Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT02906917
Sponsor trial ID:	NN5401-4266
Official title of study:	A 38 week trial comparing effect and safety of insulin degludec/insulin aspart vs. insulin glargine plus insulin aspart in subjects with type 2 diabetes treated with basal insulin with or without oral antidiabetic treatment in need of treatment intensification
Document date:	22 June 2018

16.1.1 Protocol and protocol amendments

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Redacted protocol
Includes redaction of personal identifiable information only.

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Protocol

Trial ID: NN5401-4266

A 38 week trial comparing effect and safety of insulin degludec/insulin aspart vs. insulin glargine plus insulin aspart in subjects with type 2 diabetes treated with basal insulin with or without oral antidiabetic treatment in need of treatment intensification.

Trial phase: 3b

Protocol originator

[redacted]

Clinical Operations 2, Insulin and Diabetes Outcomes

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List of abbreviations

AB	antibody
ADA	American Diabetes Association
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BG	blood glucose
BG-meter	blood glucose meter
BiAsp	biphasic insulin aspart
BHQ	baseline hypo questionnaire
BID	two times a day
CAS	Completer analysis set
CCDS	Company Core Data Sheet
CLAE	clinical laboratory adverse event
CPMP	Committee for Proprietary Medicinal Products
CRF	case report form
CRO	contract research organisation
CS	clinically significant
DFU	directions for use
DPP-4	di-peptidyl-peptidase IV

DUN	dispensing unit number
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capturing system
EMA	European Medicines Agency
EOT	end of treatment
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FPFV	first patient first visit
FPG	fasting plasma glucose
GCP	Good Clinical Practice
GLP-1 RA	glucagon-like peptide-1 receptor agonist
HbA_{1c}	glycosylated haemoglobin
IAsp	insulin aspart
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDeg	insulin degludec
IDegAsp	insulin degludec/insulin aspart
IEC	independent ethics committee
IGlar	insulin glargine

IMP	investigational medicinal product
ITT	intention-to-treat
IRB	institutional review board
IWRS	interactive voice/web response system
LLOQ	lower limit of quantification
LPFV	last patient first visit
LPLV	last patient last visit
MMRM	mixed model for Repeated Measurement
NA	not applicable
NCS	non clinically significant
ND	not done
NI	non-inferiority
NPH	neutral protamine Hagedorn
OAD	oral antidiabetic drug
OD	once daily
PG	plasma glucose
PP	per protocol
PRO	patient reported outcomes
SAE	serious adverse event
SAP	statistical analysis plan
s.c.	subcutaneous(ly)
SD	standard deviation

SDV	source data verification
SGLT-2	sodium/glucose co-transporter 2
SF-36v2®	Short-Form Health Survey 36 version 2
SmPC	summary of product characteristics
SMPG	self-measured plasma glucose
SU	sulfonylurea
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TID	three times daily
TMM	Trial Materials Manual
TE	treatment effect
TRIM-D	Treatment Related Impact Measure-Diabetes
T2DM	type 2 diabetes mellitus
U.S. LI	U.S. Label Information
UTN	Universal Trial Number
UNL	upper normal limit

1 Summary

Objectives and endpoints:

Primary objective

- To confirm the effect of insulin degludec/insulin aspart once daily versus insulin glargine once daily in combination with insulin aspart once daily in controlling glycaemia after 26 weeks in subjects with type 2 diabetes mellitus treated with basal insulin with or without oral antidiabetic treatment in need of treatment intensification.

Primary endpoint

Change from baseline in glycosylated haemoglobin (HbA_{1c}) (%) after 26 weeks.

Secondary objectives

- To compare other effect parameters and safety of insulin degludec/insulin aspart once daily versus insulin glargine once daily in combination with insulin aspart once daily after 26 weeks in subjects with type 2 diabetes mellitus treated with basal insulin with or without oral antidiabetic treatment in need of treatment intensification.
- To compare the effect and safety of insulin degludec/insulin aspart once daily or twice daily versus insulin glargine once daily in combination with insulin aspart (1-3 times daily) after 38 weeks in subjects with type 2 diabetes mellitus treated with basal insulin with or without oral antidiabetic treatment in need of treatment intensification.

Key supportive secondary efficacy endpoints

At 26 weeks

- Responder (Yes/No) for HbA_{1c} after 26 weeks
  - $HbA_{1c} < 7\%$

At 38 weeks

- Change from baseline in HbA_{1c} (%) after 38 weeks
- Responder (Yes/No) for HbA_{1c} after 38 weeks:
  - $HbA_{1c} < 7\%$

Key supportive secondary safety endpoints

During 26 weeks

- Number of treatment-emergent severe or blood glucose (BG) confirmed symptomatic hypoglycaemic episodes during 26 weeks

During 38 weeks

- Number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during 38 weeks
- Incidence of treatment-emergent adverse events (TEAEs) during 38 weeks

Trial design:

This is a 38-week, multinational, open-label, two-arm, randomised (1:1), controlled, parallel-group, treat-to-target trial in subjects with type 2 diabetes mellitus treated with basal insulin with or without oral antidiabetic drug(s) in need of treatment intensification.

In need of treatment intensification is defined as an HbA_{1c} level of 7-10% (53-85 mmol/mol), both inclusive.

Subjects will be randomised in a 1:1 manner to receive either insulin degludec/insulin aspart (IDegAsp) OD or insulin glargine (IGlar) OD in combination with insulin aspart (IAsp) OD for the first 26 weeks followed by a 12-weeks intensification period.

Pre-trial basal insulin, sulfonylurea (SU) and glinides must be discontinued at randomisation. Treatment with other oral antidiabetic drug(s) should continue unchanged during the trial.

The randomisation will be stratified based on the pre-trial basal insulin treatment regimen: OD or BID/TID (two/three times daily) dosing. Subjects on a BID/TID regimen will be shifted to OD dosing in accordance with a titration guideline, Appendix A.

Subjects will remain in the same treatment arm throughout the trial, with the possibility of intensification of their treatment as described below.

At week 26 (V28), subjects not achieving sufficient glycaemic control (V27 $HbA_{1c} \geq 7\%$) will be further intensified from either IDegAsp OD to IDegAsp BID or IGlar OD + IAsp OD to IGlar OD + IAsp BID, whereas subjects in good glycaemic control (V27 $HbA_{1c} < 7\%$) will continue their insulin treatment regimen.

At week 32 (V34), glycaemic control will be evaluated again, and subjects in good glycaemic control (V33 $HbA_{1c} < 7\%$) will continue their insulin treatment regimen. Subjects on IDegAsp OD not reaching the glycaemic target (V33 $HbA_{1c} \geq 7\%$) will be intensified to IDegAsp BID, whereas subjects in the IGlar arm not reaching glycaemic control will be intensified with one additional IAsp dose to IGlar OD + IAsp BID or TID daily for the remaining six weeks of the intensification period.

The duration of the trial will be approximately 44 weeks including screening, randomisation, a 38-week treatment period and a 30-day follow-up period.

Trial population:

Number of trial subjects
Planned number of subjects to be randomised/started on trial products: 528.

Key Inclusion criteria

- 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

- Male or female, age ≥ 18 years at the time of signing informed consent
  Algeria: Male or female, age ≥ 19 years at the time of signing informed consent

- Diagnosed with type 2 diabetes mellitus

- Treated with any basal insulin ≥ 90 days prior to the day of screening

- Subject not on any OAD(s) prior to trial participation OR subjects on stable daily dose(s) of OAD(s) for at least 90 days prior to screening visit (V1). The OAD(s) include any of the following anti-diabetic drug(s)/regimen:

  a. Biguanides (metformin ≥ 1500 mg or maximum tolerated dose documented in the subject medical record)

  b. Other OADs (≥ half of the maximum approved dose according to local label or maximum tolerated dose as documented in subject medical record):

     i. Insulin secretagogues (SU and glinides)
     ii. Di-peptidyl-peptidase IV (DPP-4) inhibitors
     iii. α-glucosidase inhibitors
     iv. Sodium/glucose co-transporter 2 (SGLT-2) inhibitors
     v. Oral combination products (of the allowed individual OADs above)

- HbA_{1c} 7.0-10.0% (53-86 mmol/mol) (both inclusive) by central laboratory analysis

- Body mass index (BMI) ≤ 45.0 kg/m^2

Key exclusion criteria:

- Participation in any clinical trial of an approved or non-approved investigational medicinal product within four weeks prior to the day of screening (V1)
- Any chronic disorder or severe disease which, in the opinion of the investigator, might jeopardise subject's safety or compliance with the protocol
- Acute decompensation of glycaemic control requiring immediate intensification of treatment to prevent severe metabolic dysregulation (e.g. diabetes ketoacidosis) ≤ 90 days prior to the day of the screening and between screening and randomisation
- Any of the following: myocardial infarction , stroke or hospitalization for unstable angina or transient ischaemic attack within the past 180 days prior to the day of screening and between screening and randomisation
- Renal impairment measured as estimated Glomerular Filtration Rate (eGFR) value of < 60 ml/min/1.73 m^2 as defined by KDIGO 2012 classification using isotope dilution mass spectrometry (IDMS) for serum creatinine measured at screening
- Impaired liver function, defined as alanine aminotransferase (ALT) ≥ 2.5 times upper normal limit (UNL) at 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 in a period of 90 days before 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)

Key assessments

Efficacy

- HbA_{1c}
- FPG
- SMPG

Safety

- Body measurements (height and body weight)
- Adverse events
- Hypoglycaemic episodes
- Dilated fundoscopy or fundus photography
- Physical examination (including electrocardiogram)
- Biochemistry and haematology (blood samples)

- Insulin antibodies (blood samples)

Other
General health status/health-related quality of life and diabetes treatment related impact measured by PRO questionnaires:

- Short-Form Health Survey 36 version 2 (SF-36v2®)
- Treatment Related Impact Measure-Diabetes (TRIM-D)

Trial products:
The below trial insulin products will be provided by Novo Nordisk A/S:

- Insulin degludec/insulin aspart (Ryzodeg®) 100 units/mL, 3 mL pre-filled pen (FlexTouch®), solution for subcutaneous injection, Novo Nordisk A/S
- Insulin glargine (Lantus®) 100 units/mL, 3 mL pre-filled pen (SoloStar®), solution for subcutaneous injection, Sanofi-Aventis
- Insulin aspart (NovoRapid®/NovoLog®), 100 units/mL, 3 mL prefilled pen (FlexPen®), solution for subcutaneous injection, Novo Nordisk A/S

2 Flow Chart

Table 2–1 Flow chart

Trial NN5401-4266	Screening	Randomisation	Treatment initiation (week 0 - 26)									Treatment Intensification (week 27 - 38)				End of treatment	Follow-up (30 days)		Pre-term discontinuation of trial insulin		
Visit Number (V)	**V1**	**V2**	**V3**	**V6**	**V10**	**V14**	**V18**	**V22**	**V25**	**V27**	**V28**	**V32**	**V33**	**V34**	**V36**	**V40**	**V41[n]**			**V28a[o]**	**V40a[o]**
☎ Weekly Phone Contact number (P)(For details see Table 2-2 below)			**P4 P5**	**P7 P8 P9**		**P11 P12 P13**	**P15 P16 P17**	**P19 P20 P21**	**P23 P24**	**P26**	**P29 P30 P31**			**P35**	**P37 P38 P39**			**P42[n]**	**Px[o]**		
Time of visit (weeks)	**-2**	**0[a]**	**1**	**4**	**8**	**12**	**16**	**20**	**23**	**25**	**26**	**30**	**31**	**32**	**34**	**38**	**39**	**42**	**X**	**26**	**38**
Visit window (days)			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+5	±3	±5	±5	±3
Subject related info/assessment																					
Informed consent	X																				
Inclusion/Exclusion criteria	X	X																			
Demography	X																				
Date of diagnosis of diabetes/Diabetes complications	X																				
Diabetes treatment history																					
Current diabetes treatment	X																				
Dose of current diabetes treatment	X																				
Stop date of current diabetes treatment [b]		X																			
Hypoglycaemia unawareness	X																				
Concomitant illness/medical history	X																				
Concomitant medication/(OAD dosing)[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[o]	X[o]	X[o]
Child bearing potential/Pregnancy[c]	X										X					X					
Tobacco use	X																				
Body measurement																					
Height	X																				
Body weight	X	X					X				X					X					
Randomisation		X																			

Trial NN5401-4266	Screening	Randomisation	Treatment initiation (week 0 - 26)									Treatment Intensification (week 27 - 38)				End of treatment	Follow-up (30 days)		Pre-term discontinuation of trial insulin		
Visit Number (V)	**V1**	**V2**	**V3**	**V6**	**V10**	**V14**	**V18**	**V22**	**V25**	**V27**	**V28**	**V32**	**V33**	**V34**	**V36**	**V40**	**V41[n]**			**V28a[o]**	**V40a[o]**
Weekly Phone Contact number (P) (For details see Table 2-2 below)			**P4 P5**	**P7 P8 P9**	**P11 P12 P13**	**P15 P16 P17**	**P19 P20 P21**	**P23 P24**	**P26**		**P29 P30 P31**			**P35**	**P37 P38 P39**			**P42[n]**	**Px[o]**		
Time of visit (weeks)	**-2**	**0[a]**	**1**	**4**	**8**	**12**	**16**	**20**	**23**	**25**	**26**	**30**	**31**	**32**	**34**	**38**	**39**	**42**	**X**	**26**	**38**
Visit window (days)			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+5	±3	±5	±5	±3
Premature discontinuation/withdrawal		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Rescue Criteria			X	X	X	X	X	X	X	X	X	X	X	X	X						
Efficacy																					
Self-measured plasma glucose																					
SMPGs for titration[d]			X	X	X	X	X	X	X	X	X	X	X	X	X	X					
9-point profile[e]		X					X				X			X		X					
Glucose metabolism																					
Fasting plasma glucose		X			X	X					X			X		X					
HbA_{1c}	X	X			X	X	X	X	X	X	X	X	X	X	X	X				X	X
Safety																					
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[o]	X[o]
Technical complaints	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Hypoglycaemic episodes		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Eye examination	X[f]										X[g]					X[g]					
Vital signs	X										X					X					
Physical examination	X										X					X					
ECG	X[h]										X[i]					X[i]					
Antibody sampling		X		X	X	X					X					X	X				
Biochemistry	X										X					X					
Haematology	X										X					X					
Other assessments																					
PRO questionnaires																					
Baseline Hypo Questionnaire		X																			
SF-36v2®		X									X					X					
TRIM-D		X									X					X					

Trial NN5401-4266	Screening	Randomisation	Treatment initiation (week 0 - 26)									Treatment Intensification (week 27 - 38)				End of treatment	Follow-up (30 days)		Pre-term discontinuation of trial insulin		
Visit Number (V)	**V1**	**V2**	**V3**	**V6**	**V10**	**V14**	**V18**	**V22**	**V25**	**V27**	**V28**	**V32**	**V33**	**V34**	**V36**	**V40**	**V41[n]**			**V28a[o]**	**V40a[o]**
Weekly Phone Contact number (P) (For details see Table 2-2 below)			**P4 P5**	**P7 P8 P9**	**P11 P12 P13**	**P15 P16 P17**	**P19 P20 P21**	**P23 P24**	**P26**		**P29 P30 P31**			**P35**	**P37 P38 P39**			**P42[n]**	**Px[o]**			
Time of visit (weeks)	**-2**	**0[a]**	**1**	**4**	**8**	**12**	**16**	**20**	**23**	**25**	**26**	**30**	**31**	**32**	**34**	**38**	**39**	**42**	**X**	**26**	**38**
Visit window (days)			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+5	±3	±5	±5	±3
Hypoglycaemia resource use see section 8.6.2				X	X	X	X	X			X	X			X	X					
Trial material																					
Administration of trial product																					
Dispensing visit		X		X	X	X	X	X			X	X		X	X	X[j]					
Doses of trial insulin on three consecutive days[d]			X	X	X	X	X	X	X	X	X	X	X	X	X	X					
New dose of trial insulin			X	X	X	X	X	X	X	X	X	X	X	X	X						
Last date and dose on trial product																X					
IWRS session	X	X		X	X	X	X	X			X	X		X	X	X[j]	X				
Drug accountability				X	X	X	X	X			X	X		X	X	X[j]	X				
Trial conduct																					
Hand out ID card	X																				
Handout and instruct in BG-meter	X																				
Handout and instruct in diary	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Attend visit fasting[k]		X		X	X	X					X			X		X	X				
Training in trial product and pen handling		X[l]	X[l]													X[m]					
Diary collect & review + enter visit data in EDC		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Make appointment for eye examination								X				X									
End of trial/ Sign off case book																		X			X

Flow chart footnotes

[a] Randomisation (V2) should take place within 14 days after the screening visit (V1). Screening results must be available and evaluated prior to randomisation.
[b] Subjects must discontinue pre-trial basal insulin, SU and glinides at randomisation. Treatment with other OADs should continue unchanged during the trial.
[c] A serum pregnancy test is required for females of childbearing potential at screening (V1), before intensification (V28) and the end of treatment (EOT) visit (V40). If a menstrual period is missed or pregnancy suspected, a urine pregnancy test must be performed as soon as possible.
[d] Recordings of SMPG values and insulin doses on three consecutive days just prior to dose adjustment as described in the Titration Guideline, Appendix A.
[e] 9-point SMPG profile should be measured starting in the morning two days prior to the scheduled visit – for timing of measurements - Section 8.3.1.2.
[f] Dilated fundoscopy/fundus photography performed for any reason unrelated to this trial within 90 days prior to Visit 2 is acceptable provided no clinical symptoms suggestive of eye disease have occurred in the meantime. It is allowed to perform the screening visit (V1) dilated fundoscopy/fundus photography between the screening visit (V1) and randomisation (V2).
[g] Dilated fundoscopy/fundus photography within a period of three weeks prior to V28 & V40 is acceptable provided no clinical symptoms suggestive of eye disease have occurred in the meantime.
[h] The baseline ECG must be performed at screening (V1) or in the period between screening (V1) and randomisation (V2). The result must be available prior to randomisation.
[i] ECGs before intensification (V28) and at the EOT visit (V40) should be performed at the day of the visit.
[j] Dispense of 'washout' insulin products (BiAsp 30 or NPH + IAsp) to be used in the period between the EOT visit (V40) and the 7-day follow-up visit (V41) – Section 8.1.8.
[k] The subjects must attend these visits fasting to collect FPG samples (Visits 2, 10, 14, 28, 34 and 40) and antibody samples (Visits 2, 6, 10, 14, 28, 40 & 41). Fasting is defined as at least eight hours without food and liquids, except for water. No diabetes treatment (neither trial insulin nor any oral antidiabetic treatment) is allowed up to eight hours prior to these measurements. Intake of other prescribed medicine is however allowed. If non-fasting, blood sampling should be re-scheduled, preferably within the next two working days.
[l] Investigator or delegate staff will ensure proper training in trial product and pen handling. For subjects in the IGlar arm, the training must include pen differentiation. Directions for use (DFU) will be provided to the subjects. Hand-out of the DFU(s) to the subject must be documented in the subject's medical file. Re-training must be performed again at V3 and should be repeated during the trial based on the individual subject's needs.
[m] At the EOT visit (V40) the subjects should be properly trained in how to handle 'washout' insulin products to be used in the period until the 7-day follow-up visit (V41). Handout of DFUs must be documented in the subject's medical file.
[n] Two follow-up visits are to be conducted. The first (V41) must take place no earlier than seven days and no later than 12 days after the EOT visit (V40). The last follow-up visit (P42) will take place approximately 30 days after the EOT visit (V40) and will be conducted as a phone contact (P42).
[o] For subjects prematurely discontinued from trial insulin products, monthly phone contacts (Px), as applicable, should be conducted after the 30-day follow-up (P42) and until the date where the EOT visit (V40) was originally planned to take place (38 weeks after Visit 2). Here an additional abbreviated visit 40 (V40a) should be performed. If the timing of a monthly phone contact is less than two weeks from a planned abbreviated visit, the phone contact can be omitted. If subject discontinues from trial product prior to Visit 28, an additional abbreviated visit 28 (V28a) should be scheduled at the date of the originally planned V28. At the abbreviated visits (V28a and V40a) HbA_{1c} samples and information on adverse events (AEs) will be collected. At these visits, only information about antidiabetic treatment will be collected.

