypoglycaemia can lead to a loss of self-control, spasms, and/or unconsciousness and, in extreme cases, death. Asymptomatic hypoglycaemia and symptoms of hypoglycaemia should be treated with carbohydrates. Mild to moderate symptoms can be treated by ingestion of carbohydrate (for example, juice). Severe hypoglycaemia resulting in the loss of consciousness should be treated with parenteral glucose, glucagon or dextrose.

For further details, please refer to the current version of faster aspart IB[24], for NovoRapid® and Tresiba® please refer to the current versions of the local labelling.[18, 19, 25, 26]

12.7 Committees related to safety

12.7.1 Novo Nordisk safety committee

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

13 Case report forms

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

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

The following will be provided as paper CRFs:

- Pregnancy forms

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

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

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

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

13.1 Corrections to case report forms

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

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

13.2 Case report form flow

The investigator must ensure that data is recorded in the eCRF as soon as possible, preferably within 5 days after the visit/phone contact. The SMPG measurements and corresponding trial drug doses for titration purpose should be entered within 24 hours after the site visit/phone contact on week days throughout the trial.

Once data has been entered, it will be available to Novo Nordisk for data verification and validation purposes. Queries will be generated in the eCRF, and the investigator should solve these queries on an ongoing basis throughout the trial.

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

14 Monitoring procedures

Monitoring will be conducted using a risk-based approach including risk assessment, monitoring plans, centralised monitoring and visits to trial sites. During the course of the trial, the monitor will visit the trial site to ensure that the protocol is adhered to, that all issues have been recorded, to perform source data verification and to monitor drug accountability. The first monitoring visit will be performed as soon as possible after FSFV at the trial site and no later than 4 weeks after. The monitoring visit intervals will depend on the outcome of the centralised monitoring of the eCRFs (remote assessment of data by Novo Nordisk), the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP.

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

For all data recorded the source document must be defined in a source document agreement at each trial site. There must only be one source defined at any time for any data element. Source data generated by the trial site can be corrected by another person than the person entering the source data if accepted by local regulations; any correction must be explained, signed and dated by the person making the correction. The monitor will ensure that the eCRFs are completed and that paper CRFs are collected.

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

- Date for obtaining informed consent
- Demography
- Screening failure reason
- SAEs, if applicable

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

15 Data management

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

17 Statistical considerations

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

General considerations

In general, for endpoints evaluated as a change from baseline and/or where a baseline adjustment is made, baseline is defined as information collected at randomisation (V10). In case a measurement is not available at randomisation, the most recent measurement prior to randomisation will be used as baseline.

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

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

The primary objective of the trial is to confirm the effect in terms of glycaemic control of treatment with faster aspart compared to NovoRapid® both in combination with insulin degludec with or without metformin in Chinese adults with T1DM or T2DM inadequately treated with a basal-bolus or a premix regimen, using a non-inferiority approach.

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

Estimand

The estimand is defined as the treatment difference in change from baseline in HbA_{1c} 16 weeks after randomisation between faster aspart and NovoRapid® both in combination with insulin degludec with or without metformin in Chinese adults with T1DM or T2DM treated on basal-bolus regimen with a basal optimisation if all had adhered to randomised treatment. This estimand aims to reflect the treatment effect for subjects that are actually able to take the drug during the intended treatment period.

17.1 Sample size calculation

The sample size is determined to ensure a sufficient power for the primary analysis. This is determined using a non-inferiority limit of 0.4%.

In the global phase 3a programme where treatment with faster aspart has been investigated, the completion rates have been high, i.e. approximately 88-94%. Therefore it will not be unexpected that treatment discontinuation might be as low as 10%.

It is expected that a larger portion of the trial population will constitute subjects with T2DM. For these calculations the proportion of subjects with T1DM is assumed to be 20%. Combining expected differences for T1DM and T2DM subjects and weighting by the proportion of expected T1DM subjects we will assume a treatment difference of -0.02% (i.e., in favour of faster aspart).

The power for the primary (non-inferiority) analysis is based on a *t*-statistic under the assumption of a one-sided test of size 2.5 %, a non-inferiority margin of 0.4% and SD of 1.2%. Using these values we get a power of 81.7% for the primary analysis with a sample size of 270. Adjusting further for a dropout rate of approximate 10%, 300 subjects will be randomised.

The power for non-inferiority for scenarios where SD = 1.0% or 1.2% and mean difference of 0.00% or -0.02% based on sample size 270 is shown in Table 17–1.

Table 17–1 The power for non-inferiority for different scenarios

Power for non-inferiority	Treatment difference = 0%	Treatment difference = -0.02%
SD = 1.0%	90.6%	93.0%
SD = 1.2%	77.9%	81.7%

The power calculation is done using proc power in SAS Version 9.4.

17.2 Definition of analysis sets

The following analysis sets are defined in accordance with the ICH-E9[45] 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 FAS, excluding subjects who:
  - Have violated any inclusion criteria
  - Have fulfilled any exclusion criteria

  Subjects in the PP analysis set will contribute to the evaluation “as treated”
- Safety Analysis Set includes all subjects receiving at least one dose of randomised treatment. Subjects in the safety analysis set will contribute to the evaluation “as treated”

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

Before data are released for statistical review, a blinded review of all data will take place to identify serious non-adherence to the protocol that may potentially affect the results. Furthermore, extreme values and outliers will be identified by the statistician during programming and data review, according to ICH-E9.[45] This will be performed by using a fake randomisation.

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

17.3 Primary endpoint

The primary endpoint is change from baseline (week 0) in HbA_{1c} to 16 weeks after randomisation.

