Cover Page for Protocol

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NCT number	NCT03175120
Sponsor trial ID:	NN9068-4166
Official title of study:	A trial comparing the efficacy and safety of insulin degludec/liraglutide and insulin degludec in combination with metformin in Chinese subjects with type 2 diabetes mellitus inadequately controlled with basal insulin therapy and metformin ± one other OAD. DUAL™ II China
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Redacted protocol
Includes redaction of personal identifiable information only.

16.1.1 Protocol and protocol amendments

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Protocol

Trial ID: NN9068-4166
DUAL™ II China

A trial comparing the efficacy and safety of insulin degludec/liraglutide and insulin degludec in combination with metformin in Chinese subjects with type 2 diabetes mellitus inadequately controlled with basal insulin therapy and metformin ± one other OAD

Trial phase: 3a

Protocol originator

[redacted]

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List of abbreviations

ADA	American Diabetes Association
AE	adverse event
AGI	α-glucose inhibitors
ALAT	alanine transaminase
ANCOVA	standard analysis of covariance
ASAT	aspartate transaminase
BG	blood glucose
BMI	body mass index
CAS	completer analysis set
CRF	case report form
DPP-4	dipeptidyl peptidase-4
DUN	dispensing unit number
EASD	European Association for the Study of Diabetes
ECG	electrocardiogram
eCRF	electronic case report form
EOT	end of treatment
FAS	full analysis set
FPG	fasting plasma glucose
GCP	good clinical practice
GLP-1	glucagon-like peptide-1
HbA_{1c}	glycosylated haemoglobin
hCG	human chorionic gonadotrophin
HDL	high density lipoprotein
HOMA-β	homeostatic model assessment
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IDeg	insulin degludec
IDegLira	insulin degludec/liraglutide

IEC	independent ethics committee
IMP	investigational medicinal product
IRB	institutional review board
IV/WRS	interactive voice/web response system
LDL	low density lipoprotein
LOCF	last observation carried forward
MAP	modelling analysis plan
MEN2	multiple endocrine neoplasia type 2
MESI	medical event of special interest
MMRM	mixed model for repeated measurement
NYHA	New York Heart Association
OAD	oral anti-diabetic drug
OD	once daily
PP	per protocol
SAE	serious adverse event
SAS	safety analysis set
SmPC	summary of product characteristics
SIF	safety information form
SMPG	self-measured plasma glucose
SU	sulphonylureas
SUSAR	suspected unexpected serious adverse reaction
T2DM	type 2 diabetes
TEAE	treatment emergent adverse event
TMM	trial materials manual
TTT	treat-to-target
TZD	thiazolidinediones
U	Unit
UNR	upper normal range
UTN	universal trial number

VLDL	very low-density lipoprotein

1 Summary

Primary objective

To confirm the superiority of insulin degludec/liraglutide versus insulin degludec in controlling glycaemia in Chinese subjects with type 2 diabetes mellitus after 26 weeks of treatment.

Primary endpoint

Change from baseline in HbA_{1c} after 26 weeks of treatment.

Secondary objective

- To confirm superiority of insulin degludec/liraglutide vs. insulin degludec on the following:
    - Change from baseline in body weight after 26 weeks of treatment
    - Number of treatment emergent severe or blood glucose confirmed hypoglycaemic episodes during 26 weeks of treatment
- To compare the overall efficacy and safety of insulin degludec/liraglutide to insulin degludec after 26 weeks of treatment.

Confirmatory secondary endpoints

- Change from baseline in body weight after 26 weeks of treatment
- Number of treatment emergent severe or blood glucose confirmed hypoglycaemic episodes during 26 weeks of treatment

Trial design

This is a 26 week, randomised, parallel two-arm, double-blind, multi-centre, treat-to-target trial in Chinese subjects with type 2 diabetes inadequately controlled with basal insulin therapy and metformin ± one other oral anti-diabetic agent: α-glucosidase inhibitors, sulphonylureas, glinides or thiazolidinediones.

Subjects will be randomised in a 2:1 manner to receive insulin degludec/liraglutide or insulin degludec once daily with metformin. The randomisation of subjects will be stratified with respect to their previous anti-diabetic treatment (basal insulin and metformin or basal insulin, metformin and one other oral anti-diabetic agent).

The total trial duration for the individual subject will be approximately 29 weeks.

Trial population:

A total of 450 subjects will be randomised.

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 procedures to determine suitability for the trial
- Male or female, age ≥ 18 years at the time of signing inform consent
- Type 2 diabetes mellitus (clinically diagnosed)
- HbA_{1c} ≥ 7.5% by central laboratory analysis, with the aim of a median of 8.5%. When approximately 50% of the randomised subjects have an HbA_{1c} above 8.5%, the remaining subjects randomised must have an HbA_{1c} below or equal to 8.5% or when approximately 50% of the subjects randomised have an HbA_{1c} below or equal to 8.5%, the remaining subjects randomised must have an HbA_{1c} above 8.5%
- Current treatment for at least 90 calendar days prior to screening with basal insulin + metformin ± α-glucosidase inhibitors, sulphonylureas, glinides or thiazolidinediones. Subjects should be on a stable dose for at least 60 calendar days prior to screening of:
  Basal insulin 20-50 units (U)/day (both inclusive)* on the day of screening in combination with
  i. Metformin (≥1500 mg or max tolerated dose) or
  ii. Metformin (≥1500 mg or max tolerated dose) and sulphonylureas (≥half of the max approved dose according to local label) or
  iii. Metformin (≥1500 mg or max tolerated dose) and glinide (≥half of the max approved dose according to local label) or
  iv. Metformin (≥1500 mg or max tolerated dose) and α-glucosidase inhibitors (AGI) (≥half of the max approved dose according to local label) or

v. Metformin (≥1500 mg or max tolerated dose) and thiazolidinediones (≥half of the max approved dose according to local label)

*Individual fluctuations of ± 5U during the 60 day period prior to the day of screening are acceptable

- Body mass index (BMI) ≥24 kg/m^2

Key exclusion criteria

- Current use of any anti-diabetic drug (except for basal insulin, metformin, α-glucosidase inhibitors, sulphonylureas, glinides or thiazolidinediones) or anticipated change in concomitant medication, that in the investigator´s opinion could interfere with glucose level (e.g. systemic corticosteroids)
- Treatment with glucagon like peptide -1 receptor agonists, or dipeptidyl peptidase -4 inhibitors or insulin (except for basal insulin) within 90 days prior to Visit 1
- Impaired liver function defined as alanine aminotransferase ≥ 2.5 times upper normal range
- Impaired renal function defined as serum-creatinine ≥133 µmol/L for males and ≥125 µmol/L for females, or as defined according to local contraindications for metformin
- Screening calcitonin ≥50 ng/L
- Personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia type 2 (MEN2)
- Cardiac disorder defined as: congestive heart failure (NYHA class III-IV), diagnosis of unstable angina pectoris, cerebral stroke and/or myocardial infarction within the last 12 months prior to screening and/or planned coronary, carotid or peripheral artery revascularisation procedures
- Severe uncontrolled treated or untreated hypertension (systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥100 mm Hg)
- Proliferative retinopathy or maculopathy (macular oedema) requiring acute treatment
- History of pancreatitis (acute or chronic)

Key efficacy assessments

- HbA_{1c}
- Weight
- Fasting plasma glucose

Key safety assessments

- Hypoglycaemic episodes
- Adverse events

Trial product(s)

The trial products for subcutaneous injection in the trial are:

- Insulin degludec/liraglutide 100 units/mL + 3.6 mg/mL, 3 mL pre-filled pen
- Insulin degludec 100 units/mL, 3 mL pre-filled pen

2 Flow chart

Screening (S) **Randomisation (R)** **Visit (V)** **Telephone contact (T)** **Follow up visit (FU)**	S	R	T	V	T	V	T	V	T	V	T	V	T	V	T	V	T	V	FU
Visit/Contact number	1	2	3	4	5	6	7 8 9	10	11 12 13 14	15	16 17 18	19	20 21 22	23	24 25 26	27	28 29 30 31 32	33	34
Timing of visit (weeks)[1]	- 2[2]	0	0.5	1	1.5	2	2.5 3 3.5	4	4.5 5 6 7	8	9 10 11	12	13 14 15	16	17 18 19	20	21 22 23 24 25	26	27
Visit window (days)			±1	±1	±1	±1	±1	±1	±1	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3
SUBJECT RELATED INFO/ASSESSMENTS																			
Informed consent	X																		
In/exclusion criteria	X	X																	
Randomisation		X																	
Withdrawal criteria			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant illness/Medical History	X																		
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Smoking Habits	X																	X	
Demography	X																		
Diagnosis of diabetes	X																		
Diabetes treatment history	X																		
Family history of diabetes	X																		
Diabetes complications	X																		
Body measurements																			
Height	X																		
Body weight	X	X						X		X		X		X		X		X	
BMI	X																	X	
Waist circumference		X										X						X	
EFFICACY																			
Glucose metabolism																			
HbA1c	X	X						X		X		X		X		X		X	
Fasting plasma glucose		X						X		X		X		X		X		X	
Fasting insulin		X										X						X	
Fasting glucagon		X										X						X	
Fasting C-peptide		X										X						X	
Self measured plasma glucose																			
9-point profile		X										X						X	

Screening (S) **Randomisation (R)** **Visit (V)** **Telephone contact (T)** **Follow up visit (FU)**	S	R	T	V	T	V	T	V	T	V	T	V	T	V	T	V	T	V	FU
Visit/Contact number	1	2	3	4	5	6	7 8 9	10	11 12 13 14	15	16 17 18	19	20 21 22	23	24 25 26	27	28 29 30 31 32	33	34
Timing of visit (weeks)[1]	- 2[2]	0	0.5	1	1.5	2	2.5 3 3.5	4	4.5 5 6 7	8	9 10 11	12	13 14 15	16	17 18 19	20	21 22 23 24 25	26	27
Visit window (days)			±1	±1	±1	±1	±1	±1	±1	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3
Once daily			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
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	X	X
ECG	X[3]																	X[4]	
Eye examination	X[5]																	X[6]	
Physical examination	X																	X	
Vital signs	X											X						X	
Antibodies		X										X						X	X
Biochemistry	X	X										X						X	
Haematology	X	X										X						X	
Hormones (calcitonin)	X	X										X						X	
Lipids		X										X						X	
Urine dipstick		X										X						X	
Pregnancy test [7]	X																	X	
TRIAL MATERIAL																			
IV/WRS call	X	X						X		X		X		X		X		X	
Administration of trial product		X						X		X		X		X		X			
Drug accountability		X						X		X		X		X		X		X	
REMINDERS																			
Hand out ID card	X																		
Handout and instruct in BG meter use	X																		
Training in trial product and pen handling		X																	
Attend visit fasting		X						X		X		X		X		X		X	X[8]
Hand out and instruct in diary	X	X		X		X		X		X		X		X		X		X	
Collect first date and dose of trial product			X																
Collect last date and dose of trial product																		X	
Dose of trial product to be			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Screening (S) **Randomisation (R)** **Visit (V)** **Telephone contact (T)** **Follow up visit (FU)**	S	R	T	V	T	V	T	V	T	V	T	V	T	V	T	V	T	V	FU
Visit/Contact number	1	2	3	4	5	6	7 8 9	10	11 12 13 14	15	16 17 18	19	20 21 22	23	24 25 26	27	28 29 30 31 32	33	34
Timing of visit (weeks)[1]	- 2[2]	0	0.5	1	1.5	2	2.5 3 3.5	4	4.5 5 6 7	8	9 10 11	12	13 14 15	16	17 18 19	20	21 22 23 24 25	26	27
Visit window (days)			±1	±1	±1	±1	±1	±1	±1	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3
taken after titration																			
Confirmation of unchanged metformin dose			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
End of trial and sign off case book																			X

[1] A 0.5 week interval is corresponding to previous visit plus three calendar days
[2] Screening must take place within 14 calendar days prior to randomisation
[3] ECG obtained within 14 calendar days prior to Visit 2 as part of routine practice may replace the screening assessment, if results are available for evaluation at visit 2. See section 8.2.11
[4] ECG obtained within 14 calendar days prior to Visit 33 is acceptable, if the results are available for evaluation at Visit 33. See section 8.2.11
[5] Eye examination performed within 90 calendar days prior to visit 2 as part of routine practise may replace the screening assessment if results are available for Visit 2. See section 8.2.10
[6] Eye examination performed within 14 calendar days prior to Visit 33 is acceptable, if the results are available for evaluation at Visit 33. See section 8.2.10
[7] For females of child bearing potential a urine pregnancy test should be performed at site, if pregnancy is suspected or if a menstrual period is missed. If the subject reports missing menstrual period at a phone contact, the subject must attend the site for an unscheduled visit as soon as possible to have a urine pregnancy test done. If positive a confirmatory serum hCG test should be sent to the central laboratory
[8] For fasting requirements prior to Visit 34 see section 8.1.6

3 Background information and rationale for the trial

The trial will be conducted in compliance with this protocol, ICH GCP[1] and applicable regulatory requirements, and in accordance with the Declaration of Helsinki[2] . In this document, the term investigator refers to the individual responsible for the overall conduct of the clinical trial at a trial site.

3.1 Background information

Type 2 diabetes mellitus (T2DM) is a progressive disorder characterised by insulin resistance and impaired insulin secretion. A number of landmark studies have demonstrated the importance of maintaining good glycaemic control to reduce the risk of long-term complications associated with diabetes [3] [4] . Given the progressive nature of T2DM, current anti-diabetic therapies, including treatment with basal insulin in combination with one or two oral anti-diabetic drugs (OADs), often fail to provide sustained glycaemic control. The current treatment cascade by the Chinese Diabetes Society and American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) consensus follows a stepwise approach comprising lifestyle changes with pharmacological intervention. Metformin is recommended as initial pharmacological therapy, followed by combination therapy with other OADs, glucagon-like peptide 1 (GLP-1) receptor agonists or insulin as the disease progresses [5] [6]. The successful outcome of recent global trials combining basal insulin and GLP-1 receptor agonist treatment as separate injections has led to the inclusion of this treatment combination in the most recent ADA/EASD position statement of hyperglycaemia in T2DM[5].