Table 2–2 Phone Contacts

NN5401-4266 Phone contacts (P)[a] Timing of visits are shown in Flow Chart Table 2-1 above	P4-P39	P42	Px[d]
Visit window (days)	± 3	±3	±5
SMPG for titration[b]	X		
Doses of trial insulin(s) on three consecutive days[b]	X		
New dose(s) of trial insulin(s)	X		
Concomitant medication	X	X[c]	X[c]
Adverse events and technical complaints	X	X	X
Hypoglycaemic episodes	X		
Rescue criteria/Premature discontinuation/Withdrawal criteria	X		X
Enter titration data in EDC – preferably within 24 hours	X		

Footnotes:

[a] A phone contact may be converted to a site visit, if needed.
[b] Recordings of self-measured plasma glucose values and insulin doses on three consecutive days just prior to dose adjustment – refer to the Titration Guideline, Appendix A.
[c] Only information about antidiabetic treatment will be collected.
[d] For subjects prematurely discontinued from trial insulin products, monthly phone contacts (Px), as applicable, should be conducted after the 30-day follow-up (P42) and until the date where the EOT visit (V40) was originally planned to take place (38 weeks after Visit 2). Here an additional abbreviated visit 40 (V40a) should be performed. If the timing of a monthly phone contact is less than two weeks from a planned abbreviated visit, the phone contact can be omitted.

3 Background information and rationale for the trial

The trial will be conducted in compliance with this protocol, International Conference on Harmonisation, Guideline for Good Clinical Practice (ICH GCP)[1] and applicable regulatory requirements, and in accordance with the Declaration of Helsinki[2].

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

3.1 Background information

3.1.1 Therapeutic area – type 2 diabetes mellitus

Type 2 diabetes mellitus (T2DM) is a progressive disorder characterized by insulin resistance, impaired insulin secretion and increased hepatic glucose output and thus chronic hyperglycaemia. A number of landmark studies have demonstrated the importance of maintaining tight glycaemic control to reduce the risk of long-term complications associated with diabetes[3-7]. The current treatment guideline by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) follows a stepwise approach comprising lifestyle changes and pharmacological intervention. Metformin is recommended as initial pharmacological therapy, followed by combination therapy with other oral antidiabetic drug(s) (OADs), glucagon-like peptide 1 receptor agonists (GLP-1 RA) or insulin as the disease progresses[8].

As T2DM progresses, intensification of treatment is needed. Basal insulin in combination with either mealtime insulin or GLP-1 RA is recommended, however the combination of basal insulin and mealtime insulin is the most commonly used[9]. Accordingly, products containing both basal and mealtime insulin are a convenient and widely used intensification option.

3.1.2 Insulin aspart

Insulin aspart (IAsp) is a rapid-acting analogue indicated for the treatment of diabetes mellitus, and is the drug substance of the currently marketed products NovoRapid®, NovoMix® and NovoLog®.

IAsp is homologous to human insulin, with the exception of the substitution of proline with aspartic acid at position B28. The rapid action of IAsp is related to a weakened tendency of the insulin molecules to self-associate due to this modification and is thereby related to faster absorption as compared with human insulin.

Compared with human insulin, IAsp has a faster onset and a shorter duration of action, resulting in superior postprandial glycaemic control by means of lowering total glucose excursion following a meal, both in subjects with Type 1 diabetes mellitus and in subjects with T2DM[10-12]. IAsp should generally be given immediately (within 5−10 minutes) prior to the start of a meal.

For further details, refer to the EU Summary of Product Characteristics (EU SmPC)[13] and/or the U.S. Label Information (U.S. LI)[14] and/or the local package insert for IAsp, and any updates thereof.

3.1.3 Insulin degludec/insulin aspart

Insulin degludec/insulin aspart (IDegAsp) is the approved international non-proprietary name for the soluble co-formulation of insulin degludec (IDeg) and insulin aspart (IAsp). The co-formulation consists of 70% IDeg and 30% IAsp and is currently marketed as Ryzodeg® and Ryzodeg® 70/30.

Insulin degludec is the approved international non-proprietary name for the insulin analogue formerly named insulin 454, and is the drug substance of the currently marketed product Tresiba®. IDeg differs from human insulin in that the threonine in position B30 has been omitted, and a side-chain consisting of glutamic acid and a fatty acid has been attached. The protracted action of insulin degludec is related to its ability to self-assemble into soluble multi-hexamers at the injection site and, to a lesser degree, through the ability to bind to albumin via the fatty-acid side-chain. This way IDeg mimics the endogenous basal insulin secretion with an ultra-long duration of action with a low risk of hypoglycaemia. When co-formulating IAsp with IDeg, the benefits of the flat and stable ultra-long-acting basal IDeg and the rapid-acting IAsp are combined in one injection with each component acting independently. Accordingly, IDegAsp provides both a basal insulin affecting fasting plasma glucose (FPG) and a mealtime insulin affecting post prandial glucose with the convenience of a single injection. For further details refer to current version of the EU SmPC[15] and/or U.S. LI[16] and the Investigator's Brochure (IB) of IDegAsp[17] and any updates thereof.

3.1.4 Insulin glargine

Insulin glargine, (IGlar, Lantus®) is a long-acting insulin analogue, indicated for treatment of diabetes mellitus in combination with oral antidiabetic agents and as part of a basal-bolus insulin regimen.

An amino-acid substitution at position A21 (compared with human insulin) causes precipitation of insulin glargine upon injection, forming a depot from which it is slowly released[18].Compared with neutral protamine Hagedorn (NPH) insulin, this results in a prolonged action, lower mean FPG levels and a lower incidence of nocturnal hypoglycaemia, whereas within-subject variation in absorption is comparable to that observed with NPH insulin[19-26].

For further details, refer to the current versions of the EU SmPC[27] and U.S. LI[18] or local package insert for IGlar, and any updates thereof.

3.1.5 Insulin antibodies

Exposure to a new insulin product can trigger antibody development. As part of the assessment of the long-term safety of IDeg or IDegAsp, antibodies specific to IDeg as well as antibodies cross reacting to human insulin were measured in some phase 3 trials. From these trials there was no evidence of neutralising antibodies following treatment with IDeg or IDegAsp. There was no correlation of antibodies to HbA_{1c}, nor to the dose in the IDeg or IDegAsp trials[17, 28].

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

3.2 Rationale for the trial

IDegAsp (Ryzodeg®) is approved for treatment of diabetes mellitus in adults in more than 60 countries worldwide including U.S., India and Europe. However, so far no clinical trials have been conducted investigating stepwise intensification of IDegAsp OD to twice daily (BID).

Further, additional efficacy and safety data for IDegAsp OD, including comparison against a fair comparator as a basal and a single daily bolus regimen (IGlar OD+ IAsp OD) is needed to further support the IDegAsp OD use.

This trial will also provide information on the efficacy and safety of a stepwise intensification with IDegAsp OD to BID compared to IGlar OD + IAsp (1-3 times daily) in subjects with T2DM inadequately controlled on basal insulin with and without OAD(s).

The immunological response to the trial insulin products will be monitored following the European Medicines Agency (EMA) guideline on this subject[29].

4 Objectives and endpoints

4.1 Objectives

The primary objective

To confirm the effect of insulin degludec/insulin aspart once daily versus insulin glargine once daily in combination with insulin aspart once daily in controlling glycaemia after 26 weeks in subjects with type 2 diabetes mellitus treated with basal insulin with or without oral antidiabetic treatment in need of treatment intensification.

The secondary objectives

- To compare other effect parameters and safety of insulin degludec/insulin aspart once daily versus insulin glargine once daily in combination with insulin aspart once daily after 26 weeks in subjects with type 2 diabetes mellitus treated with basal insulin with or without oral antidiabetic treatment in need of treatment intensification.
- To compare the effect and safety of insulin degludec/insulin aspart once daily or twice daily versus insulin glargine once daily in combination with insulin aspart (1-3 times daily) after 38 weeks in subjects with type 2 diabetes mellitus treated with basal insulin with or without oral antidiabetic treatment in need of treatment intensification.

4.2 Endpoints

4.2.1 Primary endpoint

Change from baseline in glycosylated haemoglobin (HbA_{1c}) (%) after 26 weeks

4.2.2 Supportive secondary endpoints

4.2.2.1 Supportive secondary efficacy endpoints

At 26 weeks:

- Responder (Yes/No) for HbA_{1c} after 26 weeks
  - $HbA_{1c} < 7\%$*
  - $HbA_{1c} < 7\%$ without nocturnal (00:01-05:59) blood glucose (BG) confirmed symptomatic hypoglycaemia
- Change from baseline in fasting plasma glucose (FPG) after 26 weeks

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

- Self-measured plasma glucose measurements (SMPG) after 26 weeks
  - Mean pre-breakfast measurements used for titration
  - 9-point profile
    - Post-prandial increments

At 38 weeks:

- Change from baseline in HbA_{1c} (%) after 38 weeks*
- Responder (Yes/No) for HbA_{1c} after 38 weeks:
  - $HbA_{1c} < 7\%$*
  - $HbA_{1c} < 7\%$ without nocturnal (00:01-05:59) BG confirmed symptomatic hypoglycaemia
- Change from baseline in fasting plasma glucose (FPG) after 38 weeks
- Self-measured plasma glucose measurements (SMPG) after 38 weeks
  - Mean pre-breakfast measurements used for titration
  - 9-point profile
    - Post-prandial increments

4.2.2.2 Supportive secondary safety endpoints:

During 26 weeks:

- Number of nocturnal, treatment-emergent severe or BG confirmed symptomatic hypoglycaemic episodes during 26 weeks
- Number of nocturnal, treatment-emergent severe or BG confirmed hypoglycaemic episodes during 26 weeks
- Number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during 26 weeks*
- Number of treatment-emergent severe or BG confirmed hypoglycaemic episodes during 26 weeks
- Number of nocturnal, treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during maintenance (week 16-26)
- Number of nocturnal, treatment-emergent severe or BG confirmed hypoglycaemic episodes during maintenance (week 16-26)
- Number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during maintenance (week 16-26)
- Number of treatment-emergent severe or BG confirmed hypoglycaemic episodes during maintenance (week 16-26)
- Total insulin dose at week 26
- Change in weight from baseline to week 26
- Incidence of treatment-emergent adverse events (TEAEs) from baseline to week 26

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

- Change from baseline to week 26 in:
  - Physical examination
  - Vital signs (blood pressure and pulse)
  - Dilated fundoscopy or fundus photography
  - 12-lead electrocardiogram
  - Laboratory assessments
  - Haematology (haemoglobin, haematocrit, erythrocytes, thrombocytes, leucocytes)
  - Biochemistry (creatinine, alanine aminotransferase, aspartate aminotransferase , alkaline phosphatase, sodium, potassium, albumin, total bilirubin)
  - Insulin antibodies

During 38 weeks:

- Number of nocturnal, treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during 38 weeks
- Number of nocturnal, treatment-emergent severe or BG confirmed hypoglycaemic episodes during 38 weeks
- Number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during 38 weeks*
- Number of treatment-emergent severe or BG confirmed hypoglycaemic episodes during 38 weeks
- Total insulin dose at week 38
- Change in weight from baseline to week 38
- Incidence of treatment-emergent adverse events (TEAEs) during 38 weeks*
- Change from baseline to week 38 in:
  - Physical examination
  - Vital signs (blood pressure and pulse)
  - Dilated fundoscopy or fundus photography
  - 12-lead electrocardiogram
  - Laboratory assessments:
    - Haematology (haemoglobin, haematocrit, erythrocytes, thrombocytes, leucocytes)
    - Biochemistry (creatinine, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, sodium, potassium, albumin, total bilirubin)
    - Insulin antibodies

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

Supportive secondary patient reported health economics endpoints

- Change from baseline to week 26 for:
  - Health-related quality of life as evaluated by the SF-36v2®
  - Treatment related impact as evaluated by TRIM D
- Change from baseline to week 38 for:
  - Health-related quality of life as evaluated by the SF-36v2®
  - Treatment related impact as evaluated by TRIM-D

5 Trial design

5.1 Type of trial

This is a 38-week, multinational, open-label, randomised (1:1), controlled, parallel, treat-to-target trial in subjects with T2DM treated with basal insulin with or without OAD(s) in need of treatment intensification. The aim of the trial is to compare IDegAsp OD vs IGlar OD + IAsp OD with or without OAD(s) after 26 weeks of treatment. In addition, a comparison of a stepwise treatment intensification of 12 weeks with IDegAsp OD to BID vs. IGlar OD + IAsp 1 to 3 times daily will be performed.

Subjects will be randomised in a 1:1 manner into one of the stepwise treatment intensification arms below and treated as described in Section 5.3.3.

IDegAsp arm:

- Initial 26 weeks: IDegAsp OD administered at the largest meal each day ± OAD(s)
- Intensification period – Week 26-38: IDegAsp OD/BID administered at the largest meal(s) each day based on individual needs ± OAD(s)

IGlar + IAsp arm:

- Initial 26 weeks: IGlar OD administered in accordance with local labelling and IAsp OD administered at the largest meal ± OAD(s)
- Intensification period – Week 26-38: IGlar OD administered in accordance with local labelling and IAsp 1-3 times daily administered at main meals based on individual needs ± OAD(s)

The trial design is summarised schematically in Figure 5–1

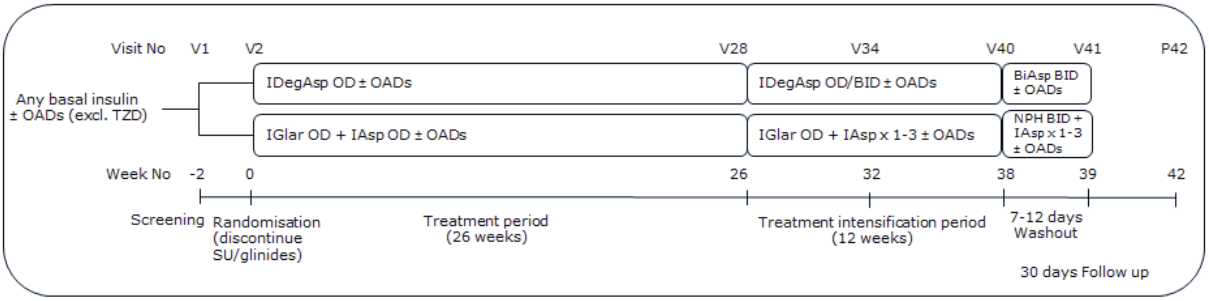


Figure 5–1 Trial Design

Randomisation will be stratified based on the pre-trial basal insulin treatment regimen: OD or BID/TID dosing. Subjects on a BID/TID regimen will be shifted to OD dosing in accordance with the Titration Guideline, Appendix A.

A population of subjects with HbA_{1c} between 7.0-10.0% (both inclusive) treated with any basal insulin with or without OAD(s), and thus not achieving the recommended treatment target, and therefore in need of treatment intensification has been chosen.

The duration of the trial will be approximately 44 weeks and includes:

- Screening Visit (V1)
- Randomisation Visit (V2)
- Weekly contacts (phone or clinic visits (V3-V40)) throughout the 38 weeks' treatment period, refer to flow chart (Section 2)
- Two Follow-up visits at 7-12 days (V41) and 30 days (P42) after the end of treatment (EOT) visit (V40)

5.2 Rationale for trial design

An open label trial design has been chosen as blinding is not feasible due to the different regimens in the two treatment arms.

The reason for stratifying according to pre-trial basal insulin dosing OD or BID/TID is to ensure that these sub-populations are equally represented in both arms. The treat to target design will be implemented using a very tight visit schedule in order to ensure optimal insulin titration based on SMPG values and to ensure improvement in glycaemic control in the treatment initiation period. The initial 26-week treatment period is expected to be sufficient to initiate and up-titrate the trial treatment to obtain data for evaluation of efficacy, safety and PROs.

Similarly the 12-week intensification period is expected to be sufficient to intensify and up-titrate the trial treatment to obtain data for evaluation of efficacy, safety and PROs.

The multinational approach is to ensure that the results are applicable for subjects with different demographic characteristics.

The primary endpoint HbA_{1c} is a laboratory parameter and consequently the probability of assessment bias is limited.

The two follow-up visits are included to ensure proper follow-up on subject safety after end of trial drug-treatment.

A 1-week interval between the EOT visit (V40) and the 7-day follow-up visit (V41) is necessary to allow for trial insulin 'washout' prior to measurement of insulin antibodies. Due to the much shorter duration of the type of basal insulins (NPH or biphasic insulin aspart 30 (BiAsp 30)) used in the 'washout' period, the levels of insulin will be lower at the sampling time point at the 7-day follow-up (V41). For insulin treatment in the 'washout' period, see Section 5.5.

A 30-day follow-up (P42) after last trial insulin treatment (V40) will be performed in order to collect information about antidiabetic treatment and adverse events (AEs) occurring between V41 and P42.

5.3 Treatment of subjects

Subjects with T2DM treated with any basal insulin with or without OAD(s) can enter the trial if they have an HbA_{1c} between 7.0-10.0% (both inclusive).

Subjects will attend a screening visit (V1) where inclusion and exclusion criteria will be assessed.

If eligible, subjects will be randomised to their trial insulin treatment at the randomisation visit (V2), refer to Sections 5.3.1 and 5.3.2.

At randomisation subjects must discontinue pre-trial insulin, SU and glinides. Treatment with other OADs should continue during the trial as described in Section 5.4.

For subjects in both treatment arms diet and exercise counselling should be continued as per the standard of care at the investigational site.

At the EOT visit (V40) subjects should be switched to 'washout' insulin as described in Section 5.5

5.3.1 Treatment regimens arms

Subjects will be randomised into a 1: 1 manner as described in Section 5.1 into the two stepwise treatment intensification arms below and treated as described in Section 5.3.3:

IDegAsp arm:

- Initial 26 weeks: IDegAsp OD administered at the largest meal each day ± OAD(s)
- Intensification period – Week 26-38: IDegAsp OD/BID administered at the largest meal(s) each day based on individual needs ± OAD(s)

IGlar + IAsp arm:

- Initial 26 weeks: IGlar OD administered in accordance with local labelling and IAsp OD administered at the largest meal ± OAD(s)
- Intensification period – Week 26-38: IGlar OD administered in accordance with local labelling and IAsp 1-3 times daily administered at main meals based on individual needs ± OAD(s)

5.3.2 Trial insulin products

The below trial insulin products will be provided by Novo Nordisk A/S:

- Insulin degludec/insulin aspart (Ryzodeg®) 100 units/mL, 3 mL pre-filled pen (FlexTouch®), solution for subcutaneous injection, Novo Nordisk A/S
- Insulin glargine (Lantus®) 100 units/mL, 3 mL pre-filled pen (SoloStar®), solution for subcutaneous injection, Sanofi-Aventis
- Insulin aspart (NovoRapid®/NovoLog®), 100 units/mL, 3 mL pre-filled pen (FlexPen®), solution for subcutaneous injection, Novo Nordisk A/S

The subjects must be trained in how to handle the above pre-filled pen-devices when handed out the first time (refer to section 8.6.3). For further information on trial insulin products, see Section 9.

5.3.3 Trial insulin treatment

Subjects will receive either IDegAsp OD or IGlar OD + IAsp OD during the first 26 weeks and continue into a 12-week intensification period.

Subjects on a pre-trial BID/TID basal insulin regimen will be shifted to OD dosing in accordance with the Titration Guideline, Appendix A.

For information about initial doses, area of injection, dosing time and the weekly dose adjustments during the initial treatment period (week 2-26), refer to the Titration Guideline, Appendix A.