Primary analysis:

The estimand will be addressed by the primary analysis on all subjects included in the full analysis set and using the data collected from date of first dose of randomised NovoRapid®/faster aspart and to 7 days after the day of last dose of randomised NovoRapid®/faster aspart. Change from baseline in HbA_{1c} after 16 weeks of randomised treatment will be analysed using a mixed-effect model for repeated measurements (MMRM) where all calculated changes in HbA_{1c} from baseline at visits will be included in the analysis. This model will include treatment and stratification (T1DM/T2DM) as fixed factors, HbA_{1c} at baseline as covariate and interactions between all fixed factors and visit. An unstructured covariance matrix will be used to describe the variability for the repeated measurements for a subject. This approach relies on the assumption that data are missing at random (MAR). From this model, the treatment difference after 16 weeks will be estimated with a 95% confidence interval calculated.

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

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

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

The trial also aims to confirm the superiority of treatment with faster aspart for the change from baseline HbA_{1c} 16 weeks after randomisation. Here superiority will be based on the same 95% CI that was used for addressing the primary analysis. Superiority will be confirmed if the upper boundary of the two-sided 95% confidence interval of the mean treatment difference is below 0%.

Additional analysis

Differences between the two populations will be investigated further by estimating the treatment differences separately for subjects with T1DM and T2DM. These treatment differences will be estimated based on the same data and a similar statistical model as the primary analysis but including interaction terms between treatment, stratification (T1DM and T2DM), and visit.

Sensitivity analysis for the primary analysis addressing the estimand

1) A tipping point analysis will be made based on the data and a similar statistical model as the primary analysis addressing the estimand but using multiple imputation. In this analysis observations for subjects with missing values are imputed based on the treatment arm they were randomised to and subjects in the faster aspart group are given a penalty. This is done to investigate the robustness of the conclusion in the primary analysis with respect to the MAR assumption and mimics a scenario where the HbA_{1c} of the subjects in the faster aspart groups evolve less favourably than predicted. As a first step imputations will be done without penalty assuming MAR. Second, the imputed values for week 16 in the faster aspart group will be added a penalty. This is done repeatedly, gradually increasing the penalty until the conclusion from the non-inferiority analysis no longer holds. This will serve as a sensitivity analysis for the non-inferiority analysis and the specific value of the penalty that changes the conclusion will be used to evaluate the robustness of the conclusion of the non-inferiority analysis.
2) A tipping point analysis using multiple imputation similar to 1) but with the modification that subjects discontinuing treatment due to non-eligibility (discontinuation due to criteria 1- 4, Section 6.6) in the faster aspart group will not have a penalty added. These analyses are motivated by the fact that data from subjects prematurely discontinuing randomised treatment due to non-eligibility can reasonably be assumed to be missing completely at random.
3) The same statistical model using MMRM and data as in the primary analysis, but restricted to the PP analysis set. This analysis will investigate the situation that subjects might have deviated from the inclusion and exclusion criteria and will serve as sensitivity analysis for the non-inferiority analysis.

17.4 Secondary endpoints

17.4.1 Supportive secondary endpoints

17.4.1.1 Efficacy endpoints

All endpoints except insulin dose in this section will be assessed using the FAS. Insulin dose will be presented using the safety analysis set.

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

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

Change from baseline in PPG and PPG increment endpoints 16 weeks after randomisation will be analysed based on the FAS using an ANOVA model including treatment and stratification (T1DM/T2DM) as factors, and with the corresponding baseline value as covariate.

Change from baseline in FPG to 16 weeks after randomisation

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

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

HbA_{1c} < 7.0%

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

This responder endpoint will be analysed based on a logistic regression model using treatment and stratification (T1DM/T2DM) as factors, and baseline HbA_{1c} as covariate. In the analysis, subjects who prematurely discontinue trial product and subjects with missing HbA_{1c} at 16 weeks will be included as non-responders.

HbA_{1c} < 7.0% without severe hypoglycaemia

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

This responder endpoint will be analysed based on a logistic regression model using treatment and stratification (T1DM/T2DM) as factors and baseline HbA_{1c} as covariate. In the analysis, subjects who prematurely discontinue trial product and subjects with missing HbA_{1c} at 16 weeks will be included as non-responders.

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

In general, analyses will be based on the entire 7-9-7-point SMPG profile.

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

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

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

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

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

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

- Change from baseline in 1-hour PPG and PPG increment (mean, breakfast, lunch and main evening meal)

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

- Fluctuation in 7-9-7-point SMPG profile

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

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

where *T*, *PG(t)* and $\overline{PG}$ denotes the length of the profile, the *PG* value at time *t* and the mean of the profile, respectively. It will be calculated using the linear trapezoidal technique.

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

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

Overall PPG (1-hour) ≤7.8 mmol/L

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

This responder endpoint will be analysed based on a logistic regression model using treatment and stratification (T1DM/T2DM) as factors, and baseline overall mean 1-hour PPG as covariate. In the analysis, subjects who prematurely discontinue randomised treatment will be included as non-responders.

Overall PPG (1-hour) ≤7.8 mmol/L without severe hypoglycaemia

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

This responder endpoint will be analysed based on a logistic regression model using treatment and stratification (T1DM/T2DM) as factors, and baseline overall mean 1-hour PPG as covariate. In the analysis, subjects who prematurely discontinue randomised treatment will be included as non-responders.

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

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

Lipids-lipoproteins profile 16 weeks after randomisation

Lipid endpoints (total cholesterol, HDL cholesterol, LDL cholesterol and triglyceride) will be logarithmically transformed and analysed separately based on all planned post baseline measurements until or at 16 weeks after randomisation using a model similar to the primary analysis except with the corresponding log-transformed baseline as covariate. Estimated treatment means and the estimated treatment difference with corresponding 95% CI will be back-transformed to the original scale, resulting in estimated geometric means, a treatment ratio and a 95% CI for the treatment ratio.