3.2 Rationale for the Trial

Insulin degludec/liraglutide (IDegLira) is a combination drug containing the long acting basal insulin analogue, insulin degludec (IDeg) and the human GLP-1 analogue, liraglutide intended for once daily (OD) use in a single injection in subjects with T2DM. IDegLira was developed to take advantage of the combined effects of a basal insulin and GLP-1 analogue on glycaemic control through the actions on fasting glucose mediated by IDeg and liraglutide, and on postprandial glycaemic control mediated by liraglutide. The global clinical development programme for IDegLira has confirmed that the modes of action of IDeg and liraglutide result in clinically important improvements in glycaemic control with low risk of hypoglycaemia and weight gain in patients with T2DM[7]. In addition, the convenience of administering both components in a single daily injection, using a titration scheme similar to that used for basal insulin products, is expected to facilitate treatment compliance for patients.

This confirmatory trial will be used for registration purposes in China to document the efficacy and safety of treatment with IDegLira OD in combination with metformin in Chinese subjects with T2DM. For detailed information on IDeg or IdegLira, see the Investigator´s Brochure, any updates hereof, and/or SmPC, as applicable.

4 Objectives and endpoints

4.1 Objectives

4.1.1 Primary objective

To confirm the superiority of IDegLira versus IDeg in controlling glycaemia in Chinese subjects with T2DM after 26 weeks of treatment.

This is done by comparing the difference in change from baseline in HbA_{1c} after 26 weeks of treatment to a superiority margin of 0.0% for IDegLira vs. IDeg.

4.1.2 Secondary objectives

- To confirm superiority of IDegLira vs. IDeg on the following:
    - Change from baseline in body weight after 26 weeks of treatment
    - Number of treatment emergent severe or blood glucose confirmed hypoglycaemic episodes during 26 weeks of treatment
- To compare the overall efficacy and safety of IDegLira to IDeg after 26 weeks of treatment.

4.2 Endpoints

4.2.1 Primary endpoint

Change from baseline in HbA_{1c} after 26 weeks of treatment

4.2.2 Secondary endpoints

4.2.2.1 Confirmatory secondary endpoints

- Change from baseline in body weight after 26 weeks of treatment
- Number of treatment emergent severe or blood glucose confirmed hypoglycaemic episodes during 26 weeks of treatment

To protect the type 1 error rate when testing the confirmatory endpoints, a closed test procedure will be used.

4.2.2.2 Supportive secondary efficacy endpoints

- Insulin dose after 26 weeks of treatment
- Responder for HbA_{1c} after 26 weeks of treatment (Yes/No)
  - $HbA_{1c} < 7.0\%$
  - $HbA_{1c} \leq 6.5\%$
  - $HbA_{1c} < 7.0\%$ and change from baseline in body weight below or equal to zero
  - $HbA_{1c} \leq 6.5\%$ and change from baseline in body weight below or equal to zero
  - $HbA_{1c} < 7.0\%$ without severe or blood glucose (BG) confirmed hypoglycaemic episodes during the last 12 weeks of treatment
  - $HbA_{1c} \leq 6.5\%$ without severe or BG confirmed hypoglycaemic episodes during the last 12 weeks of treatment
  - $HbA_{1c} < 7.0\%$ and change from baseline in body weight below or equal to zero and without severe or BG confirmed hypoglycaemic episodes during the last 12 weeks of treatment
  - $HbA_{1c} \leq 6.5\%$ of treatment and change from baseline in body weight below or equal to zero and without severe or BG confirmed hypoglycaemic episodes during the last 12 weeks of treatment
- Change from baseline after 26 weeks of treatment in:
  - Fasting plasma glucose (FPG)
  - Waist circumference
  - Mean of the 9-point profile
- Mean post prandial increment (from before meal to 90 min after for breakfast, lunch and dinner). The mean increment over all meals will be derived as the mean of all available meal incrementsFasting C-peptide, fasting insulin, and fasting glucagon after 26 weeks of treatment
- Beta-cell function, quantified by homeostatic model assessment (HOMA-β) after 26 weeks of treatment
- Fasting lipid profile after 26 weeks of treatment

4.2.2.3 Supportive secondary safety endpoints

- Number of treatment emergent adverse events (TEAEs) during 26 weeks of treatment
- Number of treatment emergent nocturnal severe or blood glucose (BG) confirmed hypoglycaemic episodes during 26 weeks of treatment
- Number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during 26 weeks of treatment
- Number of treatment emergent nocturnal severe or BG confirmed symptomatic hypoglycaemic episodes during 26 weeks of treatment
- Number of treatment emergent hypoglycaemic episodes according to ADA definition
- Change from baseline in clinical evaluations after 26 weeks of treatment
  - Physical examination

- Fundoscopy or fundus photography
- Electrocardiogram (ECG)
- Pulse
- Blood pressure

- Change from baseline in laboratory assessments during 26 weeks of treatment
  - Biochemistry
  - Haematology
  - Calcitonin
- Urinalysis (dipstick for erythrocytes, protein, glucose and ketones)
- Antibodies towards trial product

5 Trial design

5.1 Type of trial

This is a 26 week, randomised, parallel two-arm, double-blind, multi-centre, treat-to-target (TTT) trial in Chinese subjects with T2DM inadequately controlled with basal insulin therapy and metformin ± one other OAD: α-glucosidase inhibitors (AGI), sulphonylureas (SU), glinides or thiazolidinediones (TZD). Inadequately controlled diabetes will be defined as HbA_{1c} level of ≥ 7.5%.

Subjects will be randomised in a 2:1 manner, using a centralised allocation via interactive voice/web response system (IV/WRS) to receive IDegLira or IDeg both once daily in combination with metformin. Other pre-trial OAD treatment will be discontinued at randomisation. Subjects will be stratified with respect to their previous anti-diabetic treatment (basal insulin and metformin or basal insulin, metformin and one other OAD).

A total of 450 subjects will be randomised.

The duration of the trial from screening (Visit 1) to follow-up (Visit 34) will be 29 weeks with treatment duration of 26 weeks. The trial will include a screening visit (Visit 1) at which the eligibility of the subjects is determined followed by randomisation (Visit 2). The follow-up (Visit 34) will be conducted 1 week after end of treatment.

The trial design is summarised schematically below:

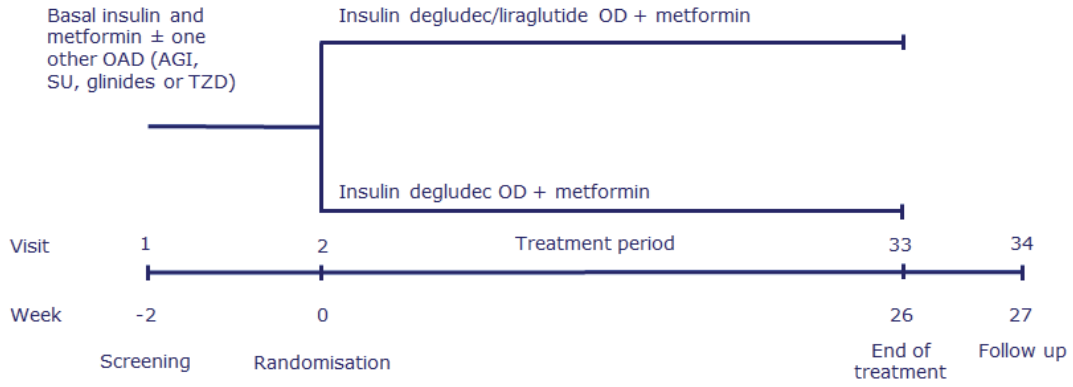


Figure 5–1 Trial design

5.2 Rationale for trial design

Based on prior experience from IDegLira trials, the treatment duration of 26 weeks is sufficient to reach a stable HbA_{1c} level and to obtain sufficient data for efficacy and safety evaluation. The parallel design has been chosen instead of a cross-over design to avoid the risk of carry-over effect and to keep the treatment period as short as possible.

The current trial is designed to demonstrate superiority in HbA_{1c} of IDegLira as compared to IDeg in subjects with T2DM. To enable an evaluation of the contribution of the liraglutide component of IDegLira to glycaemic control and secondary endpoints, the maximum dose of the IDeg in the IDeg arm is set to 50 units (U), i.e. equivalent to the maximum dose of the IDeg component with IDegLira.

A double-blind design is feasible due to the similar titration and will limit the occurrence of conscious and unconscious bias in the conduct and the interpretation of this trial arising from the influence which the knowledge of treatment may have on the subjects case, the attitudes of subjects to the treatment, the assessment of endpoints, the handling of withdrawals, the exclusion of data from the analysis etc.

To obtain improved HbA_{1c} results to allow for a valid comparison of safety endpoints the TTT approach has been chosen in order to ensure optimal treatment with frequent visits and titration of IDegLira and IDeg based on pre-breakfast self-measured plasma glucose (SMPG) values.

5.3 Treatment of subjects

Subjects with T2DM treated with basal insulin and metformin with or without one additional OAD (AGI, SU, glinides or TZD) in accordance with the inclusion criterion are eligible for the trial. At randomisation basal insulin and OADs except for metformin will be discontinued. Subjects will receive IDegLira or IDeg subcutaneous once daily in combination with metformin for the treatment duration of 26 weeks.

Because of blinding during conduct of the trial a common terminology for both trial products have been chosen to be dose steps, thus one dose step corresponds to either 1 unit of IDeg or 1 dose step of IDegLira (1 unit insulin degludec/0.036 mg liraglutide). IDegLira and IDeg added to current metformin therapy will be given subcutaneously once daily. The starting dose of IDegLira is 16 dose steps (16 units insulin degludec /0.6 mg liraglutide) and starting dose of IDeg is 16 units. The dose of IDegLira and IDeg will thereafter be titrated twice weekly according to the Titration guideline (Appendix A).

The treatment with metformin will be continued with pre-trial dose.

5.4 Treatment in follow-up period

After 26 weeks of trial product exposure, a 1 week interval between the end of treatment (Visit 33) and the follow-up (Visit 34) is necessary to allow for trial product wash out. Subjects should in this period be transferred to any other anti-diabetic treatment at the discretion of the investigator. However, treatment with IDeg, insulin detemir (Levemir ®) or any GLP-1 receptor agonist is not permitted in the periods from the end of trial (Visit 33) to the follow up (Visit 34) due to the inference with the antibody measurements performed at Visit 34. If the subject refuses to come in for the follow up (Visit 34), the subject will be switched to a suitable marketed product as recommended by the investigator.

5.5 Treatment after end of trial

When completing the trial the subject should be switched to a suitable marketed product at the discretion of the investigator.

5.6 Rationale for treatment

Subjects will be treated with IDegLira or IDeg in order to demonstrate the efficacy and safety of IDegLira.

IDeg has been included as comparator in order to demonstrate a clinical benefit in terms of HbA_{1c} reduction of the fixed combination product as compared to this individual component. Given a TTT approach, the objective can only be achieved by capping the IDeg dose at 50U, leading to insulin dose equivalence in the two treatment arms, allowing a differentiation between the treatment arms based on the additional effects of the liraglutide component of IDegLira.

Start dose is 16 dose steps of IDeglira (16 units insulin degludec and 0,6 mg liraglutide) and IDeg (16 units insulin degludec) respectively. Due to the liraglutide component in IDegLira, the highest tolerable initiation dose of GLP-1 receptor agonist in GLP-1 naïve subjects is 16 dose steps (0.6 mg liraglutide, corresponding to maximum initial dose of liraglutide).

In order to obtain differentiation between the two treatment arms as reflected in the liraglutide component of the combination, the highest dose at end of trial is pursued. Therefore, T2DM subjects already treated – and inadequately controlled - with basal insulin are included to increase the chance of high dose at end of trial (i.e. approaching 50U or 50 dose steps). Pre-trial basal insulin therapy (treatment for at least 90 days and a total daily dose within the range of 20-50U, individual fluctuations of ± 5U within the 60 days prior to screening but not on the day of screening) will be discontinued at randomisation.

The current treatment cascade by the Chinese Diabetes Society and ADA/EASD consensus follows a stepwise approach comprising lifestyle changes with pharmacological intervention. Metformin is recommended as initial pharmacological therapy, followed by combination therapy with other oral

anti-diabetic drugs (OADs), glucagon-like peptide 1 (GLP-1) receptor agonists or insulin as the disease progresses [5] [6]. Accordingly, the subjects will be on a background treatment including metformin in the present trial. The daily dose for metformin (≥ 1500 mg or maximum tolerated dose) is close to the maximum recommended dose for the treatment of T2DM according to local label.

Subjects treated with AGI, SU, glinides or TZD will have this therapy discontinued at randomisation.

6 Trial population

6.1 Number of subjects

Country planned to participate: China

Number of subjects planned to be screened: 750

Number of subjects planned to be randomised: 450 (40% screening failure rate)

Number of subjects expected to complete the trial: 382 (withdrawal rate of 15%)

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 inform consent
3. Type 2 diabetes mellitus (clinically diagnosed)
4. HbA_{1c} ≥ 7.5% by central laboratory analysis, with the aim of a median of 8.5%. When approximately 50% of the randomised subjects have an HbA_{1c} above 8.5%, the remaining subjects must have an HbA_{1c} of below or equal to 8.5% or when approximately 50% of the randomised subjects have an HbA1c below or equal to 8.5%, the remaining subjects randomised must have a HbA_{1c} above 8.5%
5. Current treatment for at least 90 calendar days prior to screening with basal insulin + metformin ± AGI, SU, glinides and TZD. Subjects should be on a stable dose for at least 60 calendar days prior to screening of:
   Basal insulin 20-50 U /day (both inclusive)* on the day of screening in combination with:
   i. Metformin (≥1500 mg or max tolerated dose) or
   ii. Metformin (≥1500 mg or max tolerated dose) and SU (≥half of the max approved dose according to local label) or
   iii. Metformin (≥1500 mg or max tolerated dose) and glinide (≥half of the max approved dose according to local label) or
   iv. Metformin (≥1500 mg or max tolerated dose) and AGI (≥half of the max approved dose according to local label) or
   v. Metformin (≥1500 mg or max tolerated dose) and TZD (≥half of the max approved dose according to local label)

*Individual fluctuations of ± 5U during the 60 day period prior to the day of screening are acceptable

6. Body mass index (BMI) ≥24 kg/m^2
7. Able and willing to adhere to the protocol including performing self-monitoring of plasma glucose profiles, keeping a trial diary and to using a pre-filled pen device

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 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 (sterilisation, intrauterine device (IUD), oral contraceptives or barrier methods)
4. Receipt of any investigational medicinal product within 30 calendar days before Visit 1
5. Current use of any anti-diabetic drug (except for basal insulin, AGI, SU, glinides and TZD) or anticipated change in concomitant medication, that in the investigator´s opinion could interfere with glucose level (e.g. systemic corticosteroids)
6. Use of non-herbal Chinese medicine or other non-herbal local medicine with unknown/unspecified content within 90 calendar days prior to screening. Herbal traditional Chinese medicine or other local herbal medicines may, at the investigator´s discretion, be continued throughout the trial
7. Treatment with GLP-1 receptor agonists, or DPP-4 inhibitors or insulin (except for basal insulin) within 90 days prior to Visit 1
8. Impaired liver function defined as alanine aminotransferase (ALAT) ≥ 2.5 times upper normal range (UNR)
9. Impaired renal function defined as serum-creatinine ≥133µmol/L (1.5 mg/dL) for males and ≥125 µmol/L (1.4 mg/dL) for females, or as defined according to local contraindications for metformin
10. Screening calcitonin ≥ 50 ng/L
11. Personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia type 2 (MEN2)
12. Cardiac disorder defined as: congestive heart failure (NYHA class III-IV), diagnosis of unstable angina pectoris, cerebral stroke and/or myocardial infarction within the last 12 months period to screening and/or planned coronary, carotid or peripheral artery revascularisation procedures
13. Severe uncontrolled treated or untreated hypertension (systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥100 mm Hg)
14. Proliferative retinopathy or maculopathy (macular oedema) requiring acute treatment
15. Subject with a clinically significant, active (during the past 12 months) disease of the gastrointestinal, pulmonary, endocrinological (except for T2DM), neurological,

genitourinary or haematological system (except for conditions associated with T2DM) that in the opinion of the investigator may confound compliance and the results of the trial or pose additional risk in administering trial drug

16. Mental incapacity, unwillingness or language barrier precluding adequate understanding of the trial procedure or cooperation with the trial site personnel
17. Known or suspected abuse of alcohol or narcotics
18. History of pancreatitis (acute or chronic)
19. Suffer from a life threatening disease including malignant neoplasms and medical history of malignant neoplasms and medical history of malignant neoplasms within the last 5 years (except basal and squamous cell skin cancer)

6.4 Withdrawal criteria

The subject may withdraw at will at any time without providing an explanation.