At week 26 (V28) , subjects not achieving sufficient glycaemic control (V27 $HbA_{1c} \geq 7\%$) will be further intensified from either IDegAsp OD to IDegAsp BID or IGlar OD + IAsp OD to IGlar OD + IAsp BID. Subjects in good glycaemic control (V27 $HbA_{1c} < 7\%$) will continue their insulin treatment regimen.

At week 32 (V34), glycaemic control will be evaluated again, and subjects in good glycaemic control (V33 $HbA_{1c} < 7\%$) will continue their insulin treatment regimen. Subjects on IDegAsp OD not reaching the glycaemic target (V 33 $HbA_{1c} \geq 7\%$) will be intensified to IDegAsp BID, whereas subjects in the IGlar arm not reaching glycaemic control will be intensified with one additional IAsp dose to IGlar OD + IAsp BID or TID daily for the remaining six weeks of the intensification period.

Information about doses, dosing time and dose adjustments during the treatment intensification period (week 27-38) can be found in the Titration Guideline, Appendix A.

Information about insulin treatment in the 'washout' period between the EOT visit (V40) and the 7-day follow-up visit (V41) can be found in Section 5.5.

5.4 Oral antidiabetic treatment

Upon trial entry, subjects treated with any of the below allowed OADs should continue their treatment unchanged, meaning subjects should not:

- start treatment with any other antidiabetic treatment
- change the pre-randomisation OAD(s) dose or dosing frequency[a)]
- start treatment with any medication known to interfere significantly with glucose metabolism

[a)] However, for safety reasons, a decrease in the OAD(s) dose is allowed if deemed necessary by the investigator.

OADs are not considered trial products and will not be supplied by Novo Nordisk A/S, refer to Section 9.1.

5.4.1.1 Allowed OADs

As prior to randomisation:

- Metformin
- α-glucosidase-inhibitors
- DPP-4 inhibitors
- SGLT2 inhibitors
- Oral combination products (of the allowed individual OADs above)

5.4.1.2 OADs prohibited during trial treatment:

Below OADs must be discontinued upon randomisation visit (V2) and must not be initiated during the trial:

- Insulin secretagogues (SU and glinides)

5.5 Treatment after discontinuation of trial product

When discontinuing trial product(s), either at the scheduled EOT visit (V40) or if trial product is discontinued prematurely, the subject should be asked to attend the trial site for completion of the following visits:

- EOT visit (V40)

At this visit the subjects randomised to the two treatment arms should be switched to the following 'washout' insulin treatment and continue other oral antidiabetic treatment until the 7-day follow-up visit (V41):

  - **IDegAsp arm:** Switch IDegAsp dose to BiAsp 30 BID. The total daily IDegAsp dose at end of the treatment period should be reduced by 20% and divided into two BiAsp 30 doses and administered with breakfast/lunch and evening meal.
  - **IGlar + IAsp arm:** Switch IGlar dose to NPH insulin BID. The IGlar dose at the end of the treatment period should be reduced by 20% and divided into two NPH doses and administered in the morning and in the evening. IAsp doses should be continued as in the treatment period.

- 7-days follow-up visit (V41):

At this visit subjects should be switched to suitable marketed insulin product(s) at the discretion of the investigator.

- A 30-day follow-up visit (P42) – refer to section 8.1.9

In addition, for subjects pre-term discontinued, monthly phone contacts (Px) as applicable, an abbreviated V28 (V28a), if applicable, and an additional abbreviated EOT visit (V40a) will be conducted as described in Sections 8.1.9 and 8.1.11 also refer to the flow chart (Section 2).

5.6 Rationale for treatment

In patients not achieving treatment target on basal insulin, addition of either mealtime insulin or GLP-1 RA is recommended by the ADA/European Association for the Study of Diabetes (EASD) guidelines. The combination of basal insulin and mealtime insulin is the most commonly used; either as basal/bolus regimens or as combination products. Accordingly, this trial will provide information on the efficacy and safety of the combination product IDegAsp OD compared to IGlar OD + IAsp OD and of the stepwise intensification of mealtime insulin with two different treatment intensification regimens.

Subjects treated with SU and glinides should discontinue the use of these at randomisation because the combination with trial insulin products could lead to an increased risk of hypoglycaemia.

Dosing is individual and the treat to target approach is used to optimise glycaemic control throughout the trial.

The subcutaneous administration form of all trial products is in accordance with approved documents as follows:

- IDegAsp: IB and/or EU SmPC and/or U.S. LI
- IGlar: U.S. LI/ EU SmPC
- IAsp: EU SmPC and/or U.S. LI

IGlar has been chosen as the comparator as it is approved for OD use only, is commonly used for insulin initiation in T2DM subjects and is currently the most widely used basal insulin in many countries.

Based on data from the clinical development programme for IDegAsp, and the fact that there is no maximum dose of IDegAsp treatment, the chosen duration of the trial is considered appropriate for the purpose of obtaining meaningful information on efficacy and safety of IDegAsp when intensifying treatment from OD to BID.

The switch from trial insulin treatment to the ‘washout’ insulin (BiAsp 30 or NPH + IAsp) between the EOT visit (V40) and the 7-day follow-up visit (V41), is done in order to provide basal insulin coverage while reducing the level of exogenous insulin present at antibody sampling and consequently to reduce the possibility for interference with antibody measurements.

6 Trial population

6.1 Number of subjects

Planned number of subjects to be screened meaning the number of subjects providing informed consent: 754.

Planned number of subjects to be randomised/started on trial products: 528.

Expected number of subjects to complete the trial: 449.

A screening failure rate of 30% and a premature discontinuation of trial drug/withdrawal rate of randomised subjects of 15% are expected.

6.2 Inclusion criteria

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

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial

2. Male or female, age ≥ 18 years at the time of signing informed consent
   Algeria: Male or female, age ≥ 19 years at the time of signing informed consent

3. Diagnosed with type 2 diabetes mellitus

4. Treated with any basal insulin ≥ 90 days prior to the day of screening

5. Subject not on any OAD(s) prior to trial participation OR subjects on stable daily dose(s) of OAD(s) for at least 90 days prior to screening visit (V1). The OAD(s) include any of the following anti-diabetic drug(s)/regimen:

   a. Biguanides (metformin ≥ 1500 mg or maximum tolerated dose documented in the subject medical record)

   b. Other OADs (≥ half of the maximum approved dose according to local label or maximum tolerated dose as documented in subject medical record):

      i. Insulin secretagogues (SU and glinides)
      ii. DPP-4 inhibitors
      iii. α-glucosidase inhibitors
      iv. SGLT-2 inhibitors
      v. Oral combination products (of the allowed individual OADs)

6. HbA_{1c} 7.0-10.0% (53-86 mmol/mol) (both inclusive) by central laboratory analysis

7. Body mass index (BMI) ≤ 45.0 kg/m^2

8. Ability and willingness to adhere to the protocol including self-measurement of plasma glucose according to the protocol

6.3 Exclusion criteria

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

1. Known or suspected hypersensitivity to trial product(s) or related products
2. Previous participation in this trial. Participation is defined as signed informed consent
3. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using adequate contraceptive methods (adequate contraceptive measures as required by local regulation or practice)
4. Participation in any clinical trial of an approved or non-approved investigationalmedicinal product within four weeks prior to the day of screening (V1)
5. Any chronic disorder or severe disease which, in the opinion of the investigator, might jeopardise subject's safety or compliance with the protocol
6. Acute decompensation of glycaemic control requiring immediate intensification of treatment to prevent severe metabolic dysregulation (e.g. diabetes ketoacidosis) $\leq$ 90 days prior to the day of the screening
7. Any of the following: myocardial infarction, stroke or hospitalization for unstable angina or transient ischaemic attack within the past 180 days prior to the day of screening and between screening and randomisation
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
10. Renal impairment measured as estimated Glomerular Filtration Rate (eGFR) value of < 60 ml/min/1.73 m^2 as defined by KDIGO 2012 classification using isotope dilution mass spectrometry (IDMS) for serum creatinine measured at screening
11. Impaired liver function, defined as ALT $\geq$ 2.5 times upper normal limit (UNL) at screening
12. Inadequately treated blood pressure defined as Grade 3 hypertension or higher (Systolic $\geq$180 mmHg or diastolic $\geq$110 mmHg) at screening
13. Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria in a period of 90 days before the day of screening
14. 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)
15. Proliferative retinopathy or maculopathy requiring acute treatment. Verified by fundus photography or dilated fundoscopy performed within 90 days prior to randomisation

16. Presence or history of malignant neoplasms within the past five years prior to the day of screening. Basal and squamous cell skin cancer and any carcinoma in-situ are allowed

6.4 Randomisation criteria

Not applicable for this trial.

6.5 Rescue criteria

If any of the fasting SMPG values taken on three consecutive days or if any of the FPG samples analysed by the central laboratory exceed the limit of:

- 15.0 mmol/L (270 mg/dL) from baseline to end of week 12
- 13.3 mmol/L (240 mg/dL) from week 13 to end of week 38

and if no treatable inter current cause for the hyperglycaemia has been identified, the subject must be called for a confirmatory FPG measurement at a scheduled or unscheduled visit as soon as possible. A confirmatory FPG must be obtained and analysed by the central laboratory. If this FPG exceeds the limits described above, the trial product must be discontinued.

The subject should be prescribed alternative therapy at investigator´s discretion, and be retained in the trial.

If prematurely withdrawn from trial drug, effort should be made to follow the procedures described in Section 8.1.11. Also refer to Section 5.5.

6.6 Criteria for premature discontinuation of trial product

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 product at the discretion of the investigator due to a safety concern or if judged non-compliant with trial procedures.

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

1. Included in the trial in violation of any of the inclusion and/or exclusion criteria
2. Pregnancy
3. Intention of becoming pregnant
4. Initiation or significant change in concomitant medications for more than 14 calendar days which in the investigator's opinion could affect weight or glucose metabolism
5. Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product
6. The fasting SMPGs values taken on three consecutive days or any FPG samples analysed by the central laboratory exceeding the limit of (refer to section 6.5):
    - 15.0 mmol/L (270 mg/dL) from baseline to end of week 12
    - 13.3 mmol/L (240 mg/dL) from week 13 to end of week 38

Subjects discontinued from trial product should be prescribed alternative therapy at investigator´s discretion, and be retained in the trial.

For procedures to be performed for subjects discontinuing trial product prematurely, see Sections 8.1.11 and 5.5.

6.7 Withdrawal from trial

The subject may withdraw consent at will at any time.

Subjects who consider withdrawing informed consent should be encouraged to have procedures performed according to end of trial visit and the follow-up contacts (V41 and P42) as described in Section 8.1.9.

A subject who agrees to provide information on HbA_{1c}, AEs and other assessments relevant for the evaluation of trial endpoints at the planned end of the trial are not to be considered withdrawn from the trial.

Only subjects who decline any further contact with the site in relation to the trial, and hence do not agree to report information should be considered as withdrawn.

Subjects who are withdrawn will not be replaced. For procedures to be performed for subjects withdrawing consent, see Section 8.1.12.

6.8 Subject replacement

Subjects who discontinue trial product prematurely will not be replaced.

6.9 Rationale for trial population

A population of subjects with T2DM treated with basal insulin with or without OAD(s) with an HbA_{1c} between 7.0-10% (both inclusive) has been chosen for this trial to confirm the efficacy of IDegAsp OD vs IGlar OD + IAsp OD with or without OAD(s) in controlling glycaemia and also to demonstrate that treatment intensification with IDegAsp OD to BID is efficacious and safe in subjects not achieving recommended treatment target on OD treatment.

The inclusion and exclusion criteria applied in this trial were selected to allow for inclusion of a trial population as broad as possible to ensure generalizability of trial results to the broad population of subjects with T2DM treated with basal insulin with or without OAD(s) in need of treatment intensification.

A BMI limit of ≤ 45.0 kg/m^2 was chosen to include as broad a population as possible only limiting extremely obese subjects with high insulin resistance.

Stable glucose lowering therapy prior to trial enrolment ensures stable levels of glycaemia which could otherwise influence the trial endpoints.

Only serious concomitant conditions (NYHA class IV, history of recent serious cardiac events, neoplastic disease, renal or hepatic impairment, and pre-planned major surgery etc.) which could interfere with subject safety and trial procedures preclude subjects from entering into the trial.

7 Milestones

Planned duration of recruitment period (i.e. first patient first visit (FPFV) – last patient first visit (LPFV)): 16 weeks

Planned date for FPFV: 20 Sep 2016

Planned date for last patient last visit (LPLV): 16 Nov 2017

End of trial is defined as LPLV.

Recruitment:
The screening and randomisation rate will be followed closely via the interactive voice/web response system (IWRS) in order to estimate when to stop screening. All investigators will be notified immediately when the recruitment period ends, after which no further subjects may be screened and the IWRS will be closed for further screening. All subjects screened during the recruitment period and found eligible for randomisation can be randomised within the timelines specified in the flow chart (Section 2).

Trial registration:
Information of the trial will be disclosed at clinicaltrials.gov and novonordisk-trials.com. According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure[30], it will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE)[31], the Food and Drug Administration Amendment Act (FDAAA)[32], European Commission Requirements[33, 34] and other relevant recommendations or regulations. If a subject requests to be included in the trial via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the subject. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

8 Methods and assessments

8.1 Visit procedures

The following Sections describe the assessments and procedures as well as how to record the results. Timing of the site visits, telephone contacts, visit windows and the assessments to be performed are specified in the flow chart (Section 2).

8.1.1 Investigator assessments

Review of the electrocardiogram (ECG) results and the eye examination reports must be documented by the dated signature on the documents and/or in the subject's medical record.

Investigator must evaluate laboratory results and document this by dated signature on the laboratory report printouts. In case any laboratory result is outside the reference range, the investigator must evaluate and document if clinically significant (CS) or not clinically significant (NCS) at the printouts.

Screening results must be evaluated, dated and signed prior to randomisation. For the subsequent visits, evaluation and sign-off should take place as soon as possible upon the receipt of the documents. The signed documents must be retained at the trial site as source documentation.

In case of abnormal CS findings (ECGs, dilated fundoscopy or fundus photography, physical examination and laboratory parameters) the investigator must state a comment in the subject's medical record. If present at screening V1, this should be documented in the concomitant illness form in the electronic case report form (eCRF). At subsequent visits, any clinically significant changes or new clinically significant findings must be reported as an AE according to Section 12.

8.1.2 Visit Schedule

It is the responsibility of the investigator to ensure that all site visits and phone contacts occur according to the flow chart (Section 2).

After the randomisation visit (V2), the visit scheduling should always be based on the actual V2 date, except for the follow-up visits V41 and P42, which should be scheduled based on the EOT visit (V40) date, refer to Section 8.1.9

8.1.3 Phone contacts

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

If for some reason a planned phone contact was not completed, the investigator should ensure to perform the phone contact within the allowed visit window.

8.1.4 Fasting requirements

The subject should attend some clinic visits in fasting condition - refer to flow chart (Section 2).

Fasting is defined as at least eight hours without food and liquids, except for water. No diabetes treatment (neither trial insulin, nor any OADs) is allowed up to eight hours prior to these measurements. Any other prescribed medication should be taken as usual.

If non-fasting, blood sampling should be re-scheduled preferably within the next two working days, refer to Section 8.5.1.2.

8.1.5 Diaries

At each clinic visit, the subjects must receive diaries related to the following visit and/or phone contact(s). The diaries dispensed to subjects should be collected at the following clinic visit. However, for the screening visit (V1), the 30-days follow-up visit (P42) and the monthly phone contacts (in case of pre-term discontinuation of trial insulin products) no diaries will be provided.

The investigator should instruct subjects how to complete the diaries and ensure completion of these in accordance with the instruction provided.

Investigator or delegated staff must review data entered in the subject diaries, including PROs. Review of the diary and PROs must be documented either on the document and/or in the subject's medical record. If clarification of entries or discrepancies in the diary is needed, the subject must be questioned and a conclusion made in the subject's medical record. Care must be taken not to bias the subject.

It is the responsibility of the investigator to review the diary for subject's notes regarding possible AEs, hypoglycaemic episodes and concomitant medication, see Sections 12, 8.4.7 and 8.2.5.

Safety data from the diaries must be handled according to timelines described in Section 12.2.

The investigator or delegated staff should transcribe diary data into the eCRF as soon as possible after each site visit/phone contact. If necessary, the investigator should convert the format of data used by the subject into the format used in the eCRF.

Titration data should preferably be entered within 24 hours (refer to Appendix A). If data is obtained via phone and a discrepancy is later detected, the values in the eCRF should be corrected to the diary.

The investigator is only allowed to record the following data in the diary:

- Subject ID
- Site contact details
- Time and date of next visit or phone contact
- Prescribed dose(s) of trial insulin(s)
- Review signature

The subject must record the following information in the diary:

- Dates and doses of trial product injection, including first and last dose of trial product (V2-V40)
- Date, time and value of SMPG measurements used for weekly titration purposes (V2-V40)
- 9-point SMPG profile measurements including: date and actual clock time (V2, V18, V28, V34 and V40)
- Medical condition(s) including: hypoglycaemic episodes, other AEs, and potential change(s) in concomitant medication during the trial (V2-P41)

8.1.6 Screening

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

Details about retention long-term storage of antibody (AB) samples will be included in the informed consent, and subjects will be asked to consent to this. For further information, refer to Section 24.2

The investigator must keep a subject screening log, a subject identification code list and a subject enrolment log. Only subjects who have signed the informed consent form should be included on the logs. The subject screening log and subject enrolment log may be combined in one log.

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

At this visit, information about the subjects' pre-trial basal insulin and OAD treatment (start date and current dose) should be captured in the subjects' medical notes and transcribed into the eCRF.

Subjects will receive a blood glucose meter (BG-meter) and a diary. Investigator or delegated staff will instruct the subject in how to use both, see Sections 8.1.5 and 8.3.1.

Each subject will be assigned a unique 6-digit subject number which will remain the same throughout the trial.

A screening session in IWRS must be made, refer to Section 10.

8.1.6.1 Screening failures

For screening failures the screening failure form in the eCRF must be completed with the reason for not continuing in the trial. Serious and non-serious AEs from screening failures must be transcribed

by the investigator into the eCRF. Follow-up on serious adverse events (SAEs) must be carried out according to Section 12.

A screening failure session must be made in the IWRS. The case book must be signed.

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

8.1.7 Randomisation visit (V2)

Randomisation (V2) should take place within 14 days after the screening visit (V1). All results from screening assessments, including laboratory results, ECG and eye examination must be available, reviewed, dated and signed by the investigator and the in/exclusion criteria carefully reviewed to ensure subject eligibility prior to randomisation.

Randomisation of subjects will be done using IWRS, see Sections 10 and 11.

At V2 trial insulin products will be supplied to the subject after having completed the IWRS dispense call, see Section 10. Investigator or delegate staff will ensure proper training in trial product and pen handling. For subjects in the IGlar arm, the training must include pen differentiation. Directions for use (DFUs) will be provided to the subjects, refer to Section 8.6.3.

Hand-out of the DFU(s) to the subject must be documented in the subject's medical file.

At randomisation subjects must discontinue their pre-trial insulin, SU and glinides and the stop-date(s) must be recorded in the subjects' medical notes and transcribed into the eCRF. Treatment with other OADs should continue unchanged during the trial, see Section 5.4.

PRO questionnaires including baseline hypoglycaemia questionnaire (BHQ) must be completed by the subjects - please refer to Section 8.6.1.

For further details on trial procedures and assessments, refer to the Flow chart (Section 2).

8.1.8 Treatment period (V3-V40)

The treatment period includes the following:

- The treatment initiation period weeks 2-26 (V3-V28)
- The intensification period weeks 27-38 (V29-V40)
- The EOT visit (V40)

After randomisation and until the EOT visit (V40), trial products to subjects will be allocated and dispensed to subjects and accounted for at pre-specified visits utilising IWRS, refer to Flow chart (Section 2) and Section 10.

For details on trial drug treatment, refer to Sections 5.3 and 9.

Subjects are instructed to return all used, partly used and unused trial product at each dispensing visit during the treatment period ending at V40 with the EOT visit. At this visit subjects must discontinue trial insulin treatment.