17.4.1.2 Safety endpoints

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

Number of treatment emergent adverse events

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

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

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

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

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

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

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

Number of treatment emergent injection site reactions

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

Classification of Hypoglycaemia

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

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

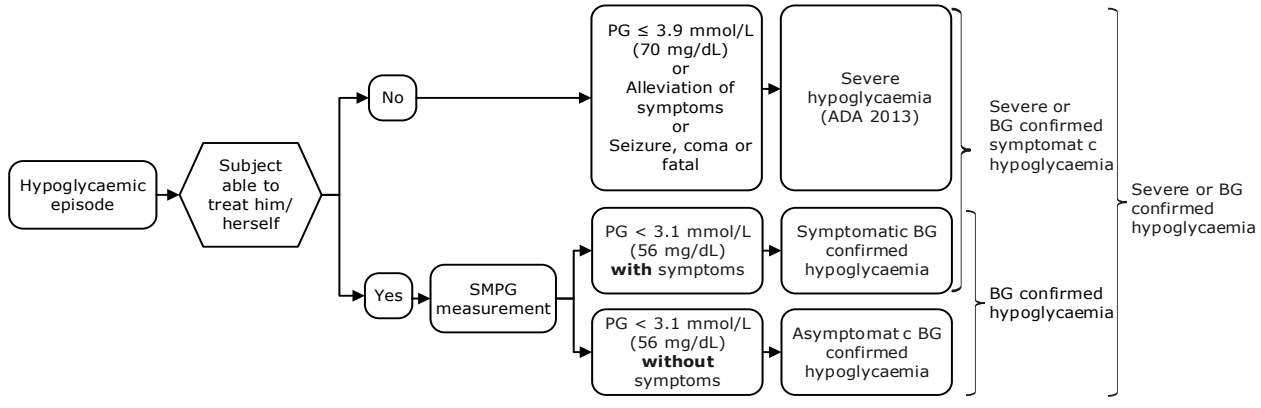
Hypoglycaemic episodes are classified according to the Novo Nordisk classification of hypoglycaemia (see Figure 17–1) and the ADA classification of hypoglycaemia (see Figure 17–2).

Novo Nordisk classification of hypoglycaemia

In normal physiology, symptoms of hypoglycaemia occur below a PG level of 3.1 mmol/L (56 mg/dL)[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 ADA classification.[39]
- Severe or BG confirmed hypoglycaemia: An episode that is severe according to the ADA classification[39] or BG confirmed by a PG value <3.1 mmol/L (56 mg/dL) **with** or **without** symptoms consistent with hypoglycaemia.



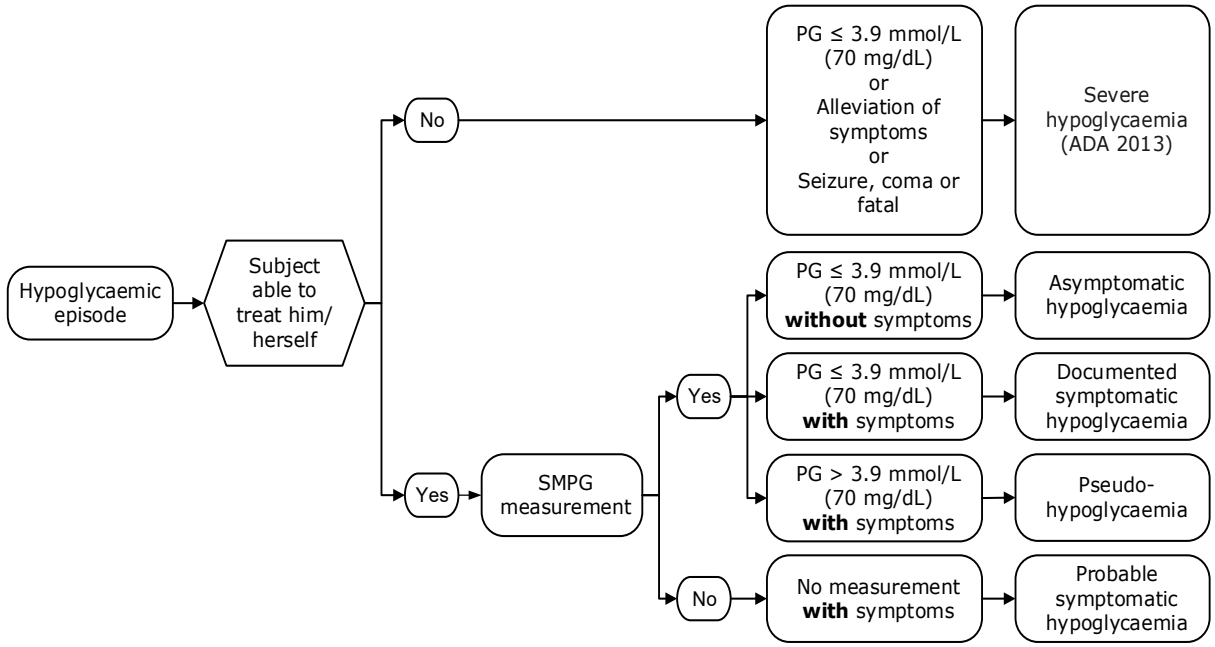
Note: Glucose measurements are performed w th capillary blood calibrated to plasma equivalent glucose values

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

Figure 17–1 Novo Nordisk classification of hypoglycaemia

ADA classification[39] of hypoglycaemia

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



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

PG: plasma glucose SMPG: Self-measured plasma glucose

Figure 17–2 ADA classification of hypoglycaemia

Treatment emergent hypoglycaemic episodes are presented in terms of the number of subjects with at least one event (N), the percentage of subjects with at least one event (%), the number of events

(E) and the event rate per 100 years of exposure (R). Separate summaries are made by severity considering all episodes, nocturnal and daytime episodes using Novo Nordisk and ADA classified episodes. All episodes will also be summarised by category, including summaries in relation to time since start of meal, as occurring during 0.5, 1, 2, and 4 hours after start of meal, and from 2 hours (exclusive) to 4 hours (inclusive) after start of meal, respectively.