The subject may be withdrawn from the trial at the discretion of the investigator due to a safety concern or if judged non-compliant with trial procedures.

The subject must be withdrawn if the following applies:

1. Included in the trial in violation of the inclusion and/or exclusion criteria
2. Pregnancy
3. Intention of becoming pregnant
4. Initiation of any systemic treatment with products which in the investigator´s opinion could interfere with glucose metabolism (e.g. systemic cortecoidsteroids)
5. If all pre-breakfast SMPG values taken on three consecutive days or if any fasting plasma glucose (FPG) samples analysed by the central laboratory exceed the limit of
    - 15.0 mmol/L after baseline to week 6
    - 13.3 mmol/L from week 6 to week 12
    - 11.1 mmol/L from week 12 to last week prior to end of treatment visit

and given there is no intercurrent cause for the hyperglycaemia, a confirmatory FPG must be performed at the next scheduled visit or, if deemed necessary by the investigator, at an unscheduled visit. If the confirmatory FPG exceeds the limits stated above, the subject must be withdrawn

6. If the investigator suspects acute pancreatitis, all drugs suspected to relate to this condition should be discontinued until confirmatory tests have been conducted, and appropriate treatment should be initiated. Subject must be withdrawn if diagnosed with acute pancreatitis must as a minimum have 2 out of 3:
    1. characteristic findings on ultrasound/computed axial tomography (CT)/magnetic resonance imaging (MRI)
    2. characteristic abdominal pain
    3. amylase and/or lipase >3x UNR

6.5 Subject replacement

Subjects who are withdrawn will not be replaced.

6.6 Rationale for trial population

Subjects with T2DM on previous basal insulin therapy in need of treatment intensification ($HbA_{1c} \geq$ 7.5%) to achieve glycaemic control are the target population for inclusion in this trial.

Subjects should be on a stable insulin dose with basal insulin 20-50U/day (both inclusive, individual fluctuations of ± 5U are acceptable but not on the day of screening) for at least 60 days prior to screening and should be overweight (BMI ≥24 kg/m^2) to ensure inclusion of subjects in which a high dose at the end of the trial can be expected. The rationale for including subjects on metformin with or without AGI, SU, glinides and TZD is to mimic common practise of diabetes treatment in subjects with T2DM failing on 1-2 OAD´s. When glycaemic control is not achieved or sustained on this background, the addition of IDegLira can be considered.

The HbA_{1c} range has been chosen to include subjects for whom diabetes is not optimally controlled on their current treatment and hence would benefit from an intensified treatment regimen. A median baseline HbA_{1c} level of 8.5% has been chosen to ensure to ensure some patients in the study will be treated with the dose between 40-50 dose steps.

Only serious concomitant conditions (NYHA class III-IV, see Appendix C, history of recent serious cardiac event, neoplastic disease, renal or hepatic impairment, major surgery etc.) which could interfere with trial schedule/procedures preclude subjects from entering the trial.

7 Milestones

Planned duration of recruitment period (first subject first visit - last subject last visit): approximately 54 weeks. End of trial is defined as last subject last visit.

Recruitment will be performed according to an arrangement made up-front with the individual investigational site. The screening will be monitored closely during the entire recruitment period. In order to secure recruitment timelines, agreed distribution of subjects between sites may be changed. The screening and randomisation rate will be followed closely via the IV/WRS in order to estimate when to stop screening. See section 11 for randomisation procedure.

Trial registration:

Information of the trial will be disclosed at clinicaltrials.gov, chinadrugtrials.org.cn and novonordisk-trials.com. According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure, it will also be disclosed according to other requirements such as those of the International Committee of Medical Journal Editors[8], the Food and Drug Administration Amendment Act [9], European Commission Regulation for EudraCT [10] 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

Timing of site visits, telephone contacts, their windows and assessments to be performed are specified in the flow chart in section 2. In the following section instructions on how to perform and record results of all assessments are describe in more details.

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

8.1.1 Fasting requirements for blood sampling

As outlined in the flow chart subject must attend most of the visits fasting, i.e. at least eight hours without food and drink intake, except for water and any other prescribed medication. Trial products and metformin should be withheld on the day of the visit until blood sampling and body weight (if applicable) has been performed. Any other prescribed medication should be taken as usual. If the subject attend the site in a non-fasting state the blood sampling should be re-scheduled, see section 8.1.7 for instructions.

See section 8.1.6 for special requirements in relation to fasting prior to the follow up (Visit 34).

8.1.2 Screening (Visit 1)

Must take place within 14 calendar days prior randomisation.

Before screening, the Investigator must provide the subject with oral and written information about the trial. See section 18.1 for instructions on informed consent. Ensure subject has signed the informed consent before any trial related procedures can take place.

At screening the subjects will be assigned a unique number which will remain the same throughout the trial. This number will be registered in the IV/WRS which will be used for screening, randomisation and allocation of trial product to each subject throughout the trial (see section 9.5 and section 10 for use of the IV/WRS). Subject numbers will automatically be transferred into an electronic case report form (eCRF) system used by the investigator or other relevant trial throughout the trial. See section 13 for more information on the eCRF.

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 visit or destroy the card after the last visit.

All inclusion/exclusion criteria must be reviewed and if any of the criteria cannot be assessed e.g. criteria related to results from blood sampling performed at screening or if a valid eye examination

is missing, the investigator must ensure these are obtained for assessment of eligibility prior to being able to randomise the subject at Visit 2. If the subject is ineligible, see section 8.1.3 how to screen fail the subject.

Eligible subjects should be instructed to continue on their current OAD treatment until Visit 2.

Subjects will be provided with diaries for completion of source data that will be reviewed by the investigator at all site visits/telephone contacts. See section 8.6 for source data to be captured in the diaries.

Subjects will be provided with a BG meter for use throughout the trial. See section 8.2.12 for instructions.

8.1.3 Screening Failures

For screening failures the screening failure form must be completed with the reason for not continuing in the trial. The date of informed consent must be transcribed to the electronic case report form (eCRF). Only serious adverse events (SAEs) from screening failures must be transcribed by the investigator into the eCRF. Follow-up of SAEs must be carried out according to section 12.3.

Screening failures experiencing an adverse event (AE) that would otherwise qualify for adjudication (see section 12.7.3) will not be adjudicated as no trial product has been administered.

A screening failure session must be made in the IV/WRS.

When data has been source data verified and all queries have been resolved, the case book must be signed by the investigator in the eCRF.

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

8.1.4 Randomisation (Visit 2)

All inclusion/exclusion criteria and results from assessments at the screening visit including blood sampling, ECG and eye examination results must be available and reviewed by the investigator prior to randomisation to ensure subject remains eligible.

To be randomised, subjects must discontinue the current insulin and OAD treatment and remain only on metformin. Subjects will then be randomised to receive IDegLira or IDeg in combination with metformin. See the Titration Guideline (Appendix A) for start doses and titration of randomised treatment. The dose of metformin should remain unchanged throughout the trial.

Subjects must be trained in correct use of the pens and directions for use of the pens must be provided in writing to randomised subjects. This must be documented in subjects' records. At Visit 2 subjects should demonstrate to the investigator, that they can use the pens correctly prior to leaving the site. Sites should, as necessary, repeat the directions for use to the subject at subsequent visits.

8.1.5 Treatment period (Visit 2 -Visit 33)

During the treatment period the investigator should ensure that subjects comply with the scheduled site visits and telephone contacts and that they record the required source data in the diaries prior to every site visit/telephone contact.

A telephone contact may be changed into a site visit if needed. It is the responsibility of the investigator to ensure that the contact regardless of the format takes place.

At the end of treatment (Visit 33) subjects will be switched from trial product to an appropriate anti-diabetic treatment at the discretion of the investigator. However, IDeg, insulin detemir (Levemir®) and any GLP-1 receptor agonists are not allowed, since they may interfere with antibodies measured at follow-up (Visit 34).

8.1.6 Follow-up visit (Visit 34)

Due to the long half-life of IDeg, the procedures of the follow-up visit should be undertaken no earlier than 7 calendar days after Visit 33. Subjects must attend this visit having fasted for 2 hours (i.e. no food or drink except water) prior to the blood sampling for antibody analysis. Subjects on any type of insulin must not have administered this within 12 hours of the blood sampling.

At Visit 34 the subjects may be switched to any other suitable marketed product at the investigator's discretion.

8.1.7 Unscheduled visit(s)

Unscheduled visits can be performed at any time at the discretion of the investigator. An unscheduled visit should be performed, if:

- An AE occurs that needs further attention
- Additional laboratory sample is needed due to a medical event of special interest (MESI)
- A confirmatory pregnancy test is needed
- A confirmatory FPG test for withdrawal criteria #5 is required
- A blood re-sampling related to a specific visit (if not possible to reschedule blood sampling within the visit window)

For all of the above an unscheduled visit form must be completed in the eCRF, indicating the reason for the visit.

An unscheduled visit form should not be completed, if the subject attends the clinic for a blood re-sampling within the visit window. Instead a requisition form must be completed with the visit number the re-sampling refers to and data must be entered into the eCRF for the corresponding visit. Also, additional trial product dispensing does not require the use of the unscheduled visit form, an additional dispensing session should be made in the IV/WRS.

8.1.8 Subject withdrawal

If a subject is withdrawn from the trial, the investigator must aim to undertake procedures similar to those for Visit 33 and 34 as soon as possible. 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 withdrawal session must be made in the IV/WRS. The case book must be signed.

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

8.2 Subject related information

8.2.1 Demography

Demography is an account of date of birth, sex, race and ethnicity.

8.2.2 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). Concomitant illness includes any pre-planned procedures/surgeries and any intermittent illness (e.g. allergy to food, medication, pollen or other) that is not apparent at the time of screening. T2DM should not be recorded as concomitant illness.

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.

8.2.3 Adverse events

AE´s will be recorded throughout the trial in accordance with the procedure described in section 12.

8.2.4 Diabetes complications and treatment history

The date of diagnosis of T2DM, current diabetes complications, diabetes treatment history and family history of diabetes must as a minimum be recorded in the eCRF at screening.

8.2.5 Smoking habits

Details of smoking habits must be recorded at Visit 1 and Visit 33. Smoking is defined as smoking at least one cigarette, cigar or pipe daily. The collected information should include whether or not the subject smokes or has smoked. If the subject smokes or has smoked, record approximately when the subject started smoking and if applicable when the subject stopped smoking.

8.2.6 Concomitant medication

A **concomitant medication** is any medication including traditional herbal Chinese medicine and other local herbal medicine, other than the trial product(s), which is taken during the trial, from Visit 1 to Visit 33.

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

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

At each contact to site the subject should confirm that their metformin treatment is unchanged. In case of safety concern the dose may be reduced at the discretion of the investigator. The reason, date and duration of the change should be recorded in the eCRF.

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

8.2.7 Body measurements

Height

Height is measured without shoes in centimetres (cm) and recorded to the nearest cm.

Body weight

Body weight should be measured without shoes and only wearing light clothing in kilograms (kg) with one decimal. The measurements are to be performed in a fasting state, except for the screening (Visit 1). Body weight should be assessed on the same equipment throughout the trial, if possible.

Body Mass Index (BMI)

Body mass index will be automatically calculated in the eCRF once height and weight are entered. At the Visit 1 the BMI must be in accordance with the relevant inclusion criterion, see section 6.2.

Waist circumference

The waist circumference is defined as the minimal abdominal circumference located midway between the lower rib margin and the iliac crest.
Three consecutive measurements of waist circumference should be taken and recorded in the eCRF. The waist circumference will be measured to the nearest 0.5 cm using a non-stretchable measuring tape (will be provided to the site by Novo Nordisk).

The subject should be measured in a standing position with an empty bladder and wearing light clothing with accessible waist. The subject should be standing with arms down their side and feet together. The tape should touch skin but not compress soft tissue and twists in the tape should be avoided. The subject should be asked to breathe normally and the measurement should be taken when the subject is breathing out gently.

8.2.8 Vital Signs (blood pressure and pulse)

The measurement of systolic, diastolic blood pressure and pulse (beats per minute) should be assessed while the subject is in a sitting position and after 5 minutes of rest.

Blood pressure must be measured three times and all three values must be entered to the eCRF. The mean value will be calculated by the eCRF and must be in accordance with the relevant exclusion criteria (see section 6.3).

If the investigator suspects white coat hypertension at Visit 1 and/or Visit 2, one re-assessment of the systolic and diastolic blood pressure (as described above) is allowed.