At the EOT visit (V40) 'washout' insulin (BiAsp 30 or NPH + IAsp) to be used in the 'washout' period between V40 and the 7-day follow-up visit (V41) will be dispensed to all subjects. A DFU must be handed out at V40 and this must be documented in the subject's medical file. For dosing of 'washout' insulin, see Section 5.5.

For other procedures and assessments performed during the treatment period, refer to the flow chart (Section 2).

8.1.9 Follow-up visits

In order to properly follow-up on subject safety after subjects have stopped their trial insulin treatment the subjects should attend two follow-up visits after the EOT visit (V40):

- Clinic Visit (V41); which will be conducted 7-12 days after V40
- Phone Contact (P42); 30-35 days after V40 (according to visit window)

Subjects should attend V41 fasting for AB sampling (refer to Section 8.1) and subjects should return 'washout' insulin products at trial site for final drug accountability. Information about concomitant medication and AEs including hypoglycaemia will be collected. Subjects will be switched to a marketed insulin product at the discretion of the investigator.

For the last follow-up visit (P42) and potential monthly phone contacts (Px), no paper diary will be provided. Consequently, source data for these phone contacts will be the notes written in the subject's medical record. At these contacts only information about antidiabetic treatment and AEs will be collected.

8.1.10 Unscheduled visits

Unscheduled visits can be performed at any time at the discretion of the investigator. An unscheduled visit should be performed if, e.g. an AE occurs that needs further attention.
An unscheduled visit form in the eCRF must be completed, stating the reason for the visit.

However, completion of the unscheduled visit form should not be carried out if the subject attends the clinic:

- For a visit rescheduled within the allowed visit window
- Only to obtain additional trial insulin products or auxiliary supplies

If a subject requires additional trial insulin products, an additional IWRS dispensing session must be performed.

If blood samples for a subject are re-taken, a laboratory requisition form should always be completed, and the visit number to which the sample belongs clearly indicated (please refer to the Laboratory Manual).

8.1.11 Premature discontinuation of trial product

In case of premature discontinuation of trial product the investigator should make all effort to call the subject in for an unscheduled visit as soon as possible and must aim to undertake procedures similar to those for the EOT visit (V40), including fasting blood sampling and hand-out of 'washout' insulin products (refer to Section 5.3.3) to be used in the period between the EOT visit (V40) and the 7-day follow-up visit (V41), where the last AB sampling will be performed.

Furthermore, the follow-up visits (V41 and P42) must be performed as described in Section 8.1.9.

For subjects prematurely discontinued from trial insulin products, monthly phone contacts (Px), as applicable, should be conducted after the 30-day follow-up (P42) and until the date where the EOT visit (V40) was originally planned to take place (38 weeks after Visit 2). Here an additional abbreviated visit 40 (V40a) should be performed. If the timing of a monthly phone contact is less than two weeks from a planned abbreviated visit, the phone contact can be omitted. If subject discontinues from trial product prior to Visit 28, an additional abbreviated visit 28 (V28a) should be scheduled at the date of the originally planned V28. At V28a and V40a HbA_{1c} samples and information of AEs and antidiabetic treatment will be collected, refer to the flow chart (Section 2).

The primary reason for premature discontinuation of trial product must be specified in the 'End of trial form' in the eCRF, and final drug accountability must be performed. Furthermore, a treatment discontinuation session must be made in the IWRS.

8.1.12 Withdrawal from trial

If a subject withdraws consent, the investigator must aim to undertake procedures similar to those for the EOT visit (V40) as soon as possible. If the subject agrees, the follow-up visits (V41 and P42) must be performed 7-12 days and approximately 30 days after discontinuation of trial product (refer to Section 8.1.9 above).

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

Subjects should be encouraged to attend the EOT visit (V40) and the 7-day' follow-up visit (V41) and to make an appointment for the 30-day follow-up phone contact (P42). If accepted, the subject should be encouraged to switch to 'washout' insulin products (BiAsp 30 or NPH + IAsp),

depending on their treatment arm, at their EOT visit (V40) which should be continued until the day prior to V41, where the last AB sample should be taken.

8.2 Subject related information/assessments

8.2.1 Demography

Demography will be recorded at screening and consists of:

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

8.2.2 Diabetes history and diabetes complications

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

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

8.2.3 Hypoglycaemia unawareness

Information on hypoglycaemia unawareness will be recorded at screening according to Clarke's questionnaire, question 8[35].

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

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

8.2.4 Concomitant illness and medical history

A **concomitant illness** is any illness that is present at the start of the trial i.e. at the screening visit (V1) or found as a result of a screening procedure or other trial procedures performed before exposure to trial product. A concomitant illness is any illness other than the diabetes history and diabetic complications (refer to Section 8.2.2 above). All concomitant illness must be recorded.

Medical history is a medical event that the subject has experienced in the past.

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

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

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

8.2.5 Concomitant medication

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

Details of any concomitant medication must be recorded at the screening visit (V1), including OAD treatment and pre-trial basal insulin, which subjects continue using between the screening visit (V1) and the randomisation visit (V2). For details on OAD treatment, refer to Section 5.4.

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, total daily dose and route of administration, start date and stop date or continuation.

If a change is due to an AE, then this must be reported according to Section 12.

In case the concomitant medication is a systemic treatment which in the investigator's opinion could interfere with the glucose metabolism (e.g. treatment with orlistat, thyroid hormones, or corticosteroids – refer to exclusion criterion 14 (Section 6.3)), this information needs to be captured in the eCRF.

If the change influences the subject's eligibility to continue in the trial or trial product treatment, the monitor must be informed.

8.2.6 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 8.5.3.2.

Female subjects of childbearing potential must be instructed to use adequate contraceptive methods throughout the trial and until 1 week after end of treatment.

Female of non-childbearing potential is defined as:

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

8.2.7 Tobacco use

Details of tobacco use (smoking status) must be recorded at the screening visit (V1). Smoking is defined as smoking at least one cigarette or equivalent daily. The collected information should include whether or not the subject smokes or has smoked as follows:
Smoking status:

- Never smoked
- Previous smoker
- Current smoker

8.3 Efficacy assessments

Assessments related to subjects' glycaemic control are listed below:

- Laboratory assessments - refer to Section 8.5.2:
  - HbA_{1c}
  - Fasting plasma glucose
- SMPG recordings - refer to Section 8.3.1

8.3.1 Self-measured plasma glucose

At screening (V1), subjects will be provided with a blood glucose meter including auxiliaries as well as instructions for use. The subjects will be instructed in how to use the device and the instruction will be repeated if applicable based on the need of each individual subject.

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 should be instructed in how to record the results of the SMPG values in the diaries. The record of each SMPG value should include date, time and value. All data from the diary must be transcribed into the eCRF during or following the contact. If obtained via phone and a discrepancy is later detected, the values in the eCRF must be corrected.

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

8.3.1.1 Self-measured plasma glucose used for insulin dose adjustment

Subjects should be asked to perform SMPG recordings on three consecutive days prior to the weekly dose adjustment. The number and timing of the SMPG measurements varying from 1 SMPG to 4 SMPGs per day, depending on the treatment arm, to which the subject is randomised and the subject's individual need for treatment intensification and thus the number of insulin dose administrations as specified below:

- IDegAsp OD: 1 SMPG/day
- IDegAsp BID: 2 SMPGs/day
- IGlar OD + IAsp OD 1-2 SMPGs/day (depending on timing of IAsp dose)
- IGlar OD + IAsp BID 2-3 SMPGs/day (depending on timing of IAsp doses)
- IGlar OD + IAsp TID 3-4 SMPGs/day (depending on the timing of IAsp doses)

These SMPG recordings are required for the individual and optimal dose adjustment and maintenance as described in the Titration Guideline, Appendix A.

8.3.1.2 9-point self-measured plasma glucose profiles

9-point SMPG profiles will be used to evaluate blood sugar fluctuations and will be performed five times during the trials, refer to the flow chart (Section 2).

9-point SMPG profiles should be measured starting in the morning two days prior to the scheduled visit at the time points described below – for details to be recorded in the diary see Section 8.1.5:

1. Before breakfast (two days prior to visit)
2. 90 minutes after start of the breakfast
3. Before lunch
4. 90 minutes after start of the lunch
5. Before dinner/main evening meal
6. 90 minutes after start of the dinner/main evening meal
7. At bedtime (two days or one day prior to visit depending on actual clock time)
8. At 4 a.m. (one day prior to visit)
9. Before breakfast at the following day (one day prior to the visit)

8.4 Safety assessments

8.4.1 Body measurements

Body measurements will be performed at time points specified in the flow chart, Section 2.

Body measurements consist of the following parameters:

- Body weight: should be measured without shoes and only wearing light clothing. It should be recorded with one decimal (kg or lb) and preferably using the same set of scales throughout the trial
- Height: should be assessed without shoes and measured in inches or meters and recorded to one or two decimal places respectively
- Body mass index (BMI): will be calculated by the eCRF system based on the height and weight

8.4.2 Vital signs

Blood pressure and pulse will be measured at time points specified in the flow chart, Section 2.

The method for measuring systolic and diastolic blood pressure needs to follow the standard clinical practice at the trial site.

8.4.3 Physical examination

A physical examination must be performed at the visits specified in the flow chart, Section 2 and must include:

- General appearance
- Head, ears, eyes, nose, throat, neck
- Respiratory system
- Cardiovascular system
- Gastrointestinal system including mouth
- Musculoskeletal system
- Central and peripheral nervous system
- Skin

Any abnormalities found at the screening visit (V1) should be recorded as concomitant illness.

Any new abnormal, clinically significant findings during the trial and any clinically significant worsening from baseline must be reported as an AE.

8.4.4 Eye examination

A dilated fundoscopy or fundus photography must be performed and interpreted locally by the investigator.

The evaluation of the dilated fundoscopy or fundus photography must follow the categories:

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

Dilated fundoscopy/fundus photography performed for any reason unrelated to this trial within 90 days prior to the randomisation visit (V2) is acceptable provided no clinical symptoms suggestive of

eye disease have occurred in the meantime. It is allowed to perform the screening visit dilated fundoscopy/fundus photography between the screening visit (V1) and the randomisation visit (V2).

A subject cannot be randomised without results confirming there is no treatment-requiring retinopathy or maculopathy.

Dilated fundoscopy/fundus photography within a period of three weeks prior to Visit 28 and the EOT visit (V40) is acceptable, provided no clinical symptoms suggestive of eye disease have occurred in the meantime.

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

8.4.5 Electrocardiogram - 12 lead

A 12-lead ECG must be performed and interpreted locally by the investigator.

The evaluation of ECGs must follow the categories:

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

The baseline ECG must be performed at screening (V1) or in the period between screening (V1) and randomisation (V2). The result must be available prior to randomisation.

ECGs at Visit 28 and the EOT visit (V40) should be performed at the day of the visit.

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

8.4.6 Adverse events

Adverse events must be reported at each visit in accordance with the procedures outlined in Section 12. AEs including those related to technical complaints will be reported in the CTR as described in section 17.5.2.

8.4.6.1 Medication error

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

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

For definition of medication errors, see Section 12.1.4.

8.4.6.2 Adverse events requiring additional data collection

For some AEs additional data collection is required and specific event forms must be completed in the eCRF in addition to the AE form.
In case any of these events fulfil the criteria for a SAE, please report accordingly, see Section 12.

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

- Acute coronary syndrome
- Cerebrovascular event
- Neoplasm

Acute coronary syndrome
If an event of acute coronary syndrome, (ranging from unstable angina pectoris to myocardial infarction) is observed during the trial the following additional information must be reported if available:

- Duration of symptoms
- Changes in ECG
- Collection of cardiac biomarkers
- Cardiac imaging
- Cardiac stress testing
- Angiography
- Use of thrombolytic drugs
- Revascularisation procedures

Cerebrovascular events
If a cerebrovascular event (e.g. transient ischaemic attack, stroke, haemorrhage) is observed during the trial the following additional information must be reported if available:

- Type of event (e.g. transient ischaemic attack, stroke, haemorrhage)
- Contributing condition
- Neurologic signs and symptoms
- History of neurologic disease
- Imaging supporting the event
- Treatment given for the event

Neoplasm
All events of benign, pre-malignant/carcinoma in-situ and malignant neoplasm must be reported during the trial and the following additional information should be obtained if available as part of standard of care:

- Type of neoplasm
- Symptoms leading to identification of event
- Diagnostic imaging
- Pathological examination results
- Treatment given for the event
- Participation in screening programs
- Relevant risk factors associated to the event
- Relevant laboratory tests
- New diagnosis or recurrence/relapse of the neoplasm

8.4.7 Technical complaints

"Only technical complains related to AEs will be reported in the clinical trial report"

For further details on technical complaints reporting please refer to sections 12.1.6 and 12.4.1.

8.4.8 Hypoglycaemic episodes

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

All plasma glucose values:

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

should be reported in the diary according to the instructions below throughout the trial from randomisation (Visit 2) to the follow-up (Visit 41).

Upon onset of a hypoglycaemic episode the subject is recommended to measure plasma glucose every 15 minutes until the SMPG value is >3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved in accordance to current guidelines[36].

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 of 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.

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

The record should include the following information:

- Start date and time of the hypoglycaemic episode
- The plasma glucose level before treating the episode (if available) and any follow-up measurements
- The lowest value measured during the hypoglycaemic episode will be reported as the plasma glucose value for the episode, the remaining values will be kept as source data in the diary
- Whether the episode was symptomatic (Yes/No)
- A hypoglycaemic episode starting without symptoms should be updated to symptomatic if the subject experiences symptoms later during the episode
- Whether the subject was able to treat him/herself

If the severity of a hypoglycaemic episode aggravates, only one hypoglycaemic episode should be reported, reflecting the most severe degree of hypoglycaemia

- Date, time and dose of last trial 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. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration[36].

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

The investigator must review the diary for low SMPG values not reported as hypoglycaemic episodes. The subject must be questioned whether any of the low values were severe, i.e. whether the subject was able to self-treat or not. If the subject was not able to self-treat, it has to be reported as a severe hypoglycaemic episode.

Low SMPG values for non-severe hypoglycaemic episodes not having a hypoglycaemic episode form completed within seven 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[38, 39].

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

If the hypoglycaemic episode fulfils the criteria for an SAE then an AE form and a safety information form must also be filled in, see Section 12.

8.5 Laboratory assessments

8.5.1 Laboratory samples

Laboratory samples should be taken at specific visits according to the flow chart (Section 2) and includes both efficacy parameters and safety parameters, refer to Sections 8.1.5 and 8.5.2.

Only laboratory samples specified in Sections 8.5.1 and 8.5.2 of the protocol should be sent to the central laboratory. If additional laboratory sampling is needed, e.g. to follow-up on AEs, this should be done at a local laboratory.

All laboratory parameters, except from antibodies will be analysed at the central laboratory. Antibody samples will be analysed at a special laboratory. For contact information related to central and special laboratories, please refer to Attachment I.

8.5.1.1 Sample collection and handling

Sampling and shipping material including requisition forms and airway bills will be provided by the central laboratory. Description of the procedures for obtaining samples, handling and storage conditions, packaging and shipment will be included in the laboratory manual or laboratory flowchart, provided by the central laboratory vendor.

8.5.1.2 Fasting samples

For some laboratory parameters sample collection in fasting condition is required, refer to Section 8.1.4. Subjects should therefore attend the clinic fasting at selected visits where the below parameters will be assessed, refer to the flow chart (Section 2):

- FPG - refer to Section 8.5.2.2
- AB samples - refer to Section 8.5.3.3

If non-fasting, blood sampling should be re-scheduled preferably within the next two working days. If blood sampling has already been done before realising that the subject was not fasting, only the FPG/ AB sampling needs to be re-scheduled.

8.5.1.3 Re-sampling

If blood samples are clotted or missed, re-sampling should be performed as an unscheduled visit, refer to Section 8.1.10.

8.5.1.4 Reporting of results to investigator

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

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

During the trial the investigator will not be able to review the results of antibody measurements in relation to AEs as these are often analysed after LPLV.

8.5.1.5 Sample destruction

Samples collected, except for AB samples, will be destroyed on an ongoing basis, and no later than at finalisation of the clinical trial report. Antibody samples will be stored and destructed as described in Section 24.2.

8.5.2 Laboratory assessments for efficacy

8.5.2.1 HbA_{1c}

The HbA_{1c} result taken at the screening visit (V1) must be available prior to the randomisation visit (V2).

HbA_{1c} is measured regularly during the trial in order to assess glycaemic control and sites will receive individual HbA_{1c} reports for each subject to be used for evaluation and subject training purposes in relation to insulin dose adjustment.

For subjects prematurely discontinuing trial product abbreviated visits (V28a and V40a) should be scheduled at the dates of the originally planned visit 28, if applicable and visit 40 in order to collect samples for HbA_{1c} analysis – refer to flow chart (Section 2).

8.5.2.2 Fasting plasma glucose

FPG is analysed six times during the trial, and is measured in order to evaluate metabolic control. The subject must attend these visits fasting. For definition of fasting, see Section 8.1.4 above.

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

8.5.3 Laboratory assessments for safety

8.5.3.1 Haematology and Biochemistry assessments

The below haematology and biochemistry parameters will be analysed at the randomisation visit (V2), prior to the intensification period (V28) and at the end-of-trial visit (V40), please refer to the flow chart (Section 2).

- Haematology
  - Haematocrit
  - Haemoglobin
  - Leucocytes
  - Erythrocytes
  - Thrombocytes

- Biochemistry
  - ALT
  - Albumin
  - AST
  - Alkaline phosphatase
  - Bilirubin, total
  - Creatinine
  - Potassium
  - Sodium
  - GFR, estimated (eGFR) (only measured at screening visit)

8.5.3.2 Pregnancy testing

A serum pregnancy test (beta-human chorionic gonadotropin (b-hCG)) is only required for females of childbearing potential. If a menstrual period is missed or pregnancy suspected, a urine pregnancy test must be performed as soon as possible.

8.5.3.3 Antibody measurements

Blood samples for detection of IDeg and IGlar ABs will be collected at baseline (V2), and every four weeks in the initial three months (V6, V10, V14), at the start of the intensification period (V28), at the end-of-treatment (V40) and at the 7-day follow-up visit (V41). The immunological response to IDeg will be monitored following the EMA guideline on this subject[10].

The following ABs will be analysed:

- For IDegAsp arm: Anti-insulin degludec AB
- For IGlar + IAsp arm: Anti-insulin glargine AB
- For both arms: Cross-reacting AB to human insulin

Subjects must attend visits fasting to collect AB samples, refer to Section 8.1.4.

8.6 Other Assessments

8.6.1 Patient reported outcomes

The PRO questionnaires must be completed by the subject without assistance of the site personnel. Instructions on how to complete the questionnaires will be provided to the subject.

The PRO questionnaires will be used to investigate the health related quality of life and diabetes treatment related impact.

The following PRO questionnaires will be supplied in addition to the diaries in a linguistically validated version in all languages relevant for this trial:

- **BHQ** is a questionnaire regarding the frequency of hypoglycaemic episodes and will be completed at baseline (randomisation visit (V2)) only.

- **SF-36v2®** Health Survey is a survey which assesses the subject's general health status and health-related quality of life utilising 36 questions covering eight concepts. The concepts cover: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health over the prior four weeks. Scores for the eight concepts and two overall scores for the physical and the mental components are calculated.

- **TRIM-D** measures treatment related impact on subjects of diabetes medication across the spectrum of pharmacological treatment over the past two weeks. The TRIM-D consists of 28 items grouped into five domains. The domains are treatment burden (six items), daily life (five items), diabetes management (five items), compliance (four items) and psychological health (eight items). A total score and scores for the five domains are calculated.

The SF-36v2® and TRIM-D will be completed at the baseline (randomisation visit (V2)), prior to the intensification period (V28) and at the EOT visit (V40). These PRO questionnaires should be completed at the day of visit, preferably before any trial related procedures, except from fasting blood sampling, which may be done before.