The number of treatment emergent severe or BG confirmed hypoglycaemic episodes (all, daytime, nocturnal, 0.5, 1, 2, and 4 hours and from 2 hours (exclusive) to 4 hours (inclusive) after start of the meal) will be analysed based on the FAS using a negative binomial regression model with a log-link function and the logarithm of the time period in which a hypoglycaemic episode is considered treatment emergent as offset. The model will include treatment and stratification (T1DM/T2DM), as factors. To the extent where data allow, separate analysis will be performed for severe hypoglycaemic episodes.

Change from baseline in clinical evaluations 16 weeks after randomisation:

Physical examination
The physical examination parameters (respiratory system, cardiovascular system, gastrointestinal system incl. mouth, central and peripheral nervous system, skin), and their change from baseline, will be summarised descriptively. All findings will be listed.

Vital signs
Vital signs include diastolic blood pressure, systolic blood pressure and pulse. The measurements will be summarised descriptively including summaries of the change from baseline.

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

Eye examination
Eye examination findings, including right eye ophthalmoscopy and left eye ophthalmoscopy, will be summarised descriptively including summaries of the change from baseline.

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

- Haematology (haemoglobin blood, erythrocytes, haematocrit blood, leucocytes, thrombocytes)
- Biochemistry (AST serum, calculated creatinine clearance serum, sodium serum, potassium serum, creatinine serum, total protein serum, albumin serum, alkaline phosphatase serum, ALT serum, total bilirubin serum, GFR from creatinine adjusted for BSA)

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 both the actual values and the low/normal/high categorisation in shift tables.

Change from baseline in body weight and body mass index 16 weeks after randomisation
The measurements will be summarised descriptively using the actual values as mean change.

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

18 Ethics

18.1 Benefit-risk assessment of the trial

Benefits

All subjects included in the trial will be treated with basal-bolus regimen with insulin degludec (marketed in China under the brand name Tresiba®) as the basal insulin. Inclusion and exclusion criteria have been chosen to ensure that subjects enrolling in the trial have T1DM or T2DM at a stage where basal-bolus treatment is needed (i.e. subjects must have been diagnosed with T1DM for one year or more or with T2DM for five years or more and must have been on a basal-bolus or premix insulin treatment regimen at least 1 year prior to screening).

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

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

The very high frequency of contacts between the subject and the investigator and the thorough evaluation of SMPG values will provide the opportunity for optimising the titration of basal and bolus insulin based on SMPG values and thereby may contribute to obtaining improved HbA_{1c} results. All subjects will have reinforced dietary training.

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

Risks

For the individual subject, the anticipated risks include hypoglycaemia, systemic allergic reactions, injection site reactions, lipodystrophy, medication errors and antibody development. The risks will be mitigated by the close supervision of the subjects.

The most common side effect of all available insulin preparations is hypoglycaemia. The investigator will explain to the subject how they should check their BG with the BG meter provided by Novo Nordisk and what precautions to take in case of low BG measurement. No maximum dose

of insulin is specified as doses are titrated individually. All subjects will perform 4-point profiles on a daily basis throughout the trial for safety purposes and for the purpose of insulin titration.

A consequence of the pharmacodynamics of rapid-acting insulin analogues is that if hypoglycaemia occurs, it may occur earlier after an injection than with soluble human insulin. A phase 3A trial with faster aspart in T2DM showed a slight shift in distribution of the occurrence of hypoglycaemic episodes in relation to a meal when comparing to NovoRapid®. A statistically significant higher rate of hypoglycaemic episodes was seen during the first 2 hours after a meal for faster aspart. This is not unexpected and reflects the pharmacokinetic and pharmacodynamic properties of faster aspart.

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

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

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

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

Subjects in this trial will be using bolus and basal insulin administered via two differently colour coded prefilled pens. This colour difference will help the subject to distinguish between the pens and thereby minimise the risk of medication errors with regard to mixing up the pens used for basal and bolus injection. Subjects will be trained in distinguishing between the pens.

Summary of clinical trials

The pharmacokinetic and pharmacodynamic profiles of faster aspart consistently demonstrated a left shift compared to that of NovoRapid® in subjects with T1DM and the profiles for faster aspart and NovoRapid® were similar in overall shape. Faster aspart produced a faster onset of exposure and increased initial absorption rate compared to NovoRapid® resulting in a faster onset of action and increased early glucose-lowering effect. Overall, the differences in the pharmacokinetic and pharmacodynamic properties for faster aspart compared to NovoRapid® were consistent across trials.[24] No safety concerns were raised during any of the trials.

Similar clinical pharmacology trials have not been performed in subjects with T2DM, however the phase 3A programme for faster aspart included trials in bolus naïve T2DM subjects. Non-inferiority to NovoRapid® with regard to HbA_{1c} change from baseline was demonstrated. In subjects with

T2DM faster aspart statistically significantly improved control of the 1-hour PPG increment when compared to NovoRapid®.[24] No safety issues for faster aspart have been identified based on data from the clinical development programme, and the safety profile is similar to NovoRapid®.[24]

Conclusion

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

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

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

18.2 Informed consent

In seeking and documenting informed consent, the investigator must comply with applicable regulatory requirement(s) and adhere to ICH GCP[44] and the requirements in the Declaration of Helsinki[47].