8.2.9 Physical Examination

Physical examination must include:

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

The investigator must interpret if the results are “normal” or “abnormal”, and if “abnormal” whether the abnormality is “not clinically significant” or “clinically significant”.

8.2.10 Eye examination

Eye examination (a fundoscopy or fundusphotography) must be performed by the investigator, a local ophthalmologist or an optometrist according to local practise. Dilation is not a requirement.

If an eye examination has been performed within 90 calendar days prior to Visit 2 the procedure does not need to be repeated, if the results are available for evaluation at Visit 2 and no worsening of visual function since the last examination has occurred. If the eye examination is performed before the subject consented to participate in the trial, it must also be stated in the subject’s medical records that this procedure was not performed in relation to the trial.

If an eye examination has been performed within 14 calendar days prior to Visit 33 the procedure does not need to be repeated, if the results are available for evaluation at Visit 33 and no worsening of visual function since the last examination has occurred.

For all eye examinations the investigator must interpret if the results are “normal” or “abnormal”, and if “abnormal” whether the abnormality is “not clinically significant” or “clinically significant”. The investigator must sign and date the eye examination results to verify the review.

8.2.11 ECG

A 12-lead ECG must be performed as part of screening procedures so that results are available at Visit 2 prior to randomisation.

ECG obtained within 14 calendar days prior to Visit 2 as part of routine practice may replace the screening assessment, if results are available for evaluation at Visit 2. If the ECG is performed before the subject consented to participate in the trial, it must also be stated in the subject´s medical records that this procedure was not performed in relation to the trial.

An ECG performed within14 calendar days prior to Visit 33 is acceptable, if the results are available for evaluation at Visit 33.

The investigator must interpret if the results are “normal” or “abnormal”, and if “abnormal” whether the abnormality is “not clinically significant” or “clinically significant”. The investigator must sign and date the ECG to verify the review.

8.2.12 Self-measured plasma glucose (SMPG)

At the screening visit, subjects will be provided with a blood glucose (BG) meter which must be used for all measurements during the trial. The subject should be supplied with oral and written

directions for use of the device including the performance of regular calibrations according to the manufacturer's instructions. Sites should, as necessary, repeat the directions for use to the subject at subsequent visits.

The BG meters use test strips calibrated to plasma glucose value. Therefore, all measurements performed with capillary blood are automatically calibrated to plasma equivalent glucose values, which will be shown on the display and hence recorded in the eCRF as self-measured plasma glucose (SMPG) values.

Subjects should be instructed how to record the values in the provided diaries and should only record the SMPG values based on measurements obtained with the provided BG meter. The recording of each measurement should include date and value.

Once daily SMPG values should be obtained fasting before breakfast. Diabetes medication should be withheld until after the measurement.

For telephone contacts the investigator or delegated site staff must transcribe the data used for the titration into the eCRF during/after the telephone contact. See Appendix A.

8.2.13 Self measured 9-point blood glucose profile

Subjects will be instructed to perform measurements and record the SMPG values for a 9-point SMPG profile within one week prior to the site Visit 2, 19 and 33 on days where the subject does not anticipate unusual strenuous exercise. Anti-diabetic medication should be withheld until after the SMPG values have been obtained from the pre-breakfast measurement.

The SMPG values should recorded in the diary (including actual clock time and date for the measurement) at the following time points, always starting with the measurement just before breakfast:

- Before breakfast
- 90 min after the start of breakfast
- Before lunch
- 90 min after the start of lunch
- Before dinner
- 90 min after the start of dinner
- At bedtime
- At 4 am
- Before breakfast the following day

8.2.14 Hypoglycaemic episodes

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

All plasma glucose values:

- ≤ 3.9 mmol/L or
- > 3.9 mmol/L

when they occur in conjunction with hypoglycaemic symptoms, should be recorded by the subject. These must be transcribed into the eCRF on the hypoglycaemic episode form throughout the trial from Visit 2 to Visit 34.

The record should include the following information:

- Date and time of hypoglycaemic episode
- The plasma glucose level before treating the episode (if available)
- Whether the episode was symptomatic
- Whether the subject was able to treat him/herself
- Date and time and dose of last trial product administration (or other anti-diabetic treatment) prior to episode
- Type of last administered product (trial product or other anti-diabetic treatment) prior to the episode
- Date and time of last main meal prior to episode
- Whether the episode occurred in relation to physical activity
- Any sign of fever or other disease
- Whether the subject was asleep when the episode occurred
- Whether the symptoms of the episode woke up the subject

The answer to the question: "Was subject able to treat him/herself?" must be answered "No" if oral carbohydrates, glucagon or IV glucose had to be administered to the subject by another person. 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 [11].

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

- Who assisted in the treatment of the hypoglycaemic episode (i.e. family/friend/co-worker or similar, paramedic, doctor or other, please specify)
- Where the treatment was administered (i.e. at home/at friends/at work or similar, in an ambulance, emergency room/hospital or other, please specify)

- Type of treatment provided by other person (i.e. oral carbohydrates, glucagon, IV glucose or other, please specify)
- Were symptoms alleviated by the administration of treatment?
- Factors contributing to the episode (i.e. physical activity, missed meal, diet changed, medication error (i.e. overdose, mix-up between products), miscalculation of insulin dose other factors not listed, please specify or none)
- Did the subject experience seizure?
- Was the subject unconscious/comatose?
- Did the subject experience any of the following symptoms? [12]
  - Autonomic: sweating, trembling, hunger or palpitations
  - Neuroglycopenic: confusion, drowsiness, speech difficulty, visual disturbances, odd behaviour, impaired balance or incoordination
  - General malaise: headache or malaise
- Did the subject experience other symptoms? Please specify
- Further description of the episode

A hypoglycaemic episode form must be filled in for each hypoglycaemic episode. 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.

8.3 Laboratory assessments

The laboratory analyses will be performed by a central laboratory unless otherwise specified in this section. Descriptions of assay methods, laboratory supplies and procedures for obtaining samples, handling and storage of samples and information regarding who will perform the assessments, will be described in a trial-specific laboratory manual, provided by the central laboratory. For laboratory details, see Attachment I.

8.3.1 Blood and urine sampling (central laboratory analysis)

The investigator must review all laboratory results, specify on the laboratory report whether any values out of range are non-clinically significant or clinically significant, and report concomitant illnesses and AEs according to section 12. Laboratory reports must be signed and dated by the investigator on the day of evaluation. The signed laboratory report is retained at the investigator's site as source documentation. Laboratory results will be sent by the central laboratory to the investigator on an ongoing basis.

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

Blood sampling will be performed on subjects throughout the trial to determine levels of the following efficacy and safety parameters:

Efficacy parameters

Glucose metabolism: $HbA_{1c,}$ FPG, Fasting insulin, Fasting glucagon, Fasting C-peptide and HOMA-β (see section 17.4.2.1 for calculation)

Safety parameters:
Haematology: Erythrocytes, Haematocrit, Haemoglobin, Leucocytes, Thrombocytes and Differential count (eosinophils, neutrophils, basophils, monocytes, and lymphocytes)

Biochemistry: Amylase, Lipase, Aspartate aminotransferase (ASAT/SGOT), Alanine aminotransferase (ALAT/SPGT), Alkaline phosphatase, Albumin, Bilirubins (total), Creatinine, Potassium, Sodium, Total protein, Urea, Creatine kinase, Calcium and Albumin corrected calcium

Lipids: Cholesterol, HDL cholesterol, LDL cholesterol, Triglycerides, VLDL cholesterol and Free fatty acids

Hormones: Calcitonin

Pregnancy test*: Serum/plasma hCG

Urine samples: Erythrocytes, Protein, Glucose and Ketones by dip stick

*For females of child bearing potential a urine pregnancy test should be performed at site, if pregnancy is suspected or if a menstrual period is missed. If the subject reports missing menstrual at a phone contact, the subject must attend the site for an unscheduled visit as soon as possible to have a urine test done. If positive a confirmatory hCG test should be sent to the central laboratory.

Blood samples analysed at the central laboratory will be analysed and destroyed on an ongoing basis.

8.3.2 Calcitonin sampling (central laboratory analysis)

Blood samples for the measurement of calcitonin concentration will be drawn as per flow chart (see section 2). Calcitonin values ≥20 ng/L will be submitted to an independent calcitonin monitoring committee (CMC) of thyroid experts. The CMC will provide guidance to the investigator with regards to treatment and further investigations. If a subject is screen failed for other reasons than calcitonin exclusion criterion # 10 (calcitonin ≥ 50 ng/L), but has a value of calcitonin ≥10 ng/L, it

is recommended that they are referred to a thyroid expert for further evaluation. For details see Appendix D.

8.3.3 Antibodies sampling

Blood samples will be drawn as per flow chart (section 2) for determination of serum antibodies to IDeg (including cross reacting antibodies to human insulin) and to liraglutide, dependent on treatment arm. Positive anti liraglutide antibody samples will be further characterised for cross reactivity to native GLP-1.

Visit 34 samples positive for anti-liraglutide antibodies will in addition be analysed for in vitro neutralising effect in a cell based assay.

Blood sampling for antibody sampling assessment should be performed prior to administering trial product.

Antibody results will not be provided to the investigator as these results will not be used for any clinical evaluation during the trial. Instead they will be included in an analytical report after end of trial and retained at Novo Nordisk. For storage of blood samples used for the analysis of antibodies see section 24.2.

8.4 Pancreatitis

Confirmed cases of pancreatitis should be followed up with investigations of other potential causes (tests such as gallbladder ultrasound, triglycerides, liver enzymes, detailed history of concomitant medications or alcohol).

8.5 Thyroid disease

Subjects scheduled for thyroidectomy (partial or total) for any reason during the trial, must be instructed to inform the investigator prior to their operation.

8.6 Subject diaries

At each site visit the subject will be provided with a new diary for recording of source data until next site visit. Here the diary must be collected and retained at site as source data in accordance with section 14.1. From hand out at a site visit a diary will hence contain source data from e.g. several telephone contacts prior to being returned at an upcoming visit.

Subjects are required to record the below source data in their diaries at the timing specified in the flow chart in section 2.

- Date and dose of first trial product
- Date and dose of last trial product

- Daily pre-breakfast SMPG values. See section 8.2.12
- Last dose of last trial product taken prior to titration
- New dose to be taken after titration
- 9-point SMPG profile, see section 8.2.13
- Any AEs, hypoglycaemic episodes and changes in concomitant medication since last site visit/telephone contact.

Based on the SMPG values the investigator/subject will assess whether the trial product dose needs adjustment according the Titration Guideline (see Appendix A).

The completed diary must be reviewed by the investigator to ensure that AEs, including any overall changes in health, and concomitant medication is reported. The review of the diary must be documented either on the front page of the diary and/or in the subjects medical records.

The investigator must transcribe data from the diary into the eCRF after each site visit or telephone contact according timelines in section 13.2.

If clarification of entries or discrepancies in the diaries is needed, the subject should be questioned and a conclusion made in the subject´s records. Care must be taken not to bias the subject.

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. Substantial failure to comply with the prescribed trial product regimen will lead to withdrawal.

9 Trial supplies

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

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

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

9.1 Trial product

The following trial products are Investigational Medicinal Products (IMPs) and will be provided by Novo Nordisk A/S, Denmark:

Table 9–1 Trial products

Trial Product (IMP)	Strength	Dosage form	Route of administration
Insulin degludec/liraglutide	100 units/mL + 3.6 mg/mL	solution in pre-filled pen	subcutaneous injection
Insulin degludec	100 units/mL		

The insulin degludec/liraglutide and insulin degludec solutions are visually identical.

9.2 Non-Investigational Medicinal Product

Metformin is Non-Investigational Medicinal Product and is not considered trial product. Metformin will not be provided by Novo Nordisk.

9.3 Labelling

IMPs will be packaged and labelled by Novo Nordisk A/S, and provided in non-subject specific boxes. Labelling of the trial products will be in accordance with Annex 13[13], local regulations and trial requirements.

Each investigator site will be supplied with sufficient trial products for the trial on an on-going basis controlled by the IV/WRS. Dispensing units will be distributed to the sites according to enrolment and randomisation. Please refer to the IV/WRS user guidelines provided for detailed instructions of the IV/WRS.

Subjects will be provided with directions for use for the pre-filled pens by the investigator at each dispensing visit according the flow chart in section 2. The investigator must document that direction for use is given to the subject orally and/or in writing at each dispensing visit.

9.4 Storage

The trial products must be stored according the storage conditions described below.

Table 9–2 Storage conditions for IMPs

Trial product	Storage conditions (not-in-use)	In-use conditions	In-use time*
Insulin degludec/liraglutide	Store in refrigerator (2°C to 8°C) Do not freeze Protect from light	Do not refrigerate. Store below 30°C Protect from light	Use within 3 weeks
Insulin degludec			

* In-use time starts when first dose is taken

The investigator must ensure the availability of proper storage conditions, 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).

Trial product that has been stored improperly must not be dispensed to any subject before it has been re-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 is the responsibility of the investigator.

For each subject the IV/WRS allocates trial product by assigning dispensing unit numbers (DUNs) where each DUN represents a box with a defined number of trial product to be handed out to the subject at a dispensing visit.

The investigator or delegated person must ensure:

- The correct DUN(s) are dispensed to the subject
- The dispense date for any dispensed DUN should be confirmed in the IV/WRS drug accountability module after each dispensing

- Drug accountability is performed using the IV/WRS drug accountability module. Only dispensed DUNs returned by the subject (used/ partly used or returned unused) is accounted for
- Subjects are instructed to return all used, partly used and unused trial products including empty packaging material at each dispensing visit. Returned trial product (used/partly used or unused including empty packaging material) trial product can be stored at room temperature and must be stored separately from non-allocated trial product

Destruction will be done according to local procedures after accountability is finalised and verified by the monitor. Destruction of products must be documented.

9.6 Auxiliary supplies

The following auxiliary supplies will be provided by Novo Nordisk:

- Directions for use
- Needles for pre-filled pens
- BG meters and BG meter auxiliaries

10 Interactive voice/web response system

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

The IV/WRS is used for tracking of subjects throughout the trial i.e. screening, randomisation and allocation of trial products according to treatment arm. This is to ensure all subjects receive a sufficient amount of trial product according to their dose regimen until end of treatment. If a subject withdraws early from the trial, this will also have to be entered into the IV/WRS in order to stop trial product allocation to this patient. More specifically the IV/WRS must be used for the below tasks in the trial:

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

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

11 Randomisation procedure and breaking of blinded codes

Randomisation will be done using the IV/WRS at Visit 2. The trial is a double-blinded trial. Randomisation will be carried out in a 2:1 manner and the subject will be assigned to one of the two treatment arms:

- IDegLira
- IDeg

Subjects will be stratified with respect to their previous anti-diabetic treatment (basal insulin and metformin or basal insulin, metformin ± one other OAD).
When randomising subjects the IV/WRS is also used to ensure a trial population with a median HbA_{1c} level of 8.5%. When the number of subjects with an HbA_{1c} below or equal to 8.5% reach 50% of the required number of subjects to be randomised, it will only be possible to randomise subjects with an HbA_{1c} above 8.5% and vice versa. The distribution of subjects having an HbA_{1c} above or below 8.5% will be followed closely and investigators will be notified in due time before randomisation is closed.