Site staff is only allowed to write in the headers and on the front page of the questionnaires.

It is the responsibility of the investigator to review the questionnaires for completeness and possible AEs. To confirm that this has been done, the review must be documented by dated signature on the PRO questionnaires and/or in the subject's medical record. Care must be taken not to bias the subject.

If clarification of entries is needed, the subject should be questioned and a conclusion made in the subject's medical record. Care should be taken not to bias the subject.

The above PRO questionnaires will be supplied as 'no carbon required' (NCR) paper CRFs. The original (first page of the NCR sample) of the completed paper CRFs will be shipped for data-entry (refer to section 15). The copy (2nd page of NCR sample) will be retained at clinical trial site.

8.6.2 Hypoglycaemia resource use

Hypoglycaemic resource use is collected as an interview administered questionnaire regarding resource use of the latest hypoglycaemic episode within the last four weeks. This interview will take place at the majority of the clinic visits during the trial - refer to flow chart (Section 2).

The questionnaire includes questions regarding the number of extra blood glucose monitoring, contact to health care professionals, and time missed at work.

The interview questionnaire will be provided to the sites and will include instructions to the interviewer and instructions to the subject to be read aloud by the investigator prior to conducting the interview. The answers given by subjects should be recorded at the paper questionnaires and kept as source data at the sites. Data collected should be transcribed by the investigator or delegated staff into the eCRF.

8.6.3 Training in use of the trial product/pre-filled pen device

The subjects must be trained in how to handle the pre-filled pen-devices: IDegAsp (FlexTouch®) or IGlar (SoloStar®) and IAsp (FlexPen®) when handed out the first time. For subjects in the IGlar arm, the training must include pen differentiation which is of outmost importance to avoid medication errors. Re-training must be performed again at V3 and should be repeated during the trial based on the individual subject's needs 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
- Priming the pen to ensure the insulin flow
- The needle should be kept in the skin after the dose counter has returned to zero after injection as follows:

    - IDegAsp and IAsp: While counting slowly to six
    - IGlar: 10 seconds or as described in the DFU

If the needle is removed too early then the full dose may not have been delivered.

At the EOT visit (V40) subjects should be properly instructed in how to handle 'washout' insulins to be used in the period until the 7-day follow-up visit (V41).

8.7 Subject compliance

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

Treatment compliance:

The investigator must assess the compliance of the subject based on adherence to visit schedule, subject diary completion and glycaemic control.

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

In addition, subject compliance will be assessed by monitoring of drug accountability at specified visits, refer to the flow chart (Section 2). The unused amount of trial insulin products (investigational medicinal products (IMPs)) and washout insulin products (Non-IMPs) will be assessed against the dispensed amount and, in case of discrepancies, the subject must be asked.

Medical judgements by investigator and delegated staff should be used when assessing treatment compliance. An overall assessment of relevant information recorded in the subject diary (e.g. completeness, available insulin doses and SMPG values) compared to the glycaemic control (HbA_{1c} and FPG) and the amount of trial insulin used will form basis of such medical judgements.

9 Trial supplies

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

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

9.1 Trial insulin products

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

Table 9–1 Trial insulin products (IMPs)

Trial insulin product (IMP)	Strength	Dosage form	Route of administration	Container/ delivery device
Insulin degludec/ insulin aspart (Ryzodeg®); Novo Nordisk A/S	100 units/mL	Solution for injection	Subcutaneous injection	3 mL pre-filled pen (FlexTouch®)
Insulin glargine (Lantus®); Sanofi-Aventis	100 units/mL	Solution for injection	Subcutaneous injection	3 mL pre-filled pen (SoloStar®)
Insulin aspart (NovoRapid®/ NovoLog®); Novo Nordisk A/S	100 units/mL	Solution for injection	Subcutaneous injection	3 mL pre-filled pen (FlexPen®)

Trial insulin products (IMPs) must not be used if they do not appear clear and colourless.

9.2 Non-IMPs

The following products are regarded as Non-IMPs:

- Washout insulin
- OADs

The 'washout' insulin products to be used in the follow-up period from the EOT visit (V40) to the 7-day follow-up visit (V41) are listed in Table 9–2.

Table 9–2 Washout insulin products

Washout insulin product (Non-IMP)	Strength	Dosage form	Route of administration	Container/ delivery device
Human isophane insulin (NPH) (Insulatard®, Protaphane®, Novolin® N) Novo Nordisk A/S	100 IU/mL	Suspension for injection	Subcutaneous injection	3 mL pre-filled pen (FlexPen®)
Biphasic insulin aspart 30 (BiAsp 30) (NovoMix® 30, NovoLog® Mix 70/30) Novo Nordisk A/S	100 units/mL	Suspension for injection	Subcutaneous injection	3 mL pre-filled pen (FlexPen®)
Insulin aspart (NovoRapid®/ NovoLog®); Novo Nordisk A/S	100 units/mL	Solution for injection	Subcutaneous injection	3 mL pre-filled pen (FlexPen®)

Washout insulins BiAsp 30 and NPH product must not be used if they do not appear uniformly white and cloudy after re-suspension.

Furthermore, the below OADs are regarded as non-IMPs:

a. Metformin
b. (DPP-IV) inhibitor
c. α-glucosidase-inhibitors
d. SGLT-2 inhibitor
e. oral combination products (of the allowed OADs above)

'Washout' insulin products will be supplied by Novo Nordisk A/S, whereas none of the OADs will be supplied by Novo Nordisk A/S. However, OADs will be reimbursed if required by the country's regulatory authority or institutional review board (IRB)/independent ethics committee (IEC).

9.3 Labelling

The trial products will be labelled in accordance with Annex 13[40], local regulations and trial requirements. Labelling will include the product related requirements and precautions.

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

The investigator must document that the DFU is given to the subject orally and in writing at the first dispensing visit (randomisation visit (V2)) and at V40.

If applicable, DFUs can be handed out to subjects at subsequent visits.

9.4 Storage

The trial products must be stored in accordance with the storage conditions listed in Table 9–3 below:

Table 9–3 Storage Conditions and In-use time for IMPs and washout insulin

Trial products	Storage conditions (not-in-use)	In-use conditions	In-use time*
Insulin degludec/ insulin aspart (Ryzodeg®) IMP	• Protect from light • Do not freeze • Store in refrigerator (2°C – 8°C/36°F-46°F)	• Protect from light • Do not freeze • Can be stored in refrigerator (2°C – 8°C • Do not store above 30°C For U.S. only: • Protect from light • Do not freeze • Do not refrigerate • Store below 30°C/ 86°F	Use within 4 weeks
Insulin glargine (Lantus®) IMP	• Protect from light • Do not freeze • Store in refrigerator (2°C – 8°C/36°F-46°F)	• Protect from light • Do not freeze • Do not refrigerate • Do not store above 30°C/86°F	Use within 4 weeks
Insulin aspart (NovoRapid® / NovoLog®) IMP & Non-IMP	• Protect from light • Do not freeze • Store in refrigerator (2°C – 8°C/36°F-46°F)	• Protect from light • Do not freeze • Do not refrigerate • Store below 30°C/86°F	Use within 4 weeks
Human isophane insulin (NPH) (Insulatard®, Protaphane®, Novolin® N) Non-IMP	• Store in refrigerator (2°C – 8°C/36° - 46°F) • Do not freeze • Protect from light	• Store below 30°C/86°F • Do not refrigerate • Do not freeze • Protect from light	Use within 6 weeks For U.S. only: Use within 14 days
Biphasic insulin aspart 30 (BiAsp 30) (NovoMix® 30, NovoLog® Mix 70/30) Non-IMP	• Store in refrigerator (2°C – 8°C/36° - 46°F) • Do not freeze • Protect from light	• Store below 30°C/86°F • Do not refrigerate • Do not freeze • Protect from light	Use within 4 weeks For U.S. only: Use within 14 days

* In-use time starts when first dose is taken or when used as spare.

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.

9.5 Drug accountability and destruction

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

Subjects are instructed to return all used, partly used and unused trial insulin products at each dispensing visit after the randomisation visit (V2) and until the EOT visit (V40). Refer to the flow chart (Section 2) for the timing of drug accountability and dispensing visits.

Subjects are instructed to return all used, partly used and unused 'washout' insulin products at their 7-day follow-up visit (V41).

The monitor will reconcile the drug accountability using the IWRS Drug Accountability module. Drug accountability will be done at pen level.

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

Non-allocated trial insulin and 'washout' insulin products including expired or damaged products must be accounted as unused at the latest at closure of the trial site.

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

9.6 Auxiliary supplies

The following auxiliary supplies will be provided by Novo Nordisk, refer to the TMM:

- DFU for all trial products (IMPs and 'washout' insulin)
- BG-meters and supplies
- Needles for pre-filled pens

Only needles provided by Novo Nordisk (no longer than 8 mm long) must be used for administration of trial insulin products.

10 Interactive voice/web response system

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

IWRS is used for:

- Screening
- Screening failure
- Randomisation
- Medication arrival
- Dispensing of trial products
- Treatment discontinuation
- Completion
- Drug accountability
- Data change

IWRS user manuals will be provided to each trial site.

At any time during the trial only dispensing unit number(s) (DUNs) allocated by the IWRS are allowed to be dispensed to a subject. By doing this it will be ensured that:

- Stock is available at a site when needed for the subjects
- No allocation of trial product that will expire before the next dispensing visit
- Drug accountability can be made in the IWRS

If a subject needs trial product between dispensing visits, the investigator must make an additional dispensing.

11 Randomisation procedure and breaking of blinded codes

At Visit 2 a randomisation session will be carried out for all eligible subjects by using the IWRS.

Subjects will be randomised 1:1 manner into the two stepwise treatment intensification arms below. The randomisation will be stratified based on pre-trial basal insulin treatment regimen: OD or BID/TID dosing:

IDegAsp arm:

- Initial 26 weeks: IDegAsp OD administered at the largest meal each day ± OAD(s)
- Intensification period – Week 26-38: IDegAsp OD/BID administered at the largest meal(s) each day based on individual needs ± OAD(s)

IGlar+IAsp arm:

- Initial 26 weeks: IGlar OD administered in accordance with local labelling and IAsp OD administered at the largest meal ± OAD(s)
- Intensification period – Week 26-38: IGlar OD administered in accordance with local labelling and IAsp 1-3 times daily administered at main meals based on individual needs ± OAD(s)

11.1 Breaking of blinded codes

Not applicable for this trial.

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

The following should **not** be reported as AEs:
- Pre-existing conditions, including those found as a result of screening or other trial procedures performed before exposure to trial product (pre-existing conditions should be reported as medical history or concomitant illness)
- Pre-planned procedures unless the condition for which the procedure was planned has worsened from the first trial related activity after the subject has signed the informed consent
- Non-serious hypoglycaemia is an AE, but is reported on a hypoglycaemic episode form instead of on an AE form, see Section 8.4.7

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

- Suspicion of transmission of infectious agents via the trial product
- Risk of liver injury defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 x upper normal limit (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 or use of wrong device
  Note: Use of wrong DUN is not considered a medication error unless it results in administration of wrong drug
- Wrong route of administration, such as intramuscular instead of subcutaneous
- Administration of an overdose with the intention to cause harm (e.g. suicide attempt), misuse or abuse of trial product
- Accidental administration of a lower or higher dose than intended. That is a dose lower or higher than ± 20 %; however, the administered dose must deviate from the intended dose to an extent where clinical consequences for the trial subject were likely to happen as judged by the investigator, although they did not necessarily occur

Medication errors must be reported on an AE form and a specific event form, see Section 8.4.6.1.

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:

- Acute coronary syndrome (myocardial infarction or hospitalisation for unstable angina)
- Cerebrovascular event (stroke, transient ischaemic attack or haemorrhage)
- Neoplasm

For details, see Section 8.4.6.2.

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

Table 12–1 lists AEs that require completion of specific event forms in the eCRFs.

Table 12–1 Adverse events requiring completion of specific event forms

Event	Specific event form
Acute coronary syndrome (myocardial infarction or hospitalisation for unstable angina)	Yes
Cerebrovascular event (stroke, transient ischaemic attack or haemorrhage)	Yes
Neoplasm	Yes
Fatal event	No
Medication errors	Yes

For details about specific event forms, see Sections 8.4.6.1 and 8.4.6.2.

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 (P42). 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 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 additional data collection: In addition to the above, the specific event form **within 14 calendar days** from the investigator's first knowledge of the AE.

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

The paper forms or safety information form must be forwarded to Novo Nordisk either by fax, e-mail or courier.

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

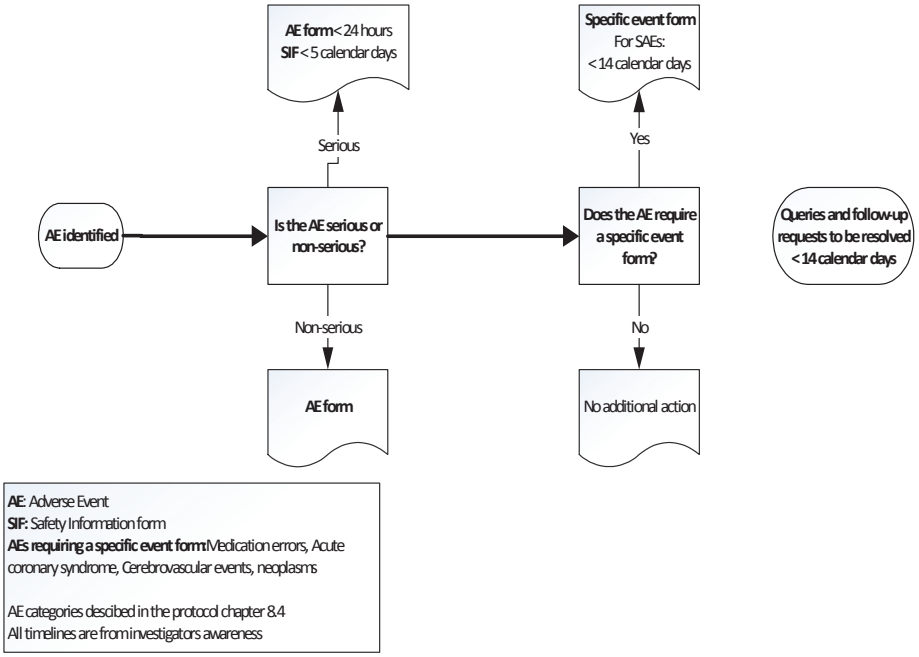


Figure 12–1 Reporting of AEs

Novo Nordisk assessment of AE expectedness:
Novo Nordisk assessment of expectedness is performed according to the following reference documents, current versions or any updates thereto:

- Insulin degludec/insulin aspart (Ryzodeg®), 100 units/mL, 3 mL prefilled pen (FlexTouch®): IB[17], and/or Company Core Data Sheet (CCDS)[41]
- Insulin aspart (NovoRapid®/NovoLog®), 100 U/mL, 3 mL prefilled pen (FlexPen®): CCDS[42] EU SmPC[13]
- Insulin glargine (Lantus®), 100 units/mL, 3 mL pre-filled pen (SoloStar®): EU SmPC[27]

Reporting of trial product-related SUSARs by Novo Nordisk:
Novo Nordisk will notify the investigator of trial product-related suspected unexpected serious adverse reactions (SUSARs) in accordance with local requirements and ICH GCP[1]. In addition, the investigator will be informed of any trial-related SAEs that may warrant a change in any trial procedure.

In accordance with regulatory requirements, Novo Nordisk will inform the regulatory authorities, including EMA, of trial product-related SUSARs. In addition, Novo Nordisk will inform the IRBs/IECs of trial product-related SUSARs in accordance with local requirement and ICH GCP[1], unless locally this is an obligation of the investigator.

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

- If an AE is considered to have a causal relationship with a Novo Nordisk marketed product used as non-investigational medicinal product (e.g. Insulin NPH, 100 IU/mL, 3 mL pre-filled pen (FlexPen®) in the trial, it is important that the suspected relationship is reported to Novo Nordisk, e.g. in the alternative aetiology section on the safety information form. Novo Nordisk may need to report this AE to relevant regulatory authorities.

12.3 Follow-up of adverse events

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

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

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

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

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

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

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

SAEs after end of trial: If the investigator becomes aware of an SAE with a suspected causal relationship to the 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 trial products:

- Insulin degludec/insulin aspart (Ryzodeg®) 100 units/ml, 3 mL pre-filled pen, FlexTouch®
- Insulin aspart (NovoRapid®/NovoLog®), 100 units/mL, 3 mL, pre-filled pen, FlexPen®
- Insulin glargine (Lantus®) 100 units/mL, 3 mL, pre-filled pen, SoloStar®
- Novo Nordisk needles for prefilled pens

and 'washout' insulin products:

- Human isophane insulin ((NPH) (Insulatard®, Protaphane®, Novolin® N), 100 IU/mL, 3 mL pre-filled pen, FlexPen®
- Biphasic insulin aspart 30 (BiAsp 30), (NovoMix® 30, NovoLog® Mix 70/30), 100 U/mL, 3 mL pre-filled pen, FlexPen®
- Insulin aspart (NovoRapid®/NovoLog®), 100 U/mL, 3 mL pre-filled pen, FlexPen®

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 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 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**
- Technical complaint on an investigational medical device that could have led to an SAE **within 24 hours**
- All other technical complaints **within 5 calendar days**

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

12.4.2 Collection, storage and shipment of technical complaint samples

The investigator must collect the technical complaint sample and notify the monitor **within 5 calendar days** of obtaining the sample at the 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 or lot number and, if available, the DUN. All parts of the DUN should be returned.

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

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

12.5 Pregnancies in female subjects

Female subjects must be instructed to notify the investigator immediately if they become pregnant during the trial. The investigator must report any pregnancy in subjects who have received trial product(s).

The investigator must follow the pregnancy until the pregnancy outcome and the newborn infant is one month of age.

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

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

1. Reporting of pregnancy information

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

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

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

2. Reporting of AE information

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

<u>Forms and timelines for reporting AEs:</u>

Non-serious AEs:

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

SAEs:

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

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

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

12.6 Precautions and/or overdose

During treatment with insulin, there is a risk of hypoglycaemia. Symptoms 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. Severe hypoglycaemia may lead to unconsciousness and even death.

Hypoglycaemic episodes should be treated following best practice at the discretion of the investigator. As with all long-acting insulin preparations, their prolonged effect may delay recovery from a hypoglycaemic episode.

Asymptomatic hypoglycaemia and symptoms of hypoglycaemia should be treated by ingestion of carbohydrate (e.g. juice). Severe hypoglycaemia resulting in loss of consciousness should be treated with parenteral glucose, glucagon or dextrose at the investigator's discretion.

Please refer to current edition and any updates to the documents related to trial products listed below:

IMPs:

- Insulin degludec/insulin aspart (Ryzodeg®) 100 units/ml, 3 mL pre-filled pen, FlexTouch®: IB[17], and/or CCDS[41], the EU SmPC[15] and the U.S. LI[16].
- Insulin aspart (NovoRapid®/NovoLog®), 100 U/mL, 3 mL, pre-filled pen, FlexPen®: the CCDS[42], the EU SmPC[13] and the U.S. LI[14].
- Insulin glargine (Lantus®) 100 units/mL, 3 mL pre-filled pen, SoloStar®: the EU SmPC[27] and U.S. LI[18].

Non-IMPs:

- Human isophane insulin (NPH), (Insulatard®, Protaphane®, Novolin® N), 100 IU/mL, 3 mL pre-filled pen, FlexPen®: the CCDS[43] and the EU SmPC[44]
- Biphasic insulin aspart (BiAsp 30), (NovoMix® 30, NovoLog® Mix 70/30, 100 U/mL, 3mL pre-filled pen, FlexPen®: the CCDS[45], the EU SmPC[46], and US LI[47].
- Insulin aspart (NovoRapid®/NovoLog®), 100 U/mL, 3 mL pre-filled pen, FlexPen®: the CCDS[42], the EU SmPC[13] and the U.S. LI[14].