Before any trial-related activity, the investigator must give the subject verbal and written information about the trial and the procedures involved in a form that the subject can read and understand.

The subjects must be fully informed of their rights and responsibilities while participating in the trial as well as possible disadvantages of being treated with the trial products.

The investigator must ensure the subject ample time to come to a decision whether or not to participate in the trial.

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

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

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

In order to avoid missing data, the subjects will be informed about the importance of completing the trial also if the subjects discontinue trial product.

18.3 Data handling

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

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

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

18.4 Information to subjects during trial

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

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

18.5 Premature termination of the trial and/or trial site

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

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

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

19 Protocol compliance

19.1 Protocol deviations

Deviations from the protocol should be avoided.

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

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

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

19.2 Prevention of missing data

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

The subjects will be carefully informed about the trial procedures before signing informed consent, so that they know the implications of participating in the trial.

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

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

20 Audits and inspections

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

21 Critical documents

Before a trial site is allowed to start screening subjects, written notification from Novo Nordisk must be received and the following documents must be available to Novo Nordisk:

- Regulatory approval and/or acknowledgement of notification as required
- Approval/favourable opinion from IRBs/IECs clearly identifying the documents reviewed as follows: protocol, any protocol amendments, subject information/informed consent form, any other written information to be provided to the subject and subject recruitment materials
- List of IRB/IEC members and/or constitution (or a general assurance number/statement of compliance)
- Curricula vitae of investigator and sub-investigator(s) (current, dated and signed - must include documented GCP training or a certificate)
- Signed receipt of Investigator's Brochure, SmPC or similar labelling.
- Signed and dated Agreement on Protocol
- Signed and dated Agreement on Protocol Amendment, if applicable
- Contract, signed by the investigator and/or appropriate parties on behalf of the investigator's site and Novo Nordisk
- Source document agreement
- Central laboratory certification and normal ranges
- Insurance statement, if applicable
- Financial disclosure form from investigator and sub-investigator(s)

Novo Nordisk will analyse and report data from all sites together. By signing the protocol agreement, each investigator agrees to comply fully with ICH GCP[44] applicable regulatory requirements and the Declaration of Helsinki[47].

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

22 Responsibilities

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

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

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

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

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

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

If the investigator is no longer able to fulfil the role as investigator (e.g. if he/she moves or retires), a new investigator will be appointed in consultation with Novo Nordisk.

The investigator and other site personnel must have sufficient English skills according to their assigned task(s).

23 Reports and publications

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

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

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

One or two investigator(s) will be appointed by Novo Nordisk to review and sign the CTR (signatory investigator) on behalf of all participating investigators. The signatory investigator(s) will be appointed based upon the criteria defined by the ICMJE for research publications[48].

23.1 Communication of results

Novo Nordisk commits to communicating, and otherwise making available for public disclosure, results of trials regardless of outcome. Public disclosure includes publication of a paper in a scientific journal, abstract submission with a poster or oral presentation at a scientific meeting, or disclosure by other means.

The results of this trial will be subject to public disclosure on external web sites according to international and national regulations, as reflected in the Novo Nordisk Code of Conduct for Clinical Trial Disclosure[33].

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

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

In all cases the trial results will be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations. All authors will be given the relevant

statistical tables, figures, and reports needed to evaluate the planned publication. In the event of any disagreement on the content of any publication, both the investigators' and Novo Nordisk opinions will be fairly and sufficiently represented in the publication.

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

Novo Nordisk maintains the right to be informed of plans by any investigator to publish and to review any scientific paper, presentation, communication or other information concerning the investigation described in this protocol. Any such communication must be submitted in writing to Novo Nordisk before submission for comments. Comments will be given within 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[48] (sometimes referred to as the Vancouver Criteria). Novo Nordisk will appoint investigator(s) to prepare publications in collaboration with Novo Nordisk.

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

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

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

23.2 Investigator access to data and review of results

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

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

24 Retention of clinical trial documentation

24.1 Retention of clinical trial documentation

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

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

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

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

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

25 Institutional Review Boards/Independent Ethics Committees and regulatory authorities

IRB/IEC:

Written approval or favourable opinion must be obtained from IRB/IEC prior to commencement of the trial.

During the trial, the investigator or Novo Nordisk, as applicable, must promptly report the following to the IRB/IEC, in accordance with local requirements: updates to IB, unexpected SAEs where a causal relationship cannot be ruled out, protocol amendments according to local requirements, deviations to the protocol implemented to eliminate immediate hazards to the subjects, new information that may affect adversely the safety of the subjects or the conduct of the trial (including new benefit-risk analysis in case it will have an impact on the planned follow-up of the subjects), annually written summaries of the trial status, and other documents as required by the local IRB/IEC.

The investigator must ensure submission of the CTR synopsis to the IRB/IEC.

Protocol amendments must not be implemented before approval or favourable opinion according to local regulations, unless necessary to eliminate immediate hazards to the subjects.

The investigator must maintain an accurate and complete record of all submissions made to the IRB/IEC. The records must be filed in the investigator trial master file and copies must be sent to Novo Nordisk.

Regulatory Authorities:

Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs, and the CTR according to national requirements.

For China, an international cooperative relevant report of related China’s Human Genetic Resources will be submitted based on local regulation 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 A1: Insulin Titration Guideline for T1DM subjects

Trial ID: NN1218-4357

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1 Introduction

The goal of insulin therapy is to achieve near normoglycemia, i.e. to reach a pre-defined glycated haemoglobin (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[1-7].