All investigators will be notified immediately when the recruitment period ends, after which no further subjects may be screened and the IV/WRS will be closed for further screening. All subjects included in the screening period and eligible for randomisation will be randomised.

11.1 Breaking of blinded codes

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

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

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

If the code has been broken the subject must be withdrawn and a withdrawal session must be completed in IV/WRS.

12 Adverse events, technical complaints, and pregnancies

12.1 Definitions

Adverse event

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

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

An AE includes:

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

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

- Pre-existing conditions, including those found as a result of screening procedures or baseline measurements for lipids (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 8.2.14.

The following three definitions are used when assessing an AE:

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

- **Causality assessment**
  The following terms are used when assessing the relationship between an AE and the relevant trial product(s):
  - **Probable** - Good reason and sufficient documentation to assume a causal relationship.
  - **Possible** - A causal relationship is conceivable and cannot be dismissed.

- **Unlikely** - The event is most likely related to aetiology other than the trial product.

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

Serious adverse event

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

- Death.
- A life-threatening[a] experience.
- In-patient hospitalisation[b] or prolongation of existing hospitalisation.
- A persistent or significant disability or incapacity[c].
- A congenital anomaly or birth defect.
- Important medical events that may not result in death, be life threatening 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].
  Suspicion of transmission of infectious agents via the trial product must always be considered an SAE.

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 dyscrasiasis or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

Non-serious adverse event

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

Medical event of special interest (MESI)

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

1. Acute coronary syndrome (myocardial infarction or hospitalisation for unstable angina)
2. Cerebrovascular event (transient ischemic attack or stroke)
3. Heart failure requiring hospital admission
4. Revascularisation procedure
5. Pancreatitis or clinical suspicion of pancreatitis, see section 8.4.
6. Neoplasm
7. Thyroid disease, see section 8.5
8. Medication errors concerning trial products:
   - Administration of wrong drug.
   - Wrong route of administration, such as intramuscular instead of subcutaneous.
   - Administration of an overdose with the intention to cause harm (e.g. suicide attempt).
   - Accidental administration of a lower or higher dose than intended. That is a dose lower or higher than 20 % of the intended dose; however the administered dose must deviate from

the intended dose to an extend where clinical consequences for the trial subject were likely to happen as judged by the investigator, although not necessarily did happen.

Technical complaint

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

Examples of technical complaints:

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

12.2 Reporting of adverse events

All events meeting the definition of an AE must be collected and reported. This includes events from the first trial-related activity after the subject has signed the informed consent (screening) until the end of the first post-treatment follow-up period (7 days after end of treatment).

Exceptions

- Non-serious events of hypoglycaemic episodes should not be reported before any trial drug is given e.g. from the randomisation visit
- Non-serious AEs should not be collected and reported for screening failures

The events must be recorded in the applicable CRF forms in a timely manner, see timelines below and Figure 12–1.

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

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

IDegLira: NN9068 Investigator´s Brochure or any updates thereto
IDeg: NN1250 CCDS or any updates thereto

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

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

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

Any event confirmed or suspected to be a MESI must be reported as such. In case the sponsor identifies potentially missed MESIs through predefined review of available data, the investigator will be asked to reconsider if the event is a MESI.

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

Timelines for initial reporting of AEs:

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

- **SAEs**: The AE form **within 24 hours** and the safety information form **within 5 calendar** days of the investigator's first knowledge of the SAE. Both forms must be signed within 7 calendar days from the date the information was entered in the eCRF
- **SAEs fulfilling the MESI criteria and/or result in fatal outcome:** In addition to above, the MESI form and/or the fatal follow up form **within 14 calendar days** of the investigator's first knowledge of the AE
- **Non-serious AE fulfilling the MESI criteria:** The AE form, and safety information form and MESI form **within 14 calendar days** of the investigator's first knowledge of the event
- **Events fulfilling the adjudication criteria:** Complete the event adjudication collection form **within 14 calendar days** of the investigator's first knowledge of the event

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

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

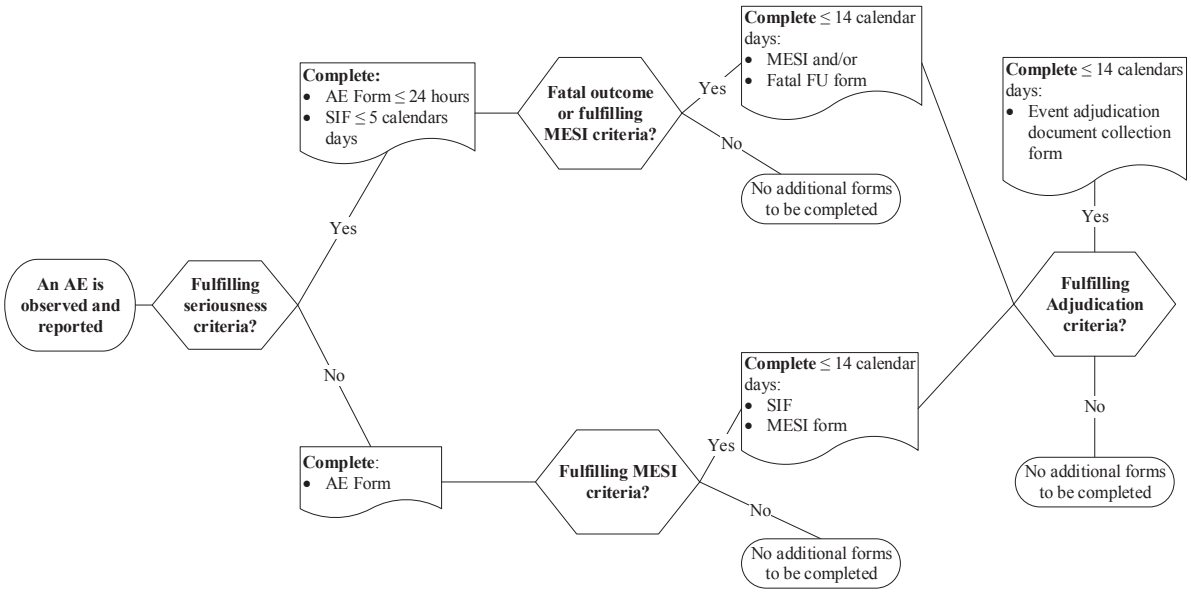


Figure 12–1 Initial reporting of AEs

Reporting of trial product-related SUSARs by the sponsor:

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

In accordance with regulatory requirements, Novo Nordisk will inform the regulatory authorities, including European Medicines Agency (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 GCP[1], unless locally this is an obligation of the investigator.

12.3 Follow-up of adverse events

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

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

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

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

- **Non-serious AEs:** Non-serious AEs must be followed until the outcome of the event is "recovering/resolving", "recovered/resolved" or "recovered/resolved with sequelae" or until the end of the follow-up period stated in the protocol, whichever comes first, and until all queries related to these AEs have been resolved. Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome "recovering/resolving" or "not recovered/not resolved". Cases can be closed with the outcome of "recovering/resolving" when the subject has completed the follow-up period and is expected by the investigator to recover.
- **Non-serious AE fulfilling the MESI criteria:** Follow-up information on MESIs should only include new (e.g. corrections or additional) information and must be reported **within 14 calendar days** of the investigator's first knowledge of the information. This is also the case for previously reported non-serious AEs which subsequently fulfil the MESI criteria

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

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

12.4 Technical complaints and technical complaint samples

12.4.1 Reporting of technical complaints

All technical complaints on any of the following products:

- Insulin degludec/liraglutide 100 units/mL + 3.6 mg/mL, 3 mL pre-filled pen.
- Insulin degludec 100 units/mL, 3 mL pre-filled pen
- Novo Nordisk needles for pre-filled pen

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

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

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

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

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

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

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

12.4.2 Collection, storage and shipment of technical complaint samples

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

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

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

Storage of the technical complaint sample must be done in accordance with the conditions prescribed for the product. The shipment of the technical complaint sample should be done in accordance with the same conditions as for storage (see section 9.4).

12.5 Pregnancies

12.5.1 Pregnancies in female subjects

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

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 related to pregnancies:</u>

Non-serious AEs:

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

SAEs:

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

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

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

12.6 Precautions and/or overdose

During treatment with insulin there is a risk of hypoglycaemia. Symptoms of hypoglycaemia usually occur suddenly and may include cold sweat, nervousness or tremor, anxious feelings, unusual tiredness, confusion, difficulty in concentrating, excessive hunger, temporary vision changes, headache, nausea and palpitation. Severe hypoglycaemia may lead to unconsciousness.

Hypoglycaemic episodes should be treated according to best practise at the discretion of the investigator. Attention should be given to the fact that the action profile of the insulin component in IDegLira and IDeg is long-acting and the prolonged effect may delay recovery from a hypoglycaemic episode.

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

From clinical trials and marketed use of Liraglutide overdoses up to 40 times the recommended maintenance dose (72 mg) have been reported. Events reported included severe nausea and severe vomiting. None of the reports included severe hypoglycaemia. All patients recovered without complications.

When initiating treatment with IDegLira the subject may in some cases experience loss of fluids/dehydration, due to vomiting, nausea or diarrhoea. It is important to avoid dehydration by drinking plenty of fluids.

For further information see the IDegLira IB or any updates thereto.
For IDeg see the IB or the SmPC or any updates thereto.

12.7 Committees related to safety

12.7.1 Novo Nordisk safety committee

Novo Nordisk will constitute an internal IDegLira/NN9068 safety committee to perform ongoing safety surveillance. The safety committee will be informed about the results of on-going safety surveillance activities for the individual mono components, insulin degludec and liraglutide. The IDegLira/NN9068 safety committee may recommend unblinding of any data for further analysis, and in this case an independent ad hoc group will be established in order to maintain the blinding of the trial personnel.

12.7.2 Calcitonin monitoring committee

An independent committee of thyroid experts is established to perform calcitonin monitoring of all calcitonin values ≥20 ng/L in subjects throughout the trial (except for screening failures). The committee will provide recommendations to investigators with regards to further investigation and treatment of the individual subject. The committee will be blinded to trial treatment.

For further instructions on calcitonin monitoring see Appendix D.

12.7.3 Event adjudication committee

An external event adjudication committee is established to perform qualitative or quantitative validation of selected AEs according to pre-defined diagnostic criteria. The validation is based on review of pre-defined clinical source data related to the specific AE.

The events are reviewed by the event adjudication committee in an independent and blinded manner.

The following AEs will be adjudicated in this trial:

- Death
- Acute coronary syndrome (myocardial infarction or hospitalisation for unstable angina)
- Cerebrovascular event (transient ischemic attack or stroke)
- Heart failure requiring hospital admission
- Coronary revascularisation
- Pancreatitis or clinical suspicion of pancreatitis
- Neoplasm
- Thyroid disorders requiring thyroidectomy

AEs for adjudication must be reported according to 12.2. In addition the specific event adjudication document collection form has to be completed and relevant pre-defined documents provided within 14 calendar days of the investigator's first knowledge of the AE, according to instructions in the event adjudication site manual. The investigator should provide the medical documentation within 4 weeks of event identification.

Event adjudication will not be performed for AEs in screening failures.

For further information regarding definitions, rationales, and events that will be adjudicated, see Appendix B.

13 Case report forms

Novo Nordisk will provide a system for the eCRF. This system and support services to the system will be supplied by a vendor.

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

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

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

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

13.1 Corrections to case report forms

Corrections to the eCRF data may be made by the investigator or the investigator's authorised 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 authorised staff after the date the investigator has signed the case book, the case book must be signed and dated again by the investigator.

Corrections to the data on paper CRFs may only be made by drawing a straight line through the incorrect data and then writing the correct entry next to the data that was crossed out. Each correction must be initialled, dated and explained (if necessary). If corrections are made by the investigator's authorised 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 or a monitor-initiated discrepancy form. If the affirmation statement for the subject has not yet been signed, any corrections must be approved by the investigator or her/his

authorised 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 5 days** after the site visit/telephone contact. The SMPG values and corresponding insulin doses for titration purpose must preferably be entered **within 24 hours** on week days after the site visit/telephone contact throughout the trial.

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

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

14 Monitoring procedures

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 and no later than 6 weeks after the FPFV. The monitoring visit intervals will depend on the outcome of the remote monitoring of the CRFs, the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP[1], but will not exceed 8 weeks. A follow up letter (paper or electronic) will be sent to the investigator following each monitoring visit addressing any action to be taken.

14.1 Source data verification and source data requirements

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

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

Monitors must review the subject´s medical records and other source data (e.g. the diaries) to ensure consistency and/or identify omissions compared to the CRF. If discrepancies are found, the investigator must be questioned about these. The original diaries must not be removed from the trial site, unless they form part of the CRF and a copy is kept at the site. The monitor will ensure that the CRFs are completed and that any paper CRFs are collected.

For SMPG values it is accepted that the earliest practically retainable record should be considered as the source data. Therefore, the data recorded by the BG meter and transcribed into the diary by the subject will be considered as the source data. The diary will be considered the source document with respect to:

- Date and fasting SMPG values
- Date, time and dose of trial product
- Date and time for hypoglycaemic episodes

The monitor will collect CRF pages and other trial related forms containing data from screening failures. Source data requirements for screening failures are described in section 8.1.3.

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.

15 Data management

Data management is the responsibility of Novo Nordisk.

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 from the laboratory performing the analyses. 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 identification number. Appropriate measures such as encryption or leaving out certain identifiers will be enforced to protect the identity of subjects in all presentations and publications as required by local, regional and national requirements.

16 Computerised systems

Novo Nordisk will capture and process clinical data using computerised systems that are described in Novo Nordisk Standard Operating Procedures and IT architecture documentation. The use and control of these systems are documented.

Investigators working on the trial may use their own electronic systems to capture source data.