12.7 Committees related to safety

12.7.1 Novo Nordisk safety committee

Novo Nordisk will constitute an internal IDegAsp safety committee to perform ongoing safety surveillance.

13 Case report forms

For this trial a combination of eCRF and paper CRF will be used.

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 only:

- Pregnancy forms
- PRO questionnaire - refer to Section 8.6.1
    - BHQ
    - SF-36v2®
    - TRIM-D

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

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

On the paper CRFs 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.

Corrections to the data in paper Pregnancy forms, AE forms, Safety information forms and Technical complaint forms may only be made by drawing a straight line through the incorrect data and then writing the correct entry next to the data that was crossed out. Each correction must be initialled, dated and explained (if necessary). If corrections are made by the investigator's delegated staff after the date of the investigator's signature on the affirmation statement, the affirmation statement must be signed and dated again by the investigator.

Corrections necessary after the CRFs have been removed from the trial site must be documented on a data clarification form (DCF) or a monitor-initiated discrepancy form (MIDF). If the affirmation statement for the subject has not yet been signed, any corrections must be approved by the investigator or her/his delegated staff. If the affirmation statement for the subject has already been signed, the investigator must approve any correction.

13.2 Case report form flow

The investigator must ensure that data is recorded in the eCRF as soon as possible, preferably within five days after the visit. During the trial, SMPG measurements and corresponding insulin doses for titration purposes should be recorded as soon as possible, preferably within 24 hours after the visit/phone contact. At the end of the trial the investigator must ensure that all remaining data have been recorded in the eCRF no later than 24 hours after last subject's last visit at the site. Once data have been entered, they will be available to Novo Nordisk for data verification and validation purposes.

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

The original (first copy of the NCR sample) of the paper CRFs completed by site staff and PRO questionnaires completed by the subjects (refer to Section 13.1 above) will be shipped from sites for data management. NN will be responsible for data management (refer to Section 15). Originals will be archived by NN upon final data entry. A copy (2nd page of the NCR) will be retained at clinical trial site.

14 Monitoring procedures

During the course of the trial, the monitor will visit the trial site to ensure that the protocol is adhered to, that all issues have been recorded, to perform source data verification and to monitor drug accountability. The first monitoring visit will be performed as soon as possible after FPFV at the trial site and no later than four weeks after. The monitoring visit intervals will depend on the outcome of the remote monitoring of the eCRFs, the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP, but will not exceed 12 weeks until LPLV at the trial site.

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

Data recorded in the diary by the subject will be considered source data.

Considering the electronic source data environment, it is accepted that the earliest practically retainable record should be considered as the location of the source data and therefore the source document.

All other data must be verifiable in source documentation other than the eCRF except for:

- Age and BMI which are calculated by the EDC system

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 original of the completed diaries and/or PROs must not be removed from the trial site, unless they form part of the CRF/eCRF and a copy is kept at the site.

The monitor will ensure that the eCRFs are completed on an ongoing basis, and that paper CRFs are collected.

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

- Date for obtaining informed consent
- Reason for screening failure
- SAEs

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

A follow-up letter (paper or electronic) will be sent to the investigator following each monitoring visit. This should address any action to be taken. For U.S.: the follow-up letter must be signed by the investigator.

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.

Entry of information captured at the PRO questionnaires BHQ, SF36v2® and TRIM-D will be done by double data entry.

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

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

Unless otherwise specified, all continuous measurements will be summarised descriptively at each visit by treatment using in-trial data. Endpoints that are analysed untransformed and endpoints that are not formally analysed are summarised by the arithmetic mean, standard deviation (SD), median, and minimum and maximum value. Endpoints that are analysed log-transformed are supplemented with the geometric mean and coefficient of variation. For measurements over time, mean values will be plotted to explore the trajectory over time. The geometric mean values will be plotted for endpoints that are analysed log-transformed. All descriptive summaries and plots will be based on in-trial data unless otherwise specified.

If an assessment has been made both at screening and randomisation, and if not otherwise specified, the value from the randomisation visit will be used as the baseline value. If the value measured at the randomisation visit is missing and the assessment has also been made at screening, then the screening value will be used as the baseline value. For summaries and statistical analysis of all endpoints the first non-missing values is used. The value should be taken according to the specification in the protocol, e.g. non-fasting FPG-values are not used. Re-tests of non-missing values are only included in subject specific listings.

Laboratory values below the lower limit of quantification (LLOQ) will be set to ½LLOQ.

Presentation of results from a statistical analysis will include the estimated mean treatment effects for absolute values and change from baseline. The estimated means are either obtained by Rubin's rule[48] weighing together estimated means from multiple imputation or directly from estimation in a parameterized statistical model. In addition estimated mean treatment differences (or ratios) will be presented together with two-sided 95% confidence intervals and corresponding two-sided p-values.

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

17.1 Primary and secondary estimands

The primary estimand will be the difference in change from baseline at week 26 or week 38 depending on the endpoint considered between IDegAsp OD and IGlar OD + IAsp OD, for all randomised subjects regardless of whether the subjects remained on initially assigned treatment until week 26 or week 38. This estimand is a de facto estimand addressing effectiveness.

The secondary estimand will be the difference in change from baseline at week 26 or week 38 depending on the endpoint considered between IDegAsp OD and IGlar OD + IAsp OD if all

randomised subjects had adhered to treatment until week 26 or week 38. This estimand is a de jure estimand addressing efficacy.

For hypoglycaemic episode endpoints, only the de jure estimand will be used. The reason for this is that data for hypoglycaemic episodes will not be systematically collected after treatment discontinuation.

17.2 Sample size calculation

The sample size is based on confirming non-inferiority of the primary estimand for the primary endpoint assessed at week 26 using the full analysis set (FAS). Sample sizes are also given for confirming non-inferiority for the primary estimand of the primary endpoint on the per-protocol set.

The primary objective is to confirm the effect of IDegAsp OD versus IGlar OD + IAsp OD in controlling glycaemia in basal insulin-treated subjects with T2DM.

This will be done by comparing the difference between IDegAsp OD and IGlar OD + IAsp OD in change from baseline in HbA_{1c} after 26 weeks to a non-inferiority limit of 0.4%. The non-inferiority limit of 0.4% is aligned with the phase 3a programme and is considered appropriate to ensure a relevant effect of IDegAsp compared to placebo since a superior treatment effect of −0.85% [−1.04; −0.66] of IGlar versus placebo was reported in a placebo controlled clinical trial in T2DM subjects[49]. Supplementing IGlar with IAsp OD would further increase the treatment effect compared to placebo.

Formally, let D be the mean treatment difference (IDegAsp OD minus IGlar OD + IAsp OD) in change from baseline in HbA_{1c}. The null-hypothesis of IDegAsp OD inferior by 0.4% or more will be tested against the alternative hypothesis of non-inferiority as given by

H_0: D ≥0.40% against H_A: D <0.40%

Non-inferiority will be considered confirmed if the upper bound of the two-sided 95% confidence interval for D is strictly below 0.4%. This is equivalent to using a one-sided test of size 2.5%, which means that the Type 1 error rate is controlled at 2.5% level.

Accordingly, the sample size is calculated using a t-statistic under the assumptions of a one-sided test of size 2.5%, a mean treatment difference of 0.0%, a standard deviation of SD=1.3%, and a non-inferiority limit of 0.40%. It is assumed that 15% of the randomised subjects will discontinue randomised treatment before week 26 or have missing data at week 26, and that 10% of the randomised subjects will be excluded from the per protocol (PP) analysis set. The assumptions are based on the results from a phase 3a trial (NN5401-3593).

When estimating the primary estimand for the evaluation of the non-inferiority hypothesis, missing data will be imputed based on in-trial data. A penalty will be added to the change in HbA_{1c} at week 26 for all subjects in the IDegAsp OD arm who discontinued trial product prior to week 26 or who have missing data at week 26. The penalty corresponds to the non-inferiority limit of 0.4%.

In total an expected 15% will have missing on-treatment data at week 26, 10% will not be part of the PP analysis set. This means that 5/90*100%= 5.56% of the PP analysis set is expected to be non-completers, hence the expected treatment differences (adjusted treatment effect (TE) resulting from the applied penalty) for the non-inferiority hypothesis of the primary estimand is:

1) FAS: 0.15*0.4=0.06

2) PP: 0.0556*0.4=0.0222

The sample size assumptions for TE and the common SD are given in Table 17–1.

From these assumptions, and based on a 1:1 randomisation, the sample size is set to 264 subjects per treatment arm, in total 528 subjects. This will ensure a nominal power of at least 85% for confirming the primary objective based on the FAS as well as on the PP analysis set.

Table 17–1 Assumptions for sample size calculation

Primary Estimand Analysis set	Non-inferiority margin	SD	TE	Adjusted TE	Randomisation Scheme	Required Power
FAS	0.4%	1.3%	0.0%	0.06%	1:1	85%
PP	0.4%	1.3%	0.0%	0.0222%	1:1	85%

Abbreviations: SD = standard deviation; TE = Treatment effect

The sample size calculation was done using SAS 9.4.

Table 17–2 Sensitivity of sample size to variations in SD and power

#subjects in total		SD=1.1%	SD=1.2%	SD=1.3%	SD=1.4%
Power 80%	**FAS**	332	394	462	536
	PP	300	356	416	482
Power 85%	**FAS**	378	450	528	612
	PP	342	406	476	552
Power 90%	**FAS**	442	526	618	716
	PP	400	474	556	644
Power 95%	**FAS**	546	650	762	884
	PP	494	586	686	796

17.3 Definition of analysis sets

The following analysis sets are defined in accordance with the ICH-E9[50].

- Full Analysis Set (FAS): includes all randomised subjects. In exceptional cases, subjects may be excluded. In such cases the elimination will be justified and documented. The statistical evaluation of the FAS will follow the intention-to-treat (ITT) principle and subjects will contribute to the evaluation "as randomised".
- Per-Protocol (PP) analysis set: includes all subjects in the Full Analysis Set who fulfils the following criteria:
    - Have not violated any inclusion criteria
    - Have not fulfilled any exclusion criteria
    - Have a non-missing HbA_{1c} at screening or randomisation
    - Have at least one non-missing HbA_{1c} after 12 weeks of exposure
    - Have at least 12 weeks of exposure

Subjects in the PP will contribute to the evaluation "as treated".

- Safety Analysis Set (SAS): includes all subjects receiving at least one dose of the investigational product or comparator. Subjects in the safety set will contribute to the evaluation "as treated".
- Completer analysis set (CAS): includes all randomised subjects who have completed the trial without discontinuation from randomised treatment. Subjects in the completer analysis set will contribute to the evaluation "as randomised".

Before data are released for statistical analysis, a review of all data will take place to ensure a sufficient data quality and to ensure the planned statistical analysis are applicable. Any data decisions not foreseen in the protocol will be documented before database lock.
Randomised subjects who are lost to follow up and where no exposure information of the investigational product or comparators is available after randomisation will be handled as unexposed.
The decision to exclude any subject or observation from the statistical analysis is the joint responsibility of the study group. The subjects or observations to be excluded, and the reasons for their exclusion will be documented before database lock. The subjects and observations excluded from the analysis sets, and the reasons for this, will be described in the clinical trial report.

Definition of the observation periods:

In-trial: This observation period will include information collected at or after date of randomisation and up to the last subject-site contact which is scheduled as a follow-up visit. For subjects who withdraw their informed consent, the in-trial observation period ends at their date of withdrawal. If a subject is lost to follow-up, the end of the in-trial period is defined as the date of the last subject-investigator contact (site or phone visit). In case a subject dies during the trial the date of death will be the end-date of the in-trial observation period regardless of the above defined end-dates. This observation period will be used for estimating the effectiveness estimand.

On-treatment: This observation period is a subset of the in-trial observation period and represents the time period in which a subject is considered exposed to trial product. For adverse events an ascertainment window of 30 days after last date on trial product will be used. The first follow-up visit is scheduled to take place seven days after the EOT visit (V40) to collect all AEs including hypoglycaemia. The second follow-up visit is scheduled to take place 30 days after EOT visit (V40) only to report AEs. This observation period will be used for estimating the efficacy estimand and for evaluating safety.

17.4 Primary endpoint

Primary statistical analysis for primary estimand

The primary estimand will be estimated based on the FAS using all post baseline HbA_{1c} measurements obtained on planned visits up until week 26, including week 26 measurements from subjects withdrawing from randomised treatment (in-trial observation period), mimicking an ITT scenario. To estimate this estimand for evaluation of non-inferiority of $HbA_{1c,}$ multiple imputation of missing values with separate imputation from each treatment arm will be applied. The use of data from prematurely treatment discontinued subjects in analyses will equalise treatment effects and the inclusion of a penalty equal to the non-inferiority margin will remedy this. Imputation will be done as follows:

- In the first step, intermittent missing values are imputed using a Markov Chain Monte Carlo (MCMC) method, in order to obtain a monotone missing data pattern. This imputation is done for each treatment arm separately and 1000 copies of the dataset will be generated.

- In the second step, for each of the 1000 copies of the dataset, an analysis of covariance (ANCOVA) for each treatment arm with region, sex, previous insulin regimen and previous OAD treatment as categorical fixed effects and baseline HbA_{1c} measurement and age as a covariate will be fitted to the change in HbA_{1c} from baseline to week 8 (visit 10). The estimated parameters and their variance from this model are used to impute missing values at week 8 for subjects in the respective treatment arms based on region, sex, previous insulin regimen, previous OAD treatment, age and HbA_{1c} at baseline.

- In the third step, for each of the 1000 copies of the dataset, an analysis of covariance model with region, sex, previous insulin regimen and previous OAD treatment as categorical fixed effects, and age, baseline HbA_{1c} and HbA_{1c} at week 8 (Visit 10) as covariates is fitted to the change in HbA_{1c} from baseline to week 12 (Visit 14) for each treatment arm. The estimated parameters and their variances from this model are used to impute missing values at week 12 for subjects in the respective treatment arms, based on region, sex, previous insulin regimen, previous OAD treatment, age and HbA_{1c} at baseline and week 8.

- Step three is repeated over the available planned visits, adding one visit at a time until week 26. In each step the model is expanded to include a covariate from the previous visit.

- Finally, a penalty equal to the non-inferiority margin 0.4% is added to the week 26 (visit 28) HbA_{1c} value for any prematurely treatment discontinued subject in the IDegAsp OD arm, irrespective if the value was retrieved (V28A) data or an imputed value from the sequential imputation.

For each of the 1000 (now complete) imputed data sets the change from baseline to week 26 will be analysed using an ANCOVA with treatment, region, sex, previous insulin treatment regimen and previous OAD treatment as categorical fixed effects and baseline HbA_{1c} and age as covariate. The estimates and standard deviations for the 1000 data sets are pooled to one estimate and associated standard deviation using Rubin's rule. From these pooled estimates the confidence interval for the treatment differences and the associated p-value are calculated.

Non-inferiority of IDegAsp OD vs. IGlar OD + IAsp OD will be considered confirmed if the 95% confidence interval for the mean treatment difference lies entirely below 0.40%. A conclusion on non-inferiority will be based on the FAS and the primary estimand. The addition of the 0.4% penalty in the last imputation step corresponds to the non-inferiority null method, as described by Koch[51].

Sensitivity analyses for the primary estimand

The following sensitivity analyses will be performed:

- The primary analysis will be repeated based on the PP analysis set in line with the Committee for Proprietary Medicinal Products (CPMP) Points to Consider (CPMP/EWP/482/99).

- The primary analysis will be repeated on the FAS but without adding the penalty for subjects in the IDegAsp OD arm. The result of this analysis is regarded to give the most fair and unbiased estimate of the difference between the two treatments, in contrast to the primary analysis that due to the penalty is biased in favour of the IGlar treatment.

- A tipping point analysis based on the FAS and the primary analysis for the primary estimand will be performed. In this analysis subjects who withdraw from the IDegAsp OD arm or have missing values at visit 26 are assumed to have an effect that is inferior to the de facto effect of IDegAsp OD . The extent of the inferiority (also termed a 'penalty') will be gradually increased to evaluate at which value IDegAsp OD is no longer non-inferior to IGlar OD + IAsp OD. This penalty value, also known as the tipping point, corresponds to the hypothetical degree of efficacy deterioration in withdrawn subjects that would change the conclusion of non-inferiority.

Primary analysis for the secondary estimand

The secondary estimand will be estimated based on the FAS using post-baseline measurements up to and including week 26 from the on-treatment observation period. To estimate this estimand, the change from baseline in HbA_{1c} after 26 weeks of treatment will be analysed using the mixed model for Repeated Measurement (MMRM) method with a restricted maximum likelihood (REML). The model will include treatment, sex, previous insulin treatment regimen, previous OAD treatment and region as factors and baseline HbA_{1c} and age as covariates, all nested within visit. An unstructured covariance matrix for HbA_{1c} measurements within the same subject will be employed, assuming measurements from different subjects are independent.

The MMRM is a well-established method that accounts for the uncertainty pertaining to missing data. This analysis assumes that the missing data mechanism is missing at random (MAR). Under this assumption the statistical behaviour of the missing data (given the observed responses and model fixed effects and covariates) is assumed to be the same as the observed data.

In a non-inferiority trial the efficacy estimand may be more appropriate than the effectiveness estimand, since it is not confounded by the effects of changing treatment from the randomised treatment to other treatments.

Sensitivity analyses for the secondary estimand

The following sensitivity analyses will be performed:

- The above MMRM analysis will be repeated on the PP and CAS using the on-treatment period. These analyses will be done to align with the reporting of the phase 3a trials.

- Using the FAS, the change in HbA_{1c} from baseline after 26 weeks of treatment will be analysed using an analysis of variance (ANOVA) method with treatment, sex, previous insulin treatment regimen, previous OAD treatment and region as fixed factors, and age and baseline HbA_{1c} as covariates, and where missing values will be imputed using the Last Observation Carried Forward (LOCF) method. This is done to align with the reporting of the phase 3a trials.

17.5 Supportive secondary endpoints

17.5.1 Efficacy endpoints

For the following continuous supportive efficacy endpoints, analyses similar to those for the primary and secondary estimands of the primary endpoint will be done, with the adjustment that the non-inferiority-penalty (NI-penalty) in step five of multiple imputation is not applied (this is only considered relevant for non-inferiority testing). Continuous safety endpoints that are analysed

statistically will also follow this procedure. A further change to the above specified model is that the model will include the baseline measurement of the endpoint as a covariate instead of the baseline HbA_{1c} measurement.

HbA_{1c}
Change from baseline in HbA_{1c} (%) after 38 weeks.

Fasting plasma glucose

- Change from baseline in FPG after 26 weeks
- Change from baseline in FPG after 38 weeks

Self-measured plasma glucose measurements (SMPG)

- **SMPG after 26 weeks**
  - Change from baseline in mean pre-breakfast measurements after 26 weeks
  - Change from baseline in post-prandial increments after 26 weeks

- **SMPG after 38 weeks**
  - Change from baseline in mean pre-breakfast measurements after 38 weeks
  - Change from baseline in post-prandial increments after 38 weeks

Furthermore, the mean PG before breakfast used for dose-titration and the 9-point profile will be calculated at each visit using the available data.

Responder for HbA_{1c}

- **Responder (Yes/No) for HbA_{1c} after 26 weeks**:
  - $HbA_{1c} < 7\%$
  - $HbA_{1c} < 7\%$ without nocturnal (00:01-05:59) (BG) confirmed symptomatic hypoglycaemia

- **Responder (Yes/No) for HbA_{1c} after 38 weeks:**

  - $HbA_{1c} < 7\%$
  - $HbA_{1c} < 7\%$ without nocturnal (00:01-05:59) BG confirmed symptomatic hypoglycaemia

Subjects with less than 16 weeks of treatment will be set as non-responders. Nocturnal hypoglycaemic episodes will be based on the available data.

Analysis of each of the responder endpoints will be based on a logistic regression model which will include treatment, sex, previous insulin treatment regimen, previous OAD treatment and region as fixed factors, and age and baseline HbA_{1c} as covariates.