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/her clinical judgement to avoid safety hazards. The investigator is responsible for the treatment of the subjects and can therefore overrule the guideline.

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

2 Treatment regimens

First dosing will take place on the day of Visit 2 (start of run-in) or the day following Visit 2.

There are no minimum or maximum doses of insulin degludec or faster aspart/NovoRapid®.

2.1 Run-in

2.1.1 Basal treatment

At Visit 2 eligible subjects will be transferred from their previous basal insulin dose or premix insulin dose to insulin degludec once daily (OD) according to Table 1.

During the following 8 weeks the investigator will focus on adjusting the insulin degludec dose according to Section 3.2.1.

2.1.2 Bolus treatment

In addition, the subjects will at Visit 2 start on or be transferred to NovoRapid® as bolus insulin (Table 2) and adjusted according to Section 3.1.2.

2.2 Randomisation

At randomisation Visit 10 (after 8 weeks) eligible subjects will be randomised 1:1 into two parallel treatment groups:

1. Faster aspart + insulin degludec
2. NovoRapid® + insulin degludec

2.3 Treatment period

During the 16-week treatment period the investigator will focus on adjusting the bolus dose according to Section 3.3.2.

2.4 Injection area

Insulin degludec should be injected subcutaneously into the abdomen, the thigh or the upper arm.

Faster aspart or NovoRapid® should be injected into the abdomen or upper arm.

The chosen region should be the same throughout the trial. Rotation of injection sites within a given region is recommended.

2.5 Time of injection

Insulin degludec should be injected once daily at any time of the day, but approximately at the same time of the day throughout the trial.

Faster aspart or NovoRapid® should be injected 0-2 minutes prior to the main meals.

Main meals are defined as breakfast, lunch and dinner. Extra bolus dosing is allowed at the investigator's recommendation.

3 Initiation and titration

3.1 Initiation at Visit 2

3.1.1 Initiation of insulin degludec

Subjects should be transferred to insulin degludec OD according to Table 1.

Table 1 Initiation of basal insulin (insulin degludec)

Pre-trial treatment	Visit 2
Basal OD/BID	Consider reducing total daily dose by 20%
Premix BID/TID	Calculate the total daily dose of insulin. Adjust the basal-to-bolus ratio* to be between 40:60 and 60:40

* According to the Chinese Diabetes Society (CDS)

The desired total daily basal and bolus doses can be found in Table 2.

Example on transfer from premix two times daily (BID) or three times daily (TID) to insulin degludec:

- The total daily dose a given subject should receive is 28 Units (U) per day.
- According to Table 2, the subject should receive a total of 11U of insulin degludec and a total of 17U of bolus insulin, if the basal: bolus ratio is 40:60. If the ratio is 60:40, the subject should receive a total of 17U of insulin degludec and a total of 11U of bolus insulin.

Table 2 Start doses of total basal (insulin degludec) and bolus insulin (NovoRapid®)

Total daily insulin dose	Basal:bolus ratio 40:60		Basal:bolus ratio 60:40	
	Total insulin degludec	Total bolus insulin	Total insulin degludec	Total bolus insulin
10	4	6	6	4
12	5	7	7	5
14	6	8	8	6
16	6	10	10	6
18	7	11	11	7
20	8	12	12	8
22	9	13	13	9
24	10	14	14	10
26	10	16	16	10
28	11	17	17	11
30	12	18	18	12
32	13	19	19	13
34	14	20	20	14
36	14	22	22	14
38	15	23	23	15
40	16	24	24	16
42	17	25	25	17
44	18	26	26	18
46	18	28	28	18
48	19	29	29	19
50	20	30	30	20
52	21	31	31	21
54	22	32	32	22
56	22	34	34	22
58	23	35	35	23
60	24	36	36	24
62	25	37	37	25
64	26	38	38	26
66	26	40	40	26
68	27	41	41	27
70	28	42	42	28
72	29	43	43	29
74	30	44	44	30
76	30	46	46	30
78	31	47	47	31
80	32	48	48	32

3.1.2 Initiation of NovoRapid®

Subjects should be switched to/start on NovoRapid® TID daily according to Table 3.

Table 3 Initiation of bolus insulin

Pre-trial treatment	Visit 2
Bolus insulin	U to U, continue using same number of units with breakfast, lunch and dinner as pre-trial
Premix BID/TID	Calculate the total daily dose of insulin. Adjust the basal-to-bolus ratio to be between 40:60 and 60:40. Use table 2 to find the total number of bolus insulin units and divide this value into three even or uneven doses of NovoRapid® to be taken with breakfast, lunch and dinner.

3.2 Titration during run-in (Visit 2 – Visit 9)

3.2.1 Titration of insulin degludec

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

The dose of insulin degludec should be adjusted based on the mean of three pre-breakfast self-measured plasma glucose (SMPG) values measured on Day -2, Day -1 and on the day of titration. The adjustment should be according to Table 4.

Table 4 Insulin degludec dose escalation

Mean pre-breakfast SMPG values		Dose adjustment
mmol/L	mg/dL	U
4.0 – 5.0	71 – 90	0
5.1 – 10.0	91 – 180	2
10.1 – 15.0	181 – 270	4
> 15.0	> 270	6

If one or more pre-meal SMPG value(s) are < 4.0 mmol/L (< 71 mg/dL) subjects should reduce insulin degludec dose according to Table 5

Table 5 Insulin degludec dose reduction

Lowest pre-breakfast SMPG value		Dose adjustment
mmol/L	mg/dL	U
3.1 – 3.9	56 – 70	-2
< 3.1	< 56	-4

3.2.2 Titration of NovoRapid®

Titration of NovoRapid® for safety reasons can be done at the discretion of the investigator.