17 Statistical considerations

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

All analyses of efficacy and safety endpoints will be based on the full analysis set (FAS). The analysis of the primary endpoint will be repeated on the per-protocol (PP) analysis set and the completer analysis set (CAS) for sensitivity purposes. All efficacy endpoints will be summarised using the FAS and safety endpoints will be summarised using the safety analysis set (SAS).

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

Unless otherwise specified, all continuous measurements will be summarised descriptively at each visit by treatment using observed data. After 26 weeks of treatment, descriptive statistics will be presented based both on observed and last observation carried forward (LOCF) imputed 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. LOCF imputed data will be used as the basis for plotting data, if not otherwise specified. For endpoints that are analysed log-transformed, the geometric mean values will be plotted.

A standard analysis of covariance (ANCOVA) model will be applied for the continuous primary and secondary endpoints. The model includes treatment and previous anti-diabetic treatment (basal insulin and metformin or basal insulin, metformin and other OAD(s)) as fixed factors and the corresponding baseline value as a covariate. In the following, this model will be referred to as the standard ANCOVA model.

Presentation of results from a statistical analysis will include the estimated mean treatment effects (Least Square Means [LSMeans]) for absolute values and change from baseline. In addition, estimated mean treatment difference (or ratio) will be presented together with the two-sided 95% confidence interval and corresponding two-sided 5% p-value.

Handling of missing data

The expected percentage of missing data is around 15%. In accordance with industry guidance[14], endpoints will be assessed at frequent visits and also on subjects who withdraw prematurely. This will facilitate an analysis in accordance with ITT principles. Also, the combined information on frequent outcomes and information on reason for drop-out is assumed to account for the missing data anticipated.

If an assessment has been made both at screening (Visit 1) and randomisation (Visit 2), 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 also has been made at screening, then the screening value will be used as the baseline value.

Missing values (including intermittent missing values) will be imputed using the LOCF method. Subjects without data after randomisation will be included by carrying forward their baseline value. LOCF has been a standard approach in diabetes trials for many years, and was used as the primary analysis in both IDegLira and IDeg phase 3a trials. LOCF is considered to be an appropriate method in the context of TTT trials, where subjects after withdrawal typically continue their therapy using commercially available insulin. In previous TTT trials with IDegLira and IDeg, LOCF has generally provided similar results to alternative methods applied to handle missing data, such as repeated measures models and completer analyses. In this trial, similar sensitivity analyses will be

made to examine the robustness of the LOCF method. The LOCF approach will also be used to impute missing values in CAS.

17.1 Sample size calculation

The primary objective of this trial is to confirm superiority of IDegLira vs. IDeg in controlling glycaemia in Chinese subjects with type 2 diabetes after 26 weeks of treatment. This is done by comparing the difference in change from baseline in HbA_{1c} after 26 weeks of treatment to a superiority margin of 0.0% for IDegLira vs. IDeg.

Superiority in the primary endpoint for IDegLira versus IDeg will be considered confirmed if the upper bound of the two-sided 95% confidence interval for the estimated mean treatment difference in change from baseline in HbA_{1c} (for IDegLira - IDeg) is strictly below 0% or equivalently if the p-value for the two-sided test of

H_0 $D=0$ against H_A $D\neq 0$,

is less than 5% and $D<0$, where D is the estimated treatment difference. 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%.

The sample size is determined using a t-statistic under the assumption of a two-sided test of size 5%, a mean difference in treatment of - 0.4%, and a standard deviation of SD=1.2%. It is also assumed that 15% of the randomised subjects will be excluded from the PP analysis set. Superiority will be investigated for both the FAS and the PP analysis set in line with the Committee for Proprietary Medicinal Products (CPMP) Points to Consider [15]. The above assumptions are based on experience from the phase 3a development programmes for IDegLira and IDeg. From these assumptions and based on a 2:1 randomisation the sample size is set to 300 subjects in the IDegLira arm and 150 subjects in the IDeg arm; in total 450 subjects will be randomised. This will ensure a power of 91.4% for confirming the primary objective in the full analysis set. Reducing the mean difference to -0.35% yields a power of 83%.

17.2 Definition of analysis sets

The following analysis sets are defined in accordance with the ICH-E9 guidance [16].

Full Analysis Set (FAS): includes all randomised subjects. In exceptional cases, subjects may be eliminated from the full analysis set. 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 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. Subjects in the completer analysis set will contribute to the evaluation "as randomised".

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

Before data are released for statistical analysis, a review of all data will take place to identify protocol deviations that could potentially affect the results. Any decision to exclude any subject or observation from the statistical analysis is the joint responsibility of the members of the study group. The subjects or observations to be excluded, and the reasons for their exclusion must be documented and signed by those responsible before database lock. The subjects and observations excluded from analysis sets, and the reason for this, will be described in the clinical trial report.

17.3 Primary endpoint

The primary endpoint is defined as change from baseline in HbA_{1c} after 26 weeks of treatment.

The change from baseline in HbA_{1c} after 26 weeks of treatment will be analysed using an ANCOVA model with treatment, previous anti-diabetic treatment (basal insulin and metformin or basal insulin, metformin and other OAD(s)) as fixed effects and baseline HbA1c as covariate. Missing values after 26 weeks of treatment will be imputed LOCF using HbA_{1c} values at and after baseline.

Superiority of IDegLira vs. IDeg will be considered as confirmed if the 95% confidence interval for the mean treatment difference for change from baseline in HbA_{1c} lies entirely below 0.0%; equivalent to a one-sided test with significance level of 2.5%. Conclusion of superiority will be based on FAS. Analysis based on the PP analysis set will be regarded as sensitivity analysis.

17.3.1 Sensitivity analysis

The primary efficacy analysis will be repeated on the PP analysis set and the CAS as sensitivity analysis. Furthermore, sensitivity analysis will be performed on FAS using the mixed model for repeated measurement (MMRM) to evaluate the sensitivity of using LOCF. All HbA_{1c} values available post baseline at scheduled measurement times will be analysed in a linear mixed normal model using an unstructured residual covariance matrix for HbA_{1c} measurements within the same subject. The model will include treatment, visit and previous anti-diabetic treatment as fixed factors and baseline HbA_{1c} as a covariate. Interactions between visit and all factors and the covariate are also included in the model. The result will be compared to the result of the ANCOVA method using LOCF for imputation of missing data. Any marked difference between the MMRM and ANCOVA LOCF approach regarding the estimated treatment difference will be commented upon in the clinical trial report.

17.4 Secondary endpoints

17.4.1 Confirmatory secondary endpoints

The following two confirmatory endpoints will be tested for superiority of IDegLira vs. IDeg.

- Change from baseline in body weight after 26 weeks of treatment.
- Number of treatment emergent severe or BG confirmed hypoglycaemic episodes during 26 weeks of treatment.

The tests for superiority of the confirmatory secondary endpoints will be based on the FAS and will only be carried out if superiority of IDegLira vs. IDeg with regards to the primary endpoint is confirmed.

In order to control the overall type I error on a 5% level with regards to the secondary endpoints, a hierarchical testing procedure will be used. If superiority is confirmed with respect to change from baseline in body weight after 26 weeks of treatment the number of treatment emergent severe or BG confirmed hypoglycaemic episodes during 26 weeks of treatment will be tested for superiority.

Superiority for change from baseline in body weight will be considered confirmed if the upper bound of the two-sided 95% confidence interval for the estimated mean treatment difference (IDegLira minus IDeg) is strictly below zero or equivalently if the p-value for the one-sided test of

H_0 $D \geq 0.0\%$ against H_A $D < 0.0\%$,

is less than 2.5%, where D is the treatment difference.

The change from baseline in body weight after 26 weeks of treatment will be analysed using an ANCOVA model with treatment and previous OAD treatment (basal insulin and metformin or basal insulin, metformin and other OAD(s)) as fixed effect and baseline weight as covariate.

Superiority for hypoglycaemic episodes will be considered confirmed if the upper bound of the two-sided 95% confidence interval for the estimated mean treatment ratio (IDegLira vs. IDeg) is strictly below one or equivalently if the p-value for the one-sided test of

H_0 RR≥1.0 against H_A RR<1.0,

is less than 2.5%, where RR is the estimated rate ratio.

The number of treatment emergent severe or BG confirmed hypoglycaemic episodes during 26 weeks of treatment will be analysed using a negative binominal regression model with a log-link function and the logarithm of the time period in which a hypoglycaemic episode is considered treatment emergent as offset. The model will include treatment and previous anti-diabetic treatment as fixed factors and baseline HbA_{1c} as covariate.

17.4.2 Supportive secondary endpoints

17.4.2.1 Efficacy endpoints

Insulin dose after 26 weeks of treatment

The actual daily insulin dose after 26 weeks of treatment will be analysed using an ANCOVA model including treatment and previous anti-diabetic treatment as fixed factors and baseline HbA_{1c} value and baseline insulin dose as covariates.

Responder for HbA_{1c} after 26 weeks of treatment

Two dichotomous endpoints (responder/non-responder) will be defined based on whether a subject has met a specific target level after 26 weeks of treatment:

- ADA HbA_{1c} target (HbA_{1c} < 7.0%)
- International Diabetes Federation (IDF) HbA_{1c} target (HbA_{1c} ≤ 6.5%)

Analysis of each of the two responder endpoints will be based on a logistic regression model with treatment and previous anti-diabetic treatment as fixed factors and baseline HbA_{1c} value as a covariate.

HbA_{1c} responder endpoints without weight gain

Responder for HbA1c without weight gain after 26 weeks of treatment will be defined as HbA_{1c} < 7.0% or ≤ 6.5% at end of treatment and change from baseline in body weight below or equal to zero. Analysis of each of the two responder endpoints will be based on a logistic regression model with treatment and previous anti-diabetic treatment as fixed factors and baseline HbA_{1c} and body weight values as covariates.

HbA_{1c} responder endpoints without hypoglycaemic episodes

Responder for HbA_{1c} without hypoglycaemic episodes after 26 weeks of treatment will be defined as HbA_{1c} < 7.0% or ≤ 6.5% at end of treatment and without severe or BG confirmed episodes during the last 12 weeks of treatment. Analysis of each of the two responder endpoints will be based on a logistic regression model with treatment and previous anti-diabetic treatment as fixed factors and baseline HbA_{1c} values as a covariate.

HbA_{1c} responder endpoints without hypoglycaemic episodes and weight gain

Responder for HbA_{1c} without hypoglycaemic episodes and weight gain after 26 weeks of treatment will be defined as HbA_{1c} < 7.0% or ≤ 6.5% at end of treatment, without severe or BG confirmed episodes during the last 12 weeks of treatment, and change from baseline in body weight below or equal to zero. Analysis of each of the two responder endpoints will be based on a logistic regression model with treatment and previous anti-diabetic treatment as fixed factors and baseline HbA_{1c} and body weight values as covariates.

Fasting plasma glucose (FPG)

Change from baseline in FPG after 26 weeks of treatment will be analysed using the standard ANCOVA model.

Waist circumference

Change from baseline in waist circumference after 26 weeks of treatment will be analysed using the standard ANCOVA model.

Beta-cell function (fasting insulin, fasting C-peptide, fasting glucagon, and HOMA-β)

In addition to fasting insulin, fasting C-peptide, and fasting glucagon, one derived parameter will be calculated; Beta-cell function (HOMA-β).

The calculation of the HOMA endpoint will be done as follows:

- Beta-cell function (%) = 20·fasting insulin[μU/mL]/(FPG[mmol/L]-3.5)

These endpoints after 26 weeks of treatment will be analysed separately using the standard ANCOVA model. In these statistical analyses the endpoint will be log-transformed and so will the baseline covariate.

Fasting lipid profile

Cholesterol, low density lipoprotein cholesterol (LDL cholesterol), high density lipoprotein cholesterol (HDL cholesterol), very low density lipoprotein cholesterol (VLDL cholesterol), triglycerides, and free fatty acids after 26 weeks of treatment will be analysed separately using the standard ANCOVA model. In these statistical analyses the endpoint will be log-transformed and so will the baseline covariate.

Self measured plasma glucose (SMPG) 9-point profile

Three endpoints from the 9 point SMPG profile will be defined:

- 9-point profile
- Mean of the 9-point profile, defined as the area under the profile (calculated using the trapezoidal method) divided by the measurement time
- Post-prandial PG increments (from before meal to 90 min after for breakfast, lunch and dinner). The mean increment over all meals will be derived as the mean of all available meal increments

A mixed effect model will be fitted to the 9-point profile data. The model will include treatment, time, interaction between treatment and time, and previous anti-diabetic treatment as fixed factors and the baseline value as a covariate. An unstructured residual covariance matrix within the same subject is employed. From the model mean profile by treatment and relevant treatment differences will be estimated and explored.

Change from baseline after 26 weeks of treatment in mean of the 9-point profile and post-prandial increment endpoints will be analysed separately using the standard ANCOVA model.

17.4.2.2 Safety endpoints

Adverse events

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

A 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 7 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 of serious TEAEs will be presented as an overview including all AEs, serious AEs, number of deaths, AEs by severity, AEs by relation to treatment and AEs of special interest including AEs leading to withdrawal.

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

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

A listing for non-treatment emergent adverse 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 TEAE.

Classification of Hypoglycaemia

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

Nocturnal hypoglycaemic episodes: are episodes with time of onset between 00:01 and 05.59 both inclusive.

Hypoglycaemic episodes are classified according to the Novo Nordisk classification of hypoglycaemia[17] (see Figure 17–1) and the ADA[7] classification of hypoglycaemia (see Figure 17–2).

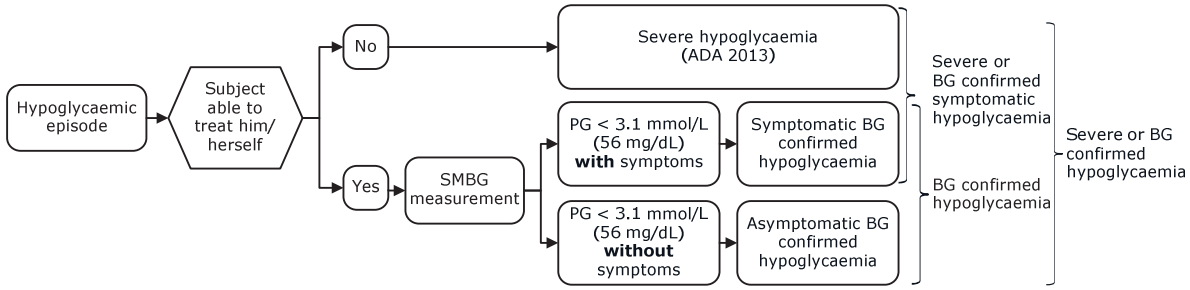
Novo Nordisk classification of hypoglycaemia

In normal physiology, symptoms of hypoglycaemia occur below a plasma glucose level of 3.1 mmol/L (56 mg/dL) [17]. Therefore, Novo Nordisk has included hypoglycaemia with plasma glucose levels below this cut-off point in the definition of blood glucose (BG) confirmed hypoglycaemia.