The primary estimand for the responder endpoints will be derived using the HbA_{1c} values from the 1000 datasets originating from multiple imputation analysis of HbA_{1c}, without applying the NI-penalty. Each of these datasets will be analysed using the above logistic regression model and the results will then be pooled using Rubin's rule.

The secondary estimand for the responder endpoints will be derived using the MMRM imputed HbA_{1c} values.

17.5.2 Safety endpoints

Adverse events

The AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities coding.

A treatment-emergent adverse event (TEAE) is defined as an event that has onset date on or after the first day of exposure to randomised treatment and no later than seven days after the last day of randomised treatment. If the event has onset date before the first day of exposure on randomised treatment and increases in severity during the treatment period and until seven days after the last drug date, then this event should also be considered as a TEAE.

TEAEs are summarised descriptively, whereas non-treatment-emergent AE's are presented in listings. TEAE data will be displayed 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).

Summaries of TEAEs and serious TEAEs will be presented as an overview including all AEs, serious AEs, number of deaths, AEs by severity, AEs by relation to treatment as assessed by the investigator and AEs of special interest including AEs leading to withdrawal and AEs leading to drug withdrawn. The EAC confirmed adverse events will be listed and summarised descriptively.

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

- All TEAEs
- Serious TEAEs
- Possibly and probably related TEAEs
- Severe, moderate and mild TEAEs

- TEAEs reported by safety area of interest
- TEAEs with preferred term that are experienced by at least 5% (1%) of the subjects in any treatment arm or by at least 5% (1%) of all subjects
- TEAEs leading to withdrawal of subject or drug withdrawn

A listing of non-treatment-emergent events with onset date before the first day of exposure to randomised treatment will be presented. A listing will also be presented for non-treatment-emergent adverse events collected after the treatment-emergent period according to the definition of the TEAE.

Hypoglycaemic episodes

The definition and classification of hypoglycaemic episodes is given after the description of the statistical analysis.

Data on treatment-emergent hypoglycaemic episodes are presented in terms of the number of subjects with at least one event (N), the percentage of subjects with at least one event (%), the number of events (E) and the event rate per 100 years (R). Separate summaries are made by severity considering all confirmed hypoglycaemic episodes, nocturnal confirmed hypoglycaemic episodes and the ADA classification of hypoglycaemia.

In addition, to the extent where data allows, the following endpoints are analysed statistically.

During 26 weeks:

- Number of nocturnal, treatment-emergent severe or blood glucose (BG) confirmed symptomatic hypoglycaemic episodes during 26 weeks
- Number of nocturnal, treatment-emergent severe or BG confirmed hypoglycaemic episodes during 26 weeks
- Number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during 26 weeks
- Number of treatment-emergent severe or BG confirmed hypoglycaemic episodes during 26 weeks
- Number of nocturnal, treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during maintenance (week 16-26)
- Number of nocturnal, treatment-emergent severe or BG confirmed hypoglycaemic episodes during maintenance (week 16-26)

- Number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during maintenance (week 16-26)

- Number of treatment-emergent severe or BG confirmed hypoglycaemic episodes during maintenance (week 16-26)

During 38 weeks:

- Number of nocturnal, treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during 38 weeks

- Number of nocturnal, treatment-emergent severe or BG confirmed hypoglycaemic episodes during 38 weeks

- Number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during 38 weeks

- Number of treatment-emergent severe or BG confirmed hypoglycaemic episodes during 38 weeks

For endpoints addressing the hypoglycaemic rate in the 26 weeks or the 38 weeks period, a negative binomial model will be used, including treatment, previous insulin treatment regimen, previous OAD treatment, sex, and region as factors and age as covariate. The model will use a log-link function and the logarithm of the time period in which a hypoglycaemic episode was considered treatment emergent as offset.

The rationale for investigating the hypoglycaemic rate during the maintenance is to reflect long term use, as prior to this period (the titration period) the glycaemic control might be unstable. For endpoints addressing hypoglycaemic rate in the maintenance period, a negative binomial regression model using data from both the titration and maintenance periods will be used. This is done to comply with the randomisation principle, i.e. to include all randomised subjects in the analyses, also those who withdrew during the titration period. The model will use a log-link function and the logarithm of the time period in which a hypoglycaemic episode was considered treatment emergent as offset. Subject will be included as a random effect. The model includes treatment, previous insulin treatment regimen, previous OAD treatment, sex, region and period (titration or maintenance) as factors and age as covariate. The interaction between each factor and covariate with period will also be included.

From the above negative binomial models the treatment rate ratios will be estimated and 95% confidence intervals will be calculated.

The analyses and data presentations of hypoglycaemic events will be based on the hypoglycaemic episode form.

Classification of Hypoglycaemia:

Hypoglycaemic episodes are recorded by the subjects in their trial diaries throughout the trial. The information collected includes PG before treating the episode and whether the subject was able treat him/herself. This information is used by Novo Nordisk to classify episodes according to the confirmed hypoglycaemia definition and the ADA definition (severe, documented symptomatic, asymptomatic, probably symptomatic and pseudo).

- Treatment-emergent: hypoglycaemic episodes will be defined as treatment-emergent if the onset of the episode occurs on or after the first day of trial product administration, and no later than 7 calendar days after the last day on trial product

- 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 plasma glucose level of 3.1 mmol/L (56 mg/dL)[52]. Therefore, Novo Nordisk has included hypoglycaemia with plasma glucose 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[36]

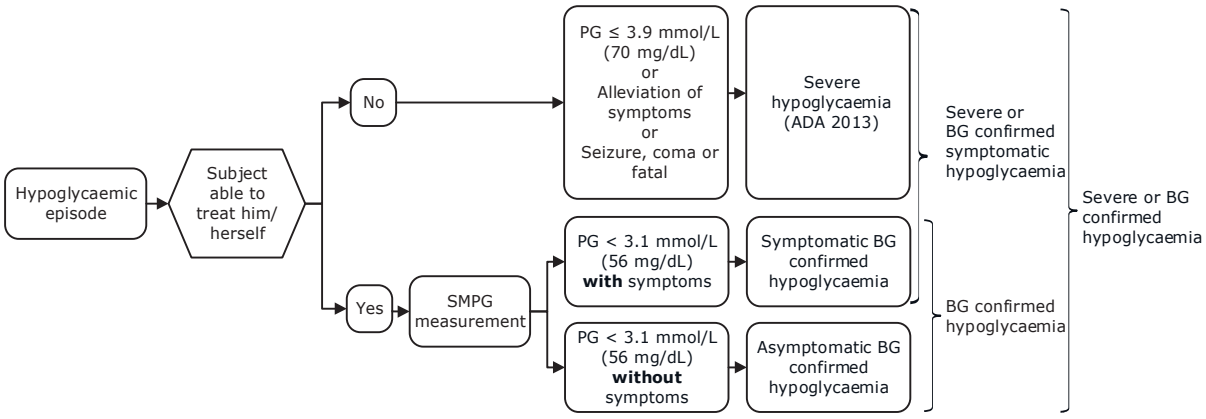
- Symptomatic BG confirmed hypoglycaemia: An episode that is BG confirmed by plasma glucose value <3.1 mmol/L (56 mg/dL) **with** symptoms consistent with hypoglycaemia.

- Asymptomatic BG confirmed hypoglycaemia: An episode that is BG confirmed by plasma glucose value <3.1 mmol/L (56 mg/dL) **without** symptoms consistent with hypoglycaemia.

- Severe or BG confirmed symptomatic hypoglycaemia: An episode that is severe according to the ADA classification[36]or BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) **with** symptoms consistent with hypoglycaemia.

- BG confirmed hypoglycaemia: An episode that is BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) **with** or **without** symptoms consistent with hypoglycaemia.

Severe or BG confirmed hypoglycaemia: An episode that is severe according to the ADA classification[36] or BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) **with** or **without** symptoms consistent with hypoglycaemia



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

Figure 17–1 Novo Nordisk classification of hypoglycaemia

ADA classification[36] of hypoglycaemia

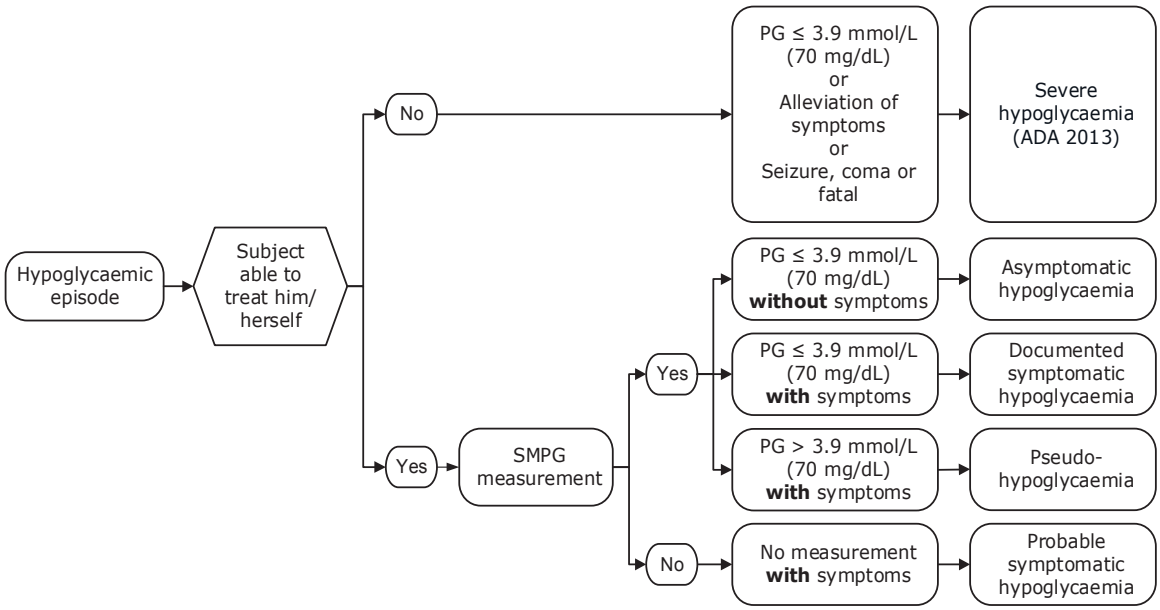
- Severe hypoglycaemia: An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

- Asymptomatic hypoglycaemia: An episode not accompanied by typical symptoms of hypoglycaemia, but with a measured plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL).

- Documented symptomatic hypoglycaemia: An episode during which typical symptoms of hypoglycaemia are accompanied by a measured plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL).

- Pseudo-hypoglycaemia: An episode during which the person with diabetes reports any of the typical symptoms of hypoglycaemia with a measured plasma glucose concentration > 3.9 mmol/L (70 mg/dL) but approaching that level.

- Probable symptomatic hypoglycaemia: An episode during which symptoms of hypoglycaemia are not accompanied by a plasma glucose determination but that was presumably caused by a plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL).



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

Figure 17–2 ADA classification of hypoglycaemia

Insulin dose

- Total insulin dose at week 26
- Total insulin dose at week 38

Observed values of total insulin dose at week 26 and week 38 will be summarised by the arithmetic mean, SD, median, and minimum and maximum value and supplemented with the geometric mean and coefficient of variation. Separate summaries will also be made for the basal insulin dose and the bolus insulin dose.

Weight

- Change in weight from baseline to week 26
- Change in weight from baseline to week 38

are summarised descriptively and analysed statistically using the primary statistical analysis for both the primary and secondary estimand.

Clinical evaluations at week 26 and week 38

- Physical examination
- Vital signs (blood pressure and pulse)
- Dilated fundoscopy or fundus photography
- 12-lead electrocardiogram

will be summarised descriptively including:

- Change from baseline to week 26
- Change from baseline to week 38

Any findings in the physical examination evaluation at screening will be presented as listings. Any clinically significant deterioration of a pre-existing condition after the screening visit, as well as any new clinically findings will be recorded as adverse events.

Laboratory assessments

- Haematology (haemoglobin, haematocrit, erythrocytes, thrombocytes, leucocytes)
- Biochemistry (creatinine, ALT, AST, AP, sodium, potassium, albumin, total bilirubin)
- Insulin antibodies

All laboratory parameters will be summarised descriptively.

The following tables will be presented based on observed data:

- Shift tables from baseline to week 26
- Shift tables from baseline to week 38
- Change from baseline to week 26
- Change from baseline to week 38

- Proportion of subjects with measurements outside reference range by treatment and week.

Laboratory values will be presented graphically as box plots by treatment and week.

For each laboratory parameter, individual values outside the reference range (abnormal values) will be listed.

17.6 Health economics and/or patient reported outcomes

The following PRO endpoints are included in the trial:

Change from baseline to week 26 for:

- Health-related quality of life as evaluated by SF-36v2® Health Survey
- Treatment related impact as evaluated by the Treatment Related Impact Measure-Diabetes (TRIM-D)

Change from baseline to week 38 for:

- Health-related quality of life as evaluated by the SF-36v2® Health Survey
- Treatment related impact as evaluated by the TRIM-D

The domain and overall scores for both SF-36 and TRIM-D will be summarised descriptively based on observed data and explorative statistical analysis may be performed.

The data collected in the BHQ will not be included in the clinical trial report, nor will the data collected in the hypoglycaemic resource use interview questionnaire. Data from the latter will be used to assess costs associated with hypoglycaemia and provide information to be used in health economic analyses.

18 Ethics

18.1 Benefit-risk assessment of the trial

The trial population will consist of subjects with T2DM. For all subjects participating in this trial the anticipated benefits include improved glycaemic control. Titration algorithms, specifying recommended adjustments of trial insulin dose for:

- IDegAsp: co-formulation of basal insulin degludec and bolus insulin aspart
- IGlar: basal insulin
- IAsp: bolus insulin

at different plasma glucose levels, are used in order to ensure that subjects receive an optimal treatment. Subjects will receive intense medical care by means of close contact to the clinical sites with at least weekly contacts.

The maximum trial duration for each subject is 44 weeks and the treatment duration for a subject is planned to be 38 weeks. Subjects will be asked to perform SMPG recordings and measure 9-point profiles at scheduled visits during the trial.

Trial products, including the 'washout' insulin will be provided by Novo Nordisk free of charge. Subjects will receive IDegAsp, IGlar and IAsp in prefilled pens that are all distinguishable in order to minimise the risk of medication errors. Both IAsp and IGlar are marketed products. Please refer to the local labelling of these products for a description of risks and benefits.

IDegAsp is currently approved worldwide in many countries within U.S., EU and Japan, although not available at the market in all countries in these regions yet.

The subjects will be provided with a BG-meter including lancets, plasma-calibrated test strips and control solutions as well as instructions for use.

Subjects randomised to the trial will be transferred to a treatment regimen anticipated to be better than or equal to the treatment they receive at the time they enter the trial.

It is expected that all subjects participating in the trial will benefit from participation through close contact to trial site, frequent follow-up visits and thereby an intensified evaluation of their diabetes.

Treatment discontinuation criteria (rescue criteria – refer to protocol 6.5) are defined in order ensure subject safety and adjust treatment if deemed necessary. Subjects may be prematurely discontinued from trial product at the discretion of the investigator due to a safety concern or if judged non-compliant with trial procedures. When prematurely discontinued from trial product, the subject will be prescribed alternative therapy at the investigator's discretion. Subjects who prematurely discontinue trial product will be offered to remain in the trial and attend and complete end of trial assessments and monthly phone contacts. An effort will be made to try to accomplish this for all prematurely discontinued subjects.

The trial products may be associated with side effects, but relevant precautions have been implemented in the design and planned conduct of the trial in order to minimise the risks and

inconveniences of participating in the trial. These precautions include thorough information regarding the correct administration of the trial products. Furthermore, subjects will be fully informed about possible AEs and inconveniences. The side effects associated with trial products are not different from what is seen with other insulins and include hypoglycaemia, hypersensitivity reactions, injection site reactions, lipodystrophy and peripheral oedema. For more detailed description, refer to the IB[17] the CCDS[41] and/or EU SmPC[15] for IDegAsp, the CCDS[42] and EU SmPC[13] for IAsp, and the EU SmPC[27] for IGlar or similar local labelling.

18.2 Informed consent

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

Before any trial-related activity, the investigator must give the subject verbal and written information about the trial and the procedures involved in a form that the subject can read and understand. This includes the use of an impartial witness where required according to local requirements.

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

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

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

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

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

18.3 Data handling

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

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

- Safety events will be reported to Novo Nordisk and regulatory authorities according to local/national requirements

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

18.4 Information to subject during trial

The site will be offered a communication package to the subject during the conduct of the trial. The package content is issued by Novo Nordisk. The communication package will contain the letters intended for distribution to the subjects. The letters will be translated and adjusted to local requirements and distributed to the subject by discretion of the investigator. The subject may receive a "Welcome to the trial letter" and a "Thank you for your participation letter" after completion of the trial. Furthermore, 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 are collected. If missing data does occur the reason will be collected via the protocol deviation process, see Section 19.1. Novo Nordisk will monitor protocol deviations on an on-going basis throughout the trial followed by appropriate actions (e.g. re-training of site staff).

20 Audits and inspections

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

21 Critical documents

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

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

Only applicable for U.S. trial sites:

- For U.S. trial sites: verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest
- For U.S. trial sites: FDA form 1572 must be completed and signed by the investigator at each site

FDA form 1572:

For U.S. sites:

- Intended for U.S. sites
- Conducted under the IND
- All U.S. investigators, as described above, will sign FDA Form 1572

For sites outside the U.S.:

- Intended for participating sites outside of the U.S.
- Not conducted under the IND
- All investigators outside of the U.S. will not sign FDA form 1572

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

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

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

22 Responsibilities

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

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

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

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

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

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

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

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

23 Reports and publications

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

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

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

One investigator will be appointed by Novo Nordisk to review and sign the clinical trial report (signatory investigator) on behalf of all participating investigators. The signatory investigator will be appointed based upon the criteria defined by the ICMJE for research publications[53]. The signatory investigator will be appointed before LPLV.

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[4].

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

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

In all cases the trial results will be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations. All authors will be given the relevant statistical tables, figures, and reports needed to evaluate the planned publication. In the event of any disagreement on the content of any publication, both the investigators' and Novo Nordisk opinions will be fairly and sufficiently represented in the publication.

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

23.1.1 Authorship

Authorship of publications should be in accordance with the Uniform Requirements of the ICMJE[53] (sometimes referred to as the Vancouver Criteria).

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

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

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

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

23.2 Investigator access to data and review of results

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

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

24 Retention of clinical trial documentation and human biosamples

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.

24.2 Retention of human biosamples

Antibody samples may be retained for later analysis for further characterisation of antibody responses towards drug if required by health authorities or for safety reasons.

The samples will be stored at a central bio-repository after end of trial and until marketing authorisation approval in all countries or until the research project terminates, but no longer than 15 years from end of trial after which they will be destroyed.

The subject's identity will remain confidential and the antibody samples will be identified only by subject number, visit number and trial identification number. No direct identification of the subject will be stored together with the samples.

Only Novo Nordisk staff and bio-repository personnel will have access to the stored antibody samples.

Subjects can contact the investigator if they wish to be informed about results derived from stored antibody samples obtained from their own body.

25 Institutional Review Boards/Independent Ethics Committees and regulatory authorities

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

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

The investigator must ensure submission of the clinical trial report synopsis to the IRB/IEC.

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

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

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

26 Indemnity statement

Novo Nordisk carries product liability for its products, and liability as assumed under the special laws, acts and/or guidelines for conducting clinical trials in any country, unless others have shown negligence.

Novo Nordisk assumes no liability in the event of negligence, or any other liability of the sites or investigators conducting the trial, or by persons for whom the said site or investigator are responsible.

If a country has specific laws, acts and/or guidelines, and the local regulatory authorities require specifically to identify such laws/acts/guidelines in the protocol, these should be referred to by stating: Novo Nordisk accepts liability in accordance with: Insert reference to local laws/acts/guidelines. Ensure these local additions are in agreement with the Head of CMR or Global Legal.