3.3 Titration during treatment period (Visit 10 – Visit 26)

3.3.1 Titration of insulin degludec

Titration of insulin degludec for safety reasons can be done at the discretion of the investigator.

3.3.2 Titration of faster aspart/NovoRapid®

At Visit 10, subjects will be randomised to receive either faster aspart or NovoRapid® as bolus insulin in a double-blind manner. Faster aspart/NovoRapid® will hereafter be called bolus insulin.

Titration of bolus insulin should be done following the bolus dosing algorithm.

Bolus insulin will be adjusted weekly by the investigator during the treatment period.

The dose of bolus insulin will be based on SMPG values measured on the last 3 days (days – 3, –2 and – 1) before the day of titration.

The adjustment should be according to Table 6 :

- Breakfast dose will be titrated according to pre-lunch SMPG values measured on the previous 3 days
- Lunch dose will be titrated according to pre-dinner SMPG values measured on the previous 3 days
- Dinner dose will be titrated according to bedtime SMPG values measured on the previous 3 days

Table 6 Faster aspart/NovoRapid® dose adjustment

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

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

3.4 Deviations from the algorithm

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

4 Data collection

The following data should be available for Novo Nordisk's Insulin Titration Group within 24 hours (on weekdays) after a site visit/phone contact:

- SMPG values
- Date, dose and time point of insulin doses taken
- New insulin doses prescribed after titration
- Reason for deviation between the recommended and the prescribed basal insulin dose
- Reason for deviation between the recommended and actual bolus insulin dose
- Hypoglycaemic episodes (Protocol Section 8.4.2)

5 Review procedure

Surveillance of titration data will be performed centrally by Novo Nordisk in an unbiased manner. It is important that titration data and hypoglycaemic episodes are entered the eCRF within 24 hours (on weekdays). If delays occur, action cannot be taken in due time before the subject's next site visit/phone contact. The aim is to reduce the time periods in which a subject may receive suboptimal treatment.

The data listed in Section 4 will be reviewed by Novo Nordisk within 24 hours (on weekdays). The reviewer may contact the investigator to get clarification regarding the reason for deviation or to request entry of missing data.

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

During the trial HbA_{1c} will be monitored by Novo Nordisk for additional surveillance of the glycaemic control. Novo Nordisk may be in contact with sites (visit or phone contact) to discuss progress in glycaemic control and titration of individual subjects based on SMPGs and HbA_{1c}.

6 References

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Appendix A2: Insulin Titration Guideline for T2DM subjects

Trial ID: NN1218-4357

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1 Introduction

The goal of insulin therapy is to achieve near normoglycemia, i.e. to reach a pre-defined glycated haemoglobin (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[1-7].

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/her clinical judgement to avoid safety hazards. The investigator is responsible for the treatment of the subjects and can therefore overrule the guideline.

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

2 Treatment regimens

First dosing will take place on the day of Visit 2 (start of run-in) or the day following Visit 2.

There are no minimum or maximum doses of insulin degludec or faster aspart/NovoRapid®.

2.1 Run-in

2.1.1 Basal treatment

At Visit 2 eligible subjects will be transferred from their previous basal insulin dose or premix insulin dose to insulin degludec once daily (OD) according to Table 1.

During the following 8 weeks the investigator will focus on adjusting the basal insulin dose according to Section 3.2.1

2.1.2 Bolus treatment

In addition, the subjects will at Visit 2 start on or be transferred to NovoRapid® as bolus insulin (Table 2) and adjusted according to Section 3.1.2.

2.2 Randomisation

At randomisation Visit 10 (after 8 weeks) eligible subjects will be randomised 1:1 into two parallel treatment groups:

1. Faster aspart + insulin degludec ± metformin
2. NovoRapid® + insulin degludec ± metformin

2.3 Treatment period

During the 16-week treatment period the investigator will focus on adjusting the bolus insulin dose according to Section 3.3.2.

2.4 Injection area

Insulin degludec should be injected subcutaneously into the abdomen, the thigh or the upper arm.

Faster aspart or NovoRapid® should be injected into the abdomen or upper arm.

The chosen region should be the same throughout the trial. Rotation of injection sites within a given region is recommended.

2.5 Time of injection

Insulin degludec should be injected once daily at any time of the day and should approximately be the same time of the day throughout the trial.

Faster aspart or NovoRapid® should be injected 0-2 minutes prior to the main meals.

Main meals are defined as breakfast, lunch and dinner. Extra bolus dosing is allowed at the investigator's recommendation.

3 Initiation and titration

3.1 Initiation at Visit 2

3.1.1 Initiation of insulin degludec

Subjects should be transferred to insulin degludec OD according to Table 1.

Table 1 Initiation of basal insulin (insulin degludec)

Pre-trial treatment	Visit 2
Basal OD	U to U
Basal BID	Reduce total daily basal dose by 20%
Premix BID/TID	Calculate the basal component of the total daily dose (basal & bolus) and reduce the basal dose by 20%

Two times daily (BID), three times daily (TID), Units (U).

3.1.2 Initiation of NovoRapid®

Subjects should be switched to/start on NovoRapid® TID according to Table 2.

Table 2 Initiation of bolus insulin

Pre-trial treatment	Visit 2
Bolus insulin	U to U, continue using same number of units with breakfast, lunch and dinner as pre-trial
Premix BID/TID	Calculate the daily bolus units from the bolus component of the total daily dose. Split the calculated number into three even or uneven doses of NovoRapid® to be taken with breakfast, lunch and dinner

3.2 Titration during run-in (Visit 2 – Visit 9)

3.2.1 Titration of insulin degludec

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

Insulin degludec should be adjusted based on the mean of three pre-breakfast SMPG values measured on Day -2, Day -1 and on the day of titration. The adjustment should be according to Table 3.

Table 3 Insulin degludec dose escalation

Mean pre-breakfast SMPG values		Dose adjustment
mmol/L	mg/dL	U
4.0 – 5.0	71 – 90	0
5.1 – 7.0	91 – 126	+2
7.1 – 8.0	127 – 144	+4
8.1 – 9.0	145 – 162	+6
> 9.0	> 162	+8

If one or more pre-meal SMPG value(s) are < 4.0 mmol/L (< 71 mg/dL) subjects should reduce insulin degludec dose according to Table 4.

Table 4 Insulin degludec dose reduction

Lowest pre-breakfast SMPG value		Dose adjustment
mmol/L	mg/dL	U
3.1 – 3.9	56 – 70	-2
< 3.1	< 56	-4

3.2.2 Titration of NovoRapid®

Titration of NovoRapid® for safety reasons can be done at the discretion of the investigator.

3.3 Titration during treatment period (Visit 10 – Visit 26)

3.3.1 Titration of insulin degludec

Titration of insulin degludec for safety reasons can be done at the discretion of the investigator.

3.3.2 Titration of faster aspart/NovoRapid®

At V10, subjects will be randomised to receive either faster aspart or NovoRapid® as bolus insulin in a double-blind manner. Faster aspart/NovoRapid® will hereafter be called bolus insulin.

Bolus insulin will be adjusted weekly by the investigator during the treatment period.

The dose of bolus insulin will be based on self-measured plasma glucose (SMPG) values measured on the 3 days (days – 3, –2 and – 1) before day of titration.

The adjustment should be according to

Table 5:

- Breakfast dose will be titrated according to pre-lunch SMPG values measured on the previous 3 days
- Lunch dose will be titrated according to pre-dinner SMPG values measured on the previous 3 days
- Dinner dose will be titrated according to bedtime SMPG values measured on the previous 3 days

Table 5 Faster aspart/NovoRapid® dose adjustment

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

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

3.4 Deviations from the algorithm

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

4 Data collection

The following data should be available for Novo Nordisk's Insulin Titration Group within 24 hours (on weekdays) after a site visit/phone contact:

- SMPG values
- Date, dose and time point of insulin doses taken
- New insulin doses prescribed after titration
- Reason for deviation between the recommended and the prescribed basal insulin dose
- Reason for deviation between the recommended and actual bolus insulin dose
- Hypoglycaemic episodes (Protocol Section 8.4.2)

5 Review procedure

Surveillance of titration data will be performed centrally by Novo Nordisk in an unbiased manner. It is important that titration data regarding dose titration is entered into the eCRF within 24 hours (on weekdays). If delays occur, action cannot be taken in due time before the subject's next site visit/phone contact. The aim is to reduce the time periods in which a subject may receive suboptimal treatment.

The data listed in Section 4 will be reviewed by Novo Nordisk within 24 hours (on weekdays). The reviewer may contact the investigator to get clarification regarding the reason for deviation or to request entry of missing data.

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

During the trial HbA_{1c} will be monitored by Novo Nordisk for additional surveillance of the glycaemic control. Novo Nordisk may be in contact with sites (visit or phone contact) to discuss progress in glycaemic control and titration of individual subjects based on SMPGs and HbA_{1c}.

6 References

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Log of Protocols

Date	Final, version	Protocol includes the following amendments
24 October 2017	1.0	NA
01 December 2017	2.0	Protocol update 2.0 rationale (VV-TMF-526750)
01 July 2019	3.0	Amendment 1.0 dated 1July2019 (VV-TMF-1095147)
03 April 2020	4.0	Amendment 2.0 dated 03 Apr 2020 (VV-TMF-1349704)
30 November 2020	5.0	All changes are documented in the Protocol track-changes version: VV-TMF-3967346

Log of Protocol Amendments

Protocol amendment no	Date	Final, Version	Country(ies) and/or trial site(s) affected	Brief content
1	01 July 2019	1.0	China	Protocol Version 2.0 dated 01 Dec 2017 has been updated with substantial- and minor changes. - Inclusion criteria 4 and 5 have been modified to better reflect clinical practice - Exclusion criterion No 7 and 14 have been deleted and modified, respectively. Criterion 7 is covered by exclusion criterion No 12. Criterion 14 has been updated to reflect clinical practice. - PK has been taken out of protocol as sufficient data is obtained from NN1218-4316 phase 1 trial and supportive global PK data. - Titration approach has been simplified from twice to once weekly titration - Carbohydrate counting has been taken out as it is not clinical practice in China

Protocol amendment no	Date	Final, Version	Country(ies) and/or trial site(s) affected	Brief content
				- Changes to section 12 to align with current safety definitions and reporting practice - All the changes are documented in protocol version 3.0 dated 1. July 2019 with track changes
2	03 Apr 2020	1.0	China	- All changes are documented in protocol version 4.0 date 03 Apr 2020 with track changes (VV-TMF-1349791)
3	30 Nov 2020	1.0	China	All changes are documented in protocol version 5.0 , Protocol amendment summary of changes table on page 2, as well as in track changes version of the protocol and the appendices a1 and a2 available in Veeva Vualt. Please note that there are no changes to Appendix a2 other than aligning date and version with the protocol.

9.1.01 Protocol Attachment

Protocol Attachment I is located in the Trial Master File.

If applicable, Protocol Attachment II is also located in the Trial Master File.

Content: Global key staff and Country key staff.