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

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

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



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

Figure 17–1 Novo Nordisk classification of hypoglycaemia

ADA classification of hypoglycaemia[11]

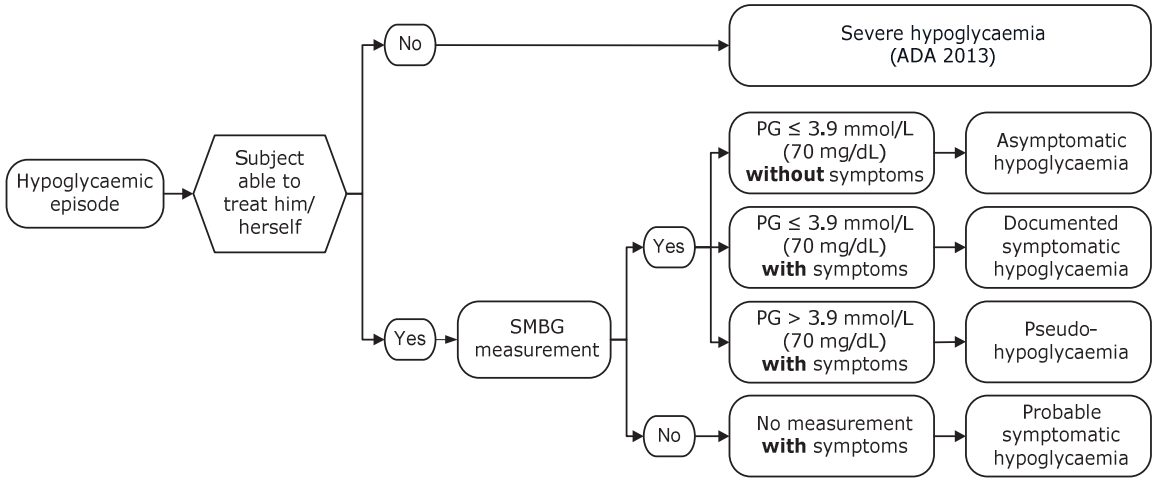
- Severe hypoglycaemia: An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is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

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 for severe or BG confirmed hypoglycaemic episodes, severe or BG confirmed symptomatic hypoglycaemic episodes, nocturnal severe or BG confirmed hypoglycaemic episodes, nocturnal severe or BG confirmed symptomatic hypoglycaemic episodes and the ADA classification of hypoglycaemia.

The number of hypoglycaemic episodes during 26 weeks of treatment will be analysed separately for each endpoint using a negative binominal regression model with a log-link function and the logarithm of the time period in which a hypoglycaemic episode is considered treatment emergent as offset. The model will include treatment and previous anti-diabetic treatment as fixed factor.

Pulse

Change from baseline in pulse after 26 weeks of treatment will be analysed using the standard ANCOVA model.

Systolic and diastolic blood pressure

Change from baseline in systolic and diastolic blood pressure after 26 weeks of treatment will be analysed using the standard ANCOVA model.

Clinical evaluations (physical examination, fundoscopy or fundus photography and ECG)

Eye examination (fundoscopy/fundus photography) and ECG findings will be summarised descriptively, including:

- summaries
- the change from baseline after 26 weeks of treatment

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 significant findings will be recorded as adverse events.

Laboratory assessments

All laboratory parameters will be summarised descriptively.

The following tables will be presented based on both observed and LOCF imputed data:

- Shift tables from baseline to after 26 weeks of treatment
- 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 ranges (abnormal values) will be listed.

For lipase and amylase the following rule will apply in the evaluation of the result:

- If the amylase or lipase baseline (at screening) value is > 3xUNR the information were recorded as medical history for that subject.

Calcitonin

The purpose of the calcitonin analysis is to evaluate longitudinal changes in calcitonin, with main focus on subjects who develop persistently high levels of calcitonin during the trial.

Calcitonin will be displayed in terms of the number of subjects (N), the percentage of subjects (%) and the event rate per 100 years of exposure (R). The following criteria are defined for tabulations:

Persistent (all post baseline measurements)

- From < UNR to persistently ≥ UNR
- From < UNR to persistently ≥ 1.5 UNR
- From < UNR to persistently ≥ 20 ng/L
- From < UNR to persistently ≥ 50 ng/L
- From < 20 ng/L to persistently ≥ 20 ng/L
- From < 50 ng/L to persistently ≥ 50 ng/L

Incidental (at least one post baseline measurements)

- From < UNR to ≥ UNR
- From < UNR to ≥ 1.5 UNR
- From < UNR to ≥ 20 ng/L
- From < UNR to ≥ 50 ng/L
- From < 20 ng/L to ≥ 20 ng/L
- From < 50 ng/L to ≥ 50 ng/L

The distribution of all calcitonin measurements across treatment groups and time will be shown with histograms and corresponding cumulative plots for actual levels of calcitonin and change from baseline. The plots will be presented by treatment group (using EOT measurement - LOCF) and within treatment group by week. Plots will be done by each gender, separately.

Summaries tables of calcitonin continuous measurements, will include number and percentage of observations < and ≥ LLOQ, minimum, Q25, median, Q75 and maximum. Summaries will be presented for all subjects and by gender.

Longitudinal changes for subjects with calcitonin levels ≥ 20 ng/L will be plotted (longitudinal plots). The plots will be done by treatment and gender. They will be done for subjects in the persistent and incidental categories, separately.

A listing of subjects with at least one post baseline value ≥ 20 ng/l will be done. The listing will include age, gender, calcitonin measurements over time and AE history (including preferred term, onset and stop dates).

Urinalysis

Categorical urinalysis parameters will be summarised descriptively by:

- Shift from baseline to EOT (using the number of subjects in the different categories)

- Subjects with at least one post baseline measurement outside reference range will be listed

Antibodies towards trial product

Anti-IDeg antibodies, anti-human insulin antibodies, anti-liraglutide antibodies, anti-liraglutide antibodies cross reacting with native GLP-1 and in vitro neutralising effect of anti-liraglutide antibodies will be summarised and tabulated. The correlation between change from baseline after 26 weeks of treatment in anti-IDeg and anti-insulin antibodies respectively to insulin dose after 26 weeks of treatment, HbA1c after 26 weeks of treatment and change from baseline after 26 weeks of treatment in HbA1c will be illustrated using scatter plots.

18 Ethics

All subjects included in the trial will be treated with IDeglira or IDeg in combination with metformin in order to improve their glycaemic control.

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. However, they will have to spend some extra time for trial related visits and some of the assessments performed during the trial go beyond normal practice.

When a subject's participation in the trial ends, the subject will consult his/her investigator to decide on the best available marketed treatment.

18.1 Informed consent

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

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

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

The investigator must ensure the subject ample time to ask questions and 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 subject must be provided with a copy of this.

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

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

If a female trial subject becomes pregnant and an abnormality is found in the foetus or newborn infant, a separate written information and informed consent form must be given to the subject's male partner for consent to obtain information on paternal health and medical history.

For all of the specific informed consents the subject and/or subject's partner must have the option to abstain from these, while still participating in the trial as per the initial informed consent.

18.2 Data handling

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

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

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

18.3 Information to subject during trial

All information provided to the subjects during the trial will be translated to local language and submitted to the health authorities and IECs/IRBs for approval according to local regulations.

18.4 Premature termination of the trial and/or trial site

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

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

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

19 Protocol compliance

Deviations from the protocol should be avoided.

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

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

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

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 trial site staff as well as Novo Nordisk staff have an obligation to cooperate and assist in audits and inspections. This includes giving auditors and inspectors direct access to all source documents and other documents at the trial site relevant to the clinical trial. This includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are relevant to the evaluation of the trial.

21 Critical documents

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

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

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

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

By signing the protocol, each investigator also agrees to allow Novo Nordisk making investigator's name and information about trial 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. If any tasks are delegated, the investigator must maintain a list of appropriately qualified persons to whom he/she has delegated specified significant trial-related duties. The investigator must ensure that there is adequate training for all staff participating in the conduct of the trial. It is the investigator's responsibility to supervise the conduct of the trial and to protect the rights, safety, and well-being of the subjects.

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

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

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

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

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

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

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

The investigator and other trial 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 Novo Nordisk for regulatory purposes and 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.

One Principal Investigator will be appointed to review and sign the clinical trial report (signatory investigator) on behalf of all participating investigators. The signatory investigator will be appointed based upon the criteria defined by the International Committee of Medical Journal Editors for research publications[8].

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.

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

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

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

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

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

23.1.1 Authorship

Authorship of publications should be in accordance with the Uniform Requirements of the International Committee of Medical Journal Editors (sometimes referred to as the Vancouver Criteria)[18].

The investigator(s) offered authorship will be asked to comment and approve the publication. No permission to publish will be granted to any vendor involved in the trial described in this protocol.

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

For a multi-centre clinical trial, analyses based on single-trial 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 trial site results until the primary manuscript is accepted for publication. As Novo Nordisk wants to live up to the industry publication policy, submission for publication of such primary policy 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 can be provided with the randomisation code after results are available if requested.

24 Retention of clinical trial documentation and human biospecimens

24.1 Retention of clinical trial documentation

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

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

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

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

The files from the investigator site/institution must be retained for 15 years after the completion of the trial, or longer if required by local regulations. The deletion process must ensure confidentiality of data and must be done in accordance with local regulatory requirements.

24.2 Retention of human biospecimens

Antibody sample will be analysed and stored at a special laboratory outside of China until final feedback from the regulatory authorities in China but no longer than 15 years from end of trial. Only Novo Nordisk will have access to these samples. Further characterisation of the antibody response may be requested by the authorities.
None of the data will be identified by name. Antibody samples will be identified only by a subject number, a visit number and a trial identification number. In the event that the collected antibody samples will be used in the future, the investigator will become directly informed by Novo Nordisk about the results if the findings are deemed clinically relevant. In such case, a written summary of the findings, including listings of subject specific values, will be provided once a firm conclusion from the results has been drawn by Novo Nordisk.

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

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

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

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

Regulatory Authorities

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

26 Indemnity statement

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

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

27 References

1 International Conference on Harmonisation (ICH). ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice. J Postgrad Med 2001; 47(3):199-203.

2 World Medical Association. Declaration of Helsinki. Ethical principles for medical research involving human subjects. J Indian Med Assoc 2009; 107(6):403-405.

3 The Diabetes Control and Complications Trial Research Group. The Effect of Intensive Treatment of Diabetes on the development and progression of Long-Term Complications in Insulin -Dependent Diabetes mellitus. N Engl J Med 1993; 329(14):977-986.

4 UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352(9131):837-853.

5 Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2012; 55(6):1577-1596.

6 Chinese diabetes society. China guideline for type 2 diabetes. Chinese J diabetes mellitus 2, 6-56. 2010.

7 Novo Nordisk A/S. Investigator's Brochure, insulin degludec/liraglutide (6th Edition). 10 Jan 2014.

8 Recommendations for the conduct, reporting, editing and publication of scholarly work in Medical Journals. International Committee of Medical Journal Editors. Dec 2013.

9 Food and Drug Administration. Food and Drug Administration Amendments Act of 2007: http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/default.htm. 2007.

10 European Commission Regulation for EudraCT. http://www.emea.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000044.jsp&mid=WC0b01ac05800260a3. 2011.

11 Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L et al. Hypoglycemia and Diabetes: A Report of a Workgroup of the American Diabetes Association and The Endocrine Society. J Clin Endocrinol Metab 2013; 98(5):1845-1859.

12 McAulay V, Deary IJ, Frier BM. Symptoms of hypoglycaemia in people with diabetes. Diabet Med 2001; 18(9):690-705.

13 European Union. The rules governing medicinal products in the European Union, volume 4, Annex 13, Manufacture of Investigational Products - Brussels. 2003.

14 Food and Drug Administration. Food and Drug Administration, Code of Federal Regulations, Guidance for Industry, Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention. Draft Guidance. Feb 2008.

15 EMEA-Committee for Proprietary Medicinal Products. CPMP/EWP/482/99 - Points to consider on switching between superiority and non-inferiority. 27 Jul 2000.

16 International Conference on Harmonisation. ICH Harmonised Tripartite Guideline. Statistical principles for clinical trials E9. International Conference on Harmonisation E9 Expert Working Group. 5 Feb 1998.

17 Schwartz NS, Clutter WE, Shah SD, Cryer PE. Glycemic thresholds for activation of glucose counterregulatory systems are higher than the threshold for symptoms. J Clin Invest 1987; 79(3):777-781.

18 De Angelius C, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. New Engl J Med 2004; 351(12):1250-1251.

Appendix A: Titration Guideline

NN9068-4166

DUAL™ II China

A trial comparing the efficacy and safety of insulin degludec/liraglutide and insulin degludec in combination with metformin in Chinese subjects with type 2 diabetes mellitus inadequately controlled with basal insulin therapy and metformin ± one other OAD

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List of in-text tables

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1 Introduction

The goal of insulin therapy is to achieve near normoglycaemia, i.e. to reach a pre-defined HbA_{1c} level with a low rate of hypoglycaemic episodes and as little weight gain as possible. Several trials have shown that this is difficult to achieve, unless plasma glucose (PG) values are intensively monitored and the insulin dose(s) frequently adjusted [1] [2] [3] [4] [5] [6] [7] To ensure treatment uniformity between the sites, as well as to ensure that subjects receive an optimal treatment, titration algorithms have been developed specifying recommended dose adjustments at different PG levels.

It is recognised that treatments differ between different regions and countries. Likewise, specific titration guidelines may not be applicable in certain clinical situations. It is important that other information, such as symptoms of hypo/hyperglycaemia, previous response to dose adjustments, other glucose measurements and other indicators of the subject's level of glycaemic control, is taken into consideration when decisions on dosing are made. The investigator should always use his 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 2:1 into two parallel treatment groups:

- Insulin degludec/liraglutide once daily + metformin
- Insulin degludec once daily+ metformin

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

Maximum dose for insulin degludec/liraglutide and insulin degludec is 50 dose steps (50 units of insulin degludec and 1.8 mg of liraglutide/50 units of insulin degludec).

There is no minimum dose for IDegLira or IDeg.

2.1 Injection area

IDegLira or IDeg should be injected subcutaneously into the thigh, upper arm (deltoid area) or the abdomen. The chosen region should be the same throughout the trial. Rotation of injection sites within a given region is recommended.

2.2 Time of injection

IDegLira or IDeg should be injected once daily at any time of the day, but should approximately be the same time of the day throughout the trial.

3 Initiation and titration

3.1 Initiation

At randomisation (Visit 2), all subjects will start on 16 dose steps of IDegLira (16 U of degludec and 0.6 mg of liraglutide) or 16 U IDeg once daily.

3.2 Titration

Dose will be adjusted twice weekly by the subject on two days 3-4 days apart. The investigator will support titration at all contacts.

Titration should be performed based on the mean of three pre-breakfast SMPG values measured two days before and on day of titration. Titration should preferably be performed on the same days of the week throughout the trial. The dose adjustment will be performed according to Table 1.

Table 1 Basal insulin adjustment

Mean of three pre-breakfast SMPGs	Dose adjustment
mmol/L	U/Dose steps
< 4.0	- 2
4.0 – 5.0	No adjustment
> 5.0	+ 2

If one or more SMPG values are missing, the adjustment should be performed on the remaining SMPG value(s). However, the first time titration is performed after randomisation all three SMPG values must be available. If this is not the case, the subject must wait for the next titration day.

3.3 Deviations from the algorithm

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

4 Data collection

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

- Per protocol pre-breakfast SMPG values measured since last visit/telephone contact as described in sections 3.2
- Last dose of trial product taken prior to the titration
- New dose of trial product to be taken after titration
- 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/telephone 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 telephone contact) to discuss progress in glycaemic control and titration of individual subjects based on SMPG values and HbA_{1c}. This will be done in an unbiased and whenever possible in a blinded manner.

6 References

1 Rosenstock J, Davies M, Home PD, Larsen J, Koenen C, Schernthaner G. A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naive people with type 2 diabetes. Diabetologia 2008; 51(3):408-416.

2 Hermansen K, Davies M, Derezinski T, Martinez RG, Clauson P, Home P. A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naive people with type 2 diabetes. Diabetes Care 2006; 29(6):1269-1274.

3 Philis-Tsimikas A, Charpentier G, Clauson P, Ravn GM, Roberts VL, Thorsteinsson B. Comparison of once-daily insulin detemir with NPH insulin added to a regimen of oral antidiabetic drugs in poorly controlled type 2 diabetes. Clin Ther 2006; 28(10):1569-1581.

4 Riddle MC, Rosenstock J, Gerich J. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care 2003; 26(11):3080-3086.

5 Garber AJ, King AB, Del PS, Sreenan S, Balci MK, Munoz-Torres M et al. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 2 diabetes (BEGIN Basal-Bolus Type 2): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. Lancet 2012; 379(9825):1498-1507.

6 Heller S, Buse J, Fisher M, Garg S, Marre M, Merker L et al. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 1 diabetes (BEGIN Basal-Bolus Type 1): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. Lancet 2012; 379(9825):1489-1497.

7 Gough S, Buse J, Woo V, Rodbard H, Linjawi S, Poulsen P et al. IDegLira, a novel fixed-ratio combination of insulin degludec and liraglutide is efficaious and safe in subjects with type 2 diabetes: a large randomised phase 3a trial. Diabetologia 2013; 56(Suppl 1):96(abstract 219).

Appendix B: Medical events of special interest and events requiring adjudication

Trial ID: NN9068-4166
DUAL™ II - China

A trial comparing the efficacy and safety of insulin degludec/liraglutide and insulin degludec in combination with metformin in Chinese subjects with type 2 diabetes mellitus inadequately controlled with basal insulin therapy and metformin ± one other OAD

1 Medical Events of Special Interest (MESI) and events requiring adjudication

Fatal events and MESIs	Definitions	Rationale	Event Adjudication Committee
Fatal events	All fatal events should be reported including all-cause mortality: • Cardiovascular death • Non-cardiovascular death • Undetermined cause of death Fatal events are not considered MESIs as per definition they will always be considered SAEs.	An FDA guidance document [1] requests that Sponsors demonstrate the cardiovascular safety profile of any new therapy for type 2 diabetes in order to ensure, that the new therapy does not increase the cardiovascular risk to an unacceptable extent.	All events will be adjudicated
Acute coronary syndrome; myocardial infarction (MI) or hospitalisation for unstable angina	All types of myocardial infarction (MI) must be reported: • Spontaneous MI (including re-infarction and MI associated with stent thrombosis) • Percutaneous coronary intervention (PCI) related MI • Coronary artery bypass graft surgery (CABG) related MI • Silent MI All events with symptoms of myocardial ischemia requiring hospitalization must be reported.	An FDA guidance document[1] requests that Sponsors demonstrate the cardiovascular safety profile of any new therapy for type 2 diabetes in order to ensure, that the new therapy does not increase the cardiovascular risk to an unacceptable extent.	All events will be adjudicated
Cerebrovascular event; stroke or transient ischemic attack	**Stroke** (ischemic, haemorrhagic or undetermined) is defined as an acute episode of neurological dysfunction, caused by focal or global brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction [2] **Transient Ischemic Attack** (TIA) is defined as a transient (<24 hours) episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction.	An FDA guidance document[1] requests that Sponsors demonstrate the cardiovascular safety profile of any new therapy for type 2 diabetes in order to ensure, that the new therapy does not increase the cardiovascular risk to an unacceptable extent.	All events will be adjudicated

Fatal events and MESIs	Definitions	Rationale	Event Adjudication Committee
Heart failure requiring hospital admission	Clinical manifestations of a new episode or worsening of existing heart failure.	An FDA guidance document[1] requests that Sponsors demonstrate the cardiovascular safety profile of any new therapy for type 2 diabetes in order to ensure, that the new therapy does not increase the cardiovascular risk to an unacceptable extent.	All cases of heart failure requiring hospitalisation, defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 24 hour stay, will be adjudicated
Revascularisation procedure	**Coronary revascularisation procedure** (Coronary Artery Bypass Graft Surgery and Percutaneous Coronary Intervention): Coronary revascularisation procedure is a catheter-based or open surgical procedure designed to improve myocardial blood flow. **Peripheral Arterial Revascularization Procedure** (lower extremity, renal, mesenteric, iliac, subclavian, aortic etc.): Peripheral arterial revascularisation procedure is a catheter-based or open surgical procedure designed to improve peripheral arterial blood flow. This procedure may include thrombectomy, embolectomy, atherectomy, dissection repair, angioplasty, and stent placement.	An FDA guidance document[1] requests that Sponsors demonstrate the cardiovascular safety profile of any new therapy for type 2 diabetes in order to ensure, that the new therapy does not increase the cardiovascular risk to an unacceptable extent.	Only coronary revascularisation will be adjudicated
Pancreatitis or clinical suspicion of pancreatitis	Two of the following three diagnostic criteria fulfilling the diagnosis of acute pancreatitis: • Severe acute upper abdominal pain • Elevated blood levels of pancreatic enzymes (lipase, amylase) > 3xUNR • Characteristic imaging finding (ultrasound, computerised axial tomography (CT), magnetic resonance imaging (MRI))	Treatment with GLP-1 receptor agonists has been associated with acute pancreatitis. Novo Nordisk therefore monitors these events closely.	All events will be adjudicated

Fatal events and MESIs	Definitions	Rationale	Event Adjudication Committee
	Chronic pancreatitis will be defined by characteristic imaging finding (ultrasound, CT, MRI) with abnormal pancreatic function tests or characteristic histological findings.		
Neoplasm	All types of neoplasms (i.e. all new growth incl. polyps, warts etc.) must be reported including: • Malign neoplasm • In situ neoplasm • Benign neoplasm • Neoplasms of uncertain or unknown behaviour (Please note: for operational reasons thyroid neoplasms will be reported as thyroid MESI and should not be reported as a Neoplasm MESI)	Fibrosarcomas has been reported in rats and mice treated with GLP-1 receptor agonists in pre-clinical studies.	All neoplasm events, irrespective of malignancy stage, will be adjudicated
Thyroid disease	All disorders of thyroid gland (incl. thyroid neoplasms) must be reported. Please refer to the protocol for further details on the assessments.	Thyroid C-cells carcinogenicity has been reported in rats and mice treated with GLP-1 receptor agonists in non-clinical studies	Only thyroid disorders requiring thyroidectomy and thyroid neoplasms will be adjudicated
Medication errors concerning trial products	a. Administration of wrong drug or use of wrong device b. Wrong route of administration, such as intramuscular instead of subcutaneous c. Administration of a high dose with the intention to cause harm, e.g. suicide attempt d. Accidental administration of a lower or higher dose than intended. That is a dose lower or higher than 20 % of the intended dose; however the administered dose must deviate from the intended dose to an extend where clinical consequences for the trial subject were likely to happen as judged by the investigator, although not necessarily did happen.	Standard MESI in all Novo Nordisk clinical trials. Medication errors are captured to collect information which may be used to improve the design, name or packaging of the product and/or information which may have an impact on product labelling (for example information about substantial overdoses)	No adjudication

2 Reference

1 Standardized Definitions for Endpoint Events Cardiovascular Trials: Draft Recommendations. Division: Draft Recommendations. FDA Center for Drug Evaluation and Research (CDER). 20 Oct 2010.

2 Karen A.Hicks HMJHKWM, Roxana Mehran, Steven E.Nissen, Norman L.Stockbridge, Shaari L.Targum, Robert Temple - on behalf of the Standardized Data Collection for Cardiovascular Trials Initiative. Standardized Definitions for Cardiovascular and Stroke End Point Events in Clinical Trials. https://www.cardiac-safety.org/think-tanks/ecrf-forms-for-posting/Draft%20Definitions%20for%20Testing%20November%209-%202012%20with%20MI%20Preamble%20CLEAN.pdf . 9 Nov 2012.

Appendix C: New York Heart Association criteria for functional capacity in heart failure

Trial ID: NN9068-4166
DUAL™ II - China

A trial comparing the efficacy and safety of insulin degludec/liraglutide and insulin degludec in combination with metformin in Chinese subjects with type 2 diabetes mellitus inadequately controlled with basal insulin therapy and metformin ± one other OAD

1 Criteria for functional capacity

Functional Capacity	**Objective Assessment**
Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	**A.** No objective evidence of cardiovascular disease.
Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	**B.** Objective evidence of minimal cardiovascular disease.
Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	**C.** Objective evidence of moderately severe cardiovascular disease.
Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	**D.** Objective evidence of severe cardiovascular disease.

*****The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

Appendix D: Monitoring of calcitonin levels

Trial ID: NN9068-4166
DUAL™ II - China

A trial comparing the efficacy and safety of insulin degludec/liraglutide and insulin degludec in combination with metformin in Chinese subjects with type 2 diabetes mellitus inadequately controlled with basal insulin therapy and metformin ± one other OAD

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1 Background

The approach that follows was developed in collaboration with two leading clinical thyroid experts: Dr. [redacted] of the [redacted] and [redacted] and Dr. [redacted] of [redacted] and represents a synthesis of the medical literature and extensive personal experience.

All previous calcitonin screening studies in the literature have been performed in patients with thyroid nodular disease. The nodular status of the subjects in the current trial will mostly be unknown. Nevertheless, for the purpose of follow-up, it will be assumed that the same calcitonin cut-offs will apply. Up to 50% of subjects in the age group to be studied in the current trial will have clinical or subclinical thyroid nodules[1] the majority of which will be clinically apparent. Subjects with a known personal or family history of medullar thyroid cancer (MTC) or multiple endocrine neoplasia type 2 (MEN 2) and subjects with a screening calcitonin of ≥ 50ng/l will be excluded from the trial.

2 Calcitonin and C-cell abnormalities - evaluation and follow-up

A blood sample will be drawn at pre-specified trial visits for measurement of calcitonin. In case a subject has an increased calcitonin value ≥ 10 ng/L the algorithm outlined below should be followed. The algorithm applies for all calcitonin values including screening values.

All calcitonin values ≥20 ng/L (except for screening failures) will be submitted to an independent Calcitonin Monitoring Committee (CMC) of thyroid experts, together with relevant supplementary data, i.e. subject's demographics, diabetes history, concomitant medical history, concomitant medications, smoking status as well as information about relevant adverse events reported during the trial.

The CMC will provide recommendations to the investigators with regards to further investigation and treatment of the individual subject. The CMC will be blinded to trial treatment.

The summary for the rationale for the use of specific calcitonin values to trigger medical evaluation and an overview of the algorithm is provided in the following section:

2.1 CT ≥ 100 ng/L

The value will be submitted to the CMC and the subject should be discontinued from trial product. If the value is a screening value the subject cannot be randomised and the subject must be referred to a thyroid specialist.

These values were found in 0.15% of the population published by Costante et al[1] and in one subject (on active comparator) in the liraglutide development program. For a calcitonin value of ≥100 ng/L, the subject should be assumed to have significant C-cell disease and a high likelihood of having medullary carcinoma of the thyroid. Diagnostic evaluation should consist of thyroid ultrasound, fine needle aspiration of any nodules >1 cm and potentially surgery with neck dissection. Family history of MTC or MEN2 should be evoked and a RET proto-oncogene analysis should be performed.

2.2 CT ≥ 50 and < 100 ng/L

The value will be submitted to the CMC and the investigator will receive guidance from the CMC with regards to continuation of trial product. If the value is a screening value the subject cannot be randomised and the subject should be referred to a thyroid specialist.

These values were found in 0.18% of a population with thyroid nodular disease published by Costante et al[1]. Diagnostic evaluation will likely include ultrasound examination and if available and if there is no contraindication, subjects should undergo a pentagastrin stimulation test. Subjects with positive pentagastrin stimulation tests will be considered to undergo surgery. Where

pentagastrin is not available, thyroid ultrasound and fine needle aspiration biopsy may add important clinical information informing the need for surgery.

2.3 CT ≥ 20 and <50 ng/L

The value will be submitted to the CMC. If a subject is screen failed for other reasons than calcitonin exclusion criterion # 10 (calcitonin ≥ 50 ng/L), but has a value of calcitonin ≥10 ng/L, it is recommended that they are referred to a thyroid expert for further evaluation.

These values are expected to be found in up to 1% of subjects. At this level of calcitonin based on data from Costante et al[1], the predictive value of the level itself for clinically significant C-cell disease begins to fall. However, up to 25% of these subjects had a positive pentagastrin stimulation