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Protocol Amendment

no 1
to Protocol, final version 3.0
dated 04 May 2016

Trial ID: NN5401-4266

A 38 week trial comparing effect and safety of insulin degludec/insulin aspart vs. insulin glargine plus insulin aspart in subjects with type 2 diabetes treated with basal insulin with or without oral antidiabetic treatment in need of treatment intensification.

Trial phase: 3b

Applicable to all countries

Amendment originator:

[redacted], [redacted]

Trial Operations 3, Insulin & Devices

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1 Introduction including rationale for the protocol amendment

Main reason for global amendment no. 1 is that recruitment period is extended. New standard for statistical data handling has been implemented to meet new requirements from the FDA. At the same time identified important errors and necessary clarifications are implemented.

In this protocol amendment:

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

2 Changes

2.1 Section 1, Summary

Correction of error:

In need of treatment intensification is defined as an HbA_{1c} level of 7-10% (53-8~~5~~*6* mmol/mol), both inclusive.

2.2 Section 2, Flow chart

Specification of visit window at P42 : ~~±3~~*+3*

Addition of 'x' for hypoglycaemic episodes at P42, table 2-1, to highlight that hypoglycaemic episodes are collected in the follow up period : *x*

Addition of 'x' for hypoglycaemic episodes at P42, table 2-2,to highlight that hypoglycaemic episodes are collected in the follow up period: *x*

Clarification of text in foot note n:
Two follow-up visits are to be conducted. The first (V41) must take place no earlier than seven days and no later than 12 days after the EOT visit (V40). The last follow-up visit (P42) will take place ~~approximately~~ *no earlier than* 30 days after the EOT visit (V40) *and no later than 33 days after the EOT visit (V40)* and will be conducted as a phone contact (P42).

Clarification of foot note o:
At the abbreviated visits (V28a and V40a) HbA_{1c} samples and information on adverse events (AEs) *including hypoglycaemic episodes* will be collected

Addition of new foot note 'p' for 9-point-profile at V40 : *p*

Addition of new foot note p, to clarify that 9-point-profile is not required at V40 for subjects prematurely discontinued :

[p] *For subjects prematurely discontinued from trial insulin products the 9-point-profile is omitted at visit corresponding to V40*

2.3 Section 4.2.2.1, Supportive secondary efficacy endpoints

Update of supportive secondary efficacy endpoints to implement new guidelines from FDA:

- At 26 weeks:
  - Responder (Yes/No) for HbA_{1c} after 26 weeks:
  - HbA_{1c} <7%
  - HbA_{1c} <7% without nocturnal (00:01-05:59) *severe or* blood glucose (BG) confirmed symptomatic hypoglycaemia
  - *HbA_{1c} < 7% without severe or BG confirmed symptomatic hypoglycaemia*

- At 38 weeks:
  - Responder (Yes/No) for HbA1c after 38 weeks:
  - HbA_{1c} <7%
  - HbA_{1c} <7% without nocturnal (00:01-05:59) *severe or* blood glucose (BG) confirmed symptomatic hypoglycaemia
  - *HbA_{1c} < 7% without severe or BG confirmed symptomatic hypoglycaemia*

2.4 Section 5.2, Rationale for trial design

Clarification of the rationale for trial design to highlight that hypoglycaemic episodes are to be collected in the follow up period:

A 30-day follow-up (P42) after last trial insulin treatment (V40) will be performed in order to collect information about antidiabetic treatment and adverse events (AEs) *including hypoglycaemic episodes* occurring between V41 and P42.

2.5 Section 6.5, Rescue criteria

Correction of rescue criteria text to clarify which SMPG values are to be used:

If ~~any of~~ the fasting SMPG values taken on three consecutive days or if any of the FPG samples analysed by the central laboratory exceed the limit of:

- 15.0 mmol/L (270 mg/dL) from baseline to end of week 12
- 13.3 mmol/L (240 mg/dL) from week 13 to end of week 38

and if no treatable inter current cause for the hyperglycaemia has been identified, the subject must be called for a confirmatory FPG measurement at a scheduled or unscheduled visit as soon as possible.

2.6 Section 7, Milestones

Change of timelines to reflect that recruitment period has been extended:

Planned duration of recruitment period (i.e. first patient first visit (FPFV) – last patient first visit (LPFV)): 1~~6~~*9* weeks *and 3 days*
Planned date for FPFV: 20 Sep 2016
Planned date for last patient last visit (LPLV): ~~16 Nov~~ *12 Dec* 2017

2.7 Section 8.1.5, Diaries

Correction to specify when diaries are provided to subjects:

At each clinic visit, the subjects must receive diaries related to the following visit and/or phone contact(s). The diaries dispensed to subjects should be collected at the following clinic visit. However, for ~~the screening visit (V1),~~ the 30-days follow-up visit (P42) and the monthly phone contacts (in case of pre-term discontinuation of trial insulin products) no diaries will be provided.

2.8 Section 8.1.9, Follow-up visits

Clarification to highlight that hypoglycaemic episodes are to be collected at last follow up visit (P42) and at potential monthly phone contacts (Px):

For the last follow-up visit (P42) and potential monthly phone contacts (Px), no paper diary will be provided. Consequently, source data for these phone contacts will be the notes written in the subject's medical record. At these contacts only information about antidiabetic treatment and AEs *including hypoglycaemic episodes* will be collected.

2.9 Section 8.1.11, Premature discontinuation of trial product

Clarification to highlight that 9-point-profile is not needed at the visit corresponding to V40 for subjects prematurely discontinued from trial product:

In case of premature discontinuation of trial product the investigator should make all effort to call the subject in for an unscheduled visit as soon as possible and must aim to undertake procedures similar to those for the EOT visit (V40), *except 9-point-profile but* including fasting blood sampling and hand-out of 'washout' insulin products (refer to Section 5.3.3) to be used in the period between the EOT visit (V40) and the 7-day follow-up visit (V41), where the last AB sampling will be performed.

2.10 Section 8.2.5, Concomitant medication

To clarify the definition and the reporting requirements for concomitant medications:

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

Details of any concomitant medication must be recorded at the screening visit (V1), including OAD treatment and pre-trial basal insulin, which subjects continue using between the screening visit (V1) and the randomisation visit (V2). For details on OAD treatment, refer to Section 5.4.

The information collected for each anti-diabetic concomitant medication includes trade name or generic name, indication, total daily dose and route of administration, start date and stop date or continuation. For concomitant medication other than anti-diabetic concomitant medication only trade name or generic name, indication, start date and stop date or continuation are to be collected.

In case the concomitant medication is a systemic treatment which in the investigator's opinion could interfere with the glucose metabolism (e.g. treatment with orlistat, thyroid hormones, or corticosteroids – refer to exclusion criterion 14 (Section 6.3)), this information needs to be captured in the eCRF.

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, total daily dose and route of administration, start date and stop date or continuation.~~

If a change is due to an AE, then this must be reported according to Section 12.

~~In case the concomitant medication is a systemic treatment which in the investigator's opinion could interfere with the glucose metabolism (e.g. treatment with orlistat, thyroid hormones, or corticosteroids – refer to exclusion criterion 14 (Section 6.3)), this information needs to be captured in the eCRF.~~

If the change influences the subject's eligibility to continue in the trial or trial product treatment *(refer to premature discontinuation criterion 4, section 6.6)*, the monitor must be informed.

2.11 Section 8.4.8, Hypoglycaemic episodes

Specification of process for recording of hypoglycaemic episodes during follow-up period:

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

should be reported in the diary according to the instructions below throughout the trial from

randomisation (Visit 2) to the follow-up (Visit 41). *Hypoglycaemic episodes occurring between Visit 41 and the last follow up visit (P42) should be recorded on a hypoglycaemic episode form in the eCRF.*

2.12 Section 8.5.3.1, Haematology and Biochemistry assessments

Clarification that lab parameters will be analysed at screening and not at randomisation as previously indicated:

The below haematology and biochemistry parameters will be analysed at the ~~randomisation~~ *screening visit* (~~V2~~*V1*), prior to the intensification period (V28) and at the end-of-trial visit (V40), please refer to the flow chart (Section 2).

2.13 Section 12.1.1, Adverse event

Correction of cross-reference to a wrong section in the protocol:

Non-serious hypoglycaemia is an AE, but is reported on a hypoglycaemic episode form instead of an AE form, see Section ~~8.4.7.~~ *8.4.8*

2.14 Section 14, Monitoring procedures

Deletion of US requirement as this is wrong:

A follow-up letter (paper or electronic) will be sent to the investigator following each monitoring visit. This should address any action to be taken. ~~For U.S.: the follow-up letter must be signed by the investigator.~~

2.15 Section 17.5.1, Efficacy endpoints

Update of supportive secondary efficacy endpoints to implement new guidelines from FDA:

Responder for HbA_{1c}

- **Responder (Yes/No) for HbA_{1c} after 26 weeks:**
  - HbA_{1c} <7%
  - HbA_{1c} <7% without nocturnal (00:01-05:59) ~~(BG)~~ *severe or BG* confirmed symptomatic hypoglycaemia
  - *HbA_{1c} < 7% without severe or BG confirmed symptomatic hypoglycaemia*

- **Responder (Yes/No) for HbA1c after 38 weeks:**
  - HbA_{1c} <7%
  - HbA_{1c} <7% without nocturnal (00:01-05:59) ~~(BG)~~ *severe or BG* confirmed symptomatic hypoglycaemia

- *HbA_{1c} < 7% without severe or BG confirmed symptomatic hypoglycaemia*

Subjects with less than 16 weeks of treatment will be set as non-responders. ~~Nocturnal~~ *H~~n~~*ypoglycaemic episodes will be based on the available data.

2.16 Section 17.5.2, Safety endpoints

Update of supportive secondary efficacy endpoints to implement new guidelines from FDA:

For endpoints addressing the hypoglycaemic rate in the 26 weeks or the 38 weeks period, a negative binomial model will be used, including treatment, previous insulin treatment regimen, previous OAD treatment, sex, and region as factors and age as covariate. The model will use a log-link function and the logarithm of the time period in which a hypoglycaemic episode was considered treatment emergent as offset. *The treatment rate ratios will be estimated and 95% confidence intervals will be calculated.*

~~The rationale for investigating the hypoglycaemic rate during the maintenance is to reflect long term use, as prior to this period (the titration period) the glycaemic control might be unstable. For endpoints addressing hypoglycaemic rate in the maintenance period, a negative binomial regression model using data from both the titration and maintenance periods will be used. This is done to comply with the randomisation principle, i.e. to include all randomised subjects in the analyses, also those who withdrew during the titration period. The model will use a log-link function and the logarithm of the time period in which a hypoglycaemic episode was considered treatment emergent as offset. Subject will be included as a random effect. The model includes treatment, previous insulin treatment regimen, previous OAD treatment, sex, region and period (titration or maintenance) as factors and age as covariate. The interaction between each factor and covariate with period will also be included.~~

~~From the above negative binomial models the treatment rate ratios will be estimated and 95% confidence intervals will be calculated.~~

The rationale for investigating the hypoglycaemic rate during the maintenance is to reflect long term use, as prior to this period (the titration period) the glycaemic control might be unstable. For endpoints addressing hypoglycaemic rate in the maintenance period, subjects that discontinue randomised treatment during the maintenance period will contribute with the available data from the maintenance period. For subjects that discontinue randomised treatment during the 16 week titration period, the number of events in the maintenance period will be imputed based on data from the maintenance period for subjects that discontinued randomised treatment during the maintenance period. For these subjects, the number of events will be imputed corresponding to a 10 weeks maintenance period as follows:

- *In the first step, 1000 samples from the posterior distribution of model parameters are extracted. The model is fitted to the on-treatment maintenance data for subjects that discontinued randomised treatment during the maintenance period for each treatment arm separately. This is done using a Bayes negative binomial log-link model with the same factors, covariates and offset as in the analyses of hypoglycaemic episodes described above. The 1000 samples are used as sampled parameter estimates in the next step.*
- *For each sample of model parameters, the total number of hypoglycaemic events in the maintenance period for subjects that discontinued randomised treatment in the titration period is imputed as a random number of events from a negative binomial distribution using the sampled parameters.*
- *For each of the 1000 imputed data sets, that now have maintenance period data for all randomised subjects, the mean treatment ratio is estimated using the same negative binomial model as in the analyses of hypoglycaemic episodes described above.*
- *The estimates and standard deviations for the 1000 imputed data sets are pooled to one estimate and associated standard deviation using Rubin's formula. From these the 95% confidence interval for the treatment ratio and the associated p-value are calculated.*

If the above model cannot fit due to sparse data, the model in step 1 is fitted to the on-treatment data for subjects that discontinued randomised treatment during either titration or maintenance, i.e. do not complete the scheduled 26 weeks of treatment. If this model cannot fit either, factors will be left out one by-one in the model using data from all subjects discontinuing randomised treatment before week 26 in the following order, until a model fits:

- *sex*
- *age*
- *region*
- *previous insulin treatment regimen*
- *previous OAD treatment*

2.17 Appendix A, section 3.6.2

Clarification of titration procedure:

If HbA_{1c} a~~A~~t week 32 *is ≥ 7.0% IAsp treatment should* ~~, subjects can~~ be ~~further~~ intensified with an additional dose of IAsp initiated at 4U~~, if deemed necessary by the investigator~~.

Global and country key Novo Nordisk staff

Attachments I and II (if applicable) to the protocol are located in the Trial Master File.

Content: Global key staff and Country key staff

Appendix A: Insulin Titration Guideline

Trial ID: NN5401-4266

A 38 week trial comparing effect and safety of insulin degludec/insulin aspart vs. insulin glargine plus insulin aspart in subjects with type 2 diabetes treated with basal insulin with or without oral antidiabetic treatment in need of treatment intensification

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1 Introduction

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

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

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

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

2 Treatment regimens

At randomisation all subjects will be randomised in a 1:1 manner into two parallel treatment groups:

- Insulin degludec/insulin aspart (IDegAsp) OD ± OADs
- Insulin glargine (IGlar) OD + insulin aspart (IAsp) OD ± OADs

First dosing should take place on day of randomisation or on the day following randomisation.

There are no minimum or maximum doses for IDegAsp, IGlar or IAsp.

2.1 Injection area

Both IDegAsp, IGlar and IAsp should be injected subcutaneously into the thigh, upper arm (deltoid region) or the abdomen.

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

2.2 Time of injection

IDegAsp OD will be administered with the largest meal. From week 26 subjects in need of intensification will be administered IDegAsp BID with the two largest meals; one being dinner.

During intensification the timing of IDegAsp (BID) dosing can be changed at the discretion of the investigator, but one of doses must be administered with the dinner.

IGlar will be administered OD according to local labelling.

IAsp OD should be administered with the largest meal. From week 26 subjects in need of intensification should be administered IAsp BID with the largest and second largest meal. From week 32 subjects in need of further intensification should be administered IAsp TID with largest and second largest meals and the third meal of the day. Extra bolus dosing should be avoided, except for short term safety reasons. Extra bolus doses and reasons should be documented in the diary.

3 Initiation and titration

3.1 Initiation of IGlar

Subjects receiving OD basal insulin will transfer unit-to-unit to IGlar OD. Subjects receiving more than OD basal insulin should reduce the initial total daily dose by 20% or according to local labelling and transfer to IGlar OD.

3.2 Initiation of IDegAsp

Subjects receiving basal insulin OD or more will transfer unit-to-unit to IDegAsp OD.

3.3 Initiation of IAsp

IAsp will be initiated at 4U with the largest meal.

3.4 Treatment of IGlar

During the entire treatment period IGlar doses will be titrated once weekly by the investigator based upon the subject's SMPG levels and the insulin titration guideline in connection with the scheduled visits/phone contacts.

Dose adjustment will be based on the three pre-breakfast SMPG values measured on the day of the titration and the two days prior to the titration in accordance with Table 1 and Table 2.

Table 1 Increase of IGlar

Mean pre-breakfast SMPG		Dose adjustment
mmol/L	**mg/dL**	**U**
4.0 – 5.0	71 – 90	No adjustment
5.1 – 7.0	91 – 126	+2
7.1 –8.0	127 – 144	+4
8.1 – 9.0	145 – 162	+6
> 9.0	> 162	+8

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

Table 2 Dose reduction of IGlar

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

3.5 Treatment during week 1-26 of IDegAsp and IAsp

During the entire treatment period insulin doses will be titrated once weekly by the investigator based upon the subject's SMPG levels and the insulin titration guideline in connection with the scheduled visits/phone contacts.

3.5.1 Titration of IDegAsp OD

Dose adjustment will be based on the three pre-breakfast SMPG values measured on the day of the titration and the two days prior to the titration in accordance with Table 3 and Table 4.

Table 3 Increase of IDegAsp OD

Mean pre-breakfast SMPG		Dose adjustment
mmol/L	**mg/dL**	**U**
4.0 – 5.0	71 – 90	No adjustment
5.1 – 7.0	91 – 126	+2
7.1 –8.0	127 – 144	+4
8.1 – 9.0	145 – 162	+6
> 9.0	> 162	+8

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

Table 4 Dose reduction of IDegAsp OD

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

3.5.2 Titration of IAsp

IAsp will be dosed once daily with the largest meal.

Dose adjustment will be based on the three pre-prandial or bedtime SMPG values measured on the three days prior to titration in accordance with Table 5.

- Breakfast dose will be adjusted based on pre-lunch SMPG values
- Lunch dose will be adjusted based on pre-dinner SMPG values
- Dinner dose will be adjusted based on bedtime SMPG values

Table 5 Adjustment of IAsp

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

3.6 Treatment after week 26 of IDegAsp and IAsp

If HbA_{1c} taken at week 25 is <7.0%, the subject should be titrated at week 26 according to Table 3 and Table 4.

If HbA_{1c} taken at week 25 is ≥ 7.0% IDegAsp treatment should be intensified to BID at week 26 as described below.

At week 32 subjects still on IDegAsp OD should be intensified to BID if HbA_{1c} taken at week 31 is ≥ 7.0%.

Intensification from IDegAsp OD to BID should be done by splitting the total daily dose of IDegAsp OD into two doses of IDegAsp. The split can be even or uneven as based on the size of the meals. Subjects with HbA_{1c} < 7.0% measured at week 25 or 31 can be switched to IDegAsp BID at weeks 26 or 32 at the discretion of the investigator based on the needs of the individual subject.

3.6.1 Titration of IDegAsp BID

The breakfast/lunch dose adjustment will be based on the three pre-dinner SMPG values measured on three days prior to the titration in accordance with Table 6 and Table 7.

The dinner dose adjustment will be based on the mean of three pre-breakfast SMPG values measured on the day of titration and the two days prior to the titration in accordance with Table 6 and Table 7.

Table 6 Increase of IDegAsp BID

Mean pre-breakfast or pre-dinner SMPG		Dose adjustment
mmol/L	**mg/dL**	**U**
4.0 – 5.0	71 – 90	No adjustment
5.1 – 7.0	91 – 126	+2
7.1 –8.0	127 – 144	+4
8.1 – 9.0	145 – 162	+6
> 9.0	> 162	+8

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

Table 7 Dose reduction of IDegAsp BID

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

3.6.2 Titration of IAsp

If HbA_{1c} at week 26 is <7.0%, the subject should continue on IAsp OD and titration according to Table 5.

If HbA_{1c} at week 26 is ≥ 7.0% IAsp treatment should be intensified with a second dose of IAsp. The second dose should be initiated at 4U. Titration should be performed according to Table 5.

If HbA_{1c} at week 32 is ≥ 7% IAsp treatment should be intensified with an additional dose of IAsp initiated at 4U. Titration should be performed according to Table 5.

3.7 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 into the eCRF.

4 Data collection

The following data should be entered into the eCRF within 24 hours (on weekdays) after a site visit/phone contact:

- Per protocol SMPG values measured since last visit/telephone
- Date, time and doses of IDegAsp, IGlar and IAsp
- Prescribed doses of IDegAsp, IGlar and IAsp
- Reasons for deviation from the titration algorithms, if applicable
- Hypoglycaemic episodes

5 Review procedure

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

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

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

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

6 References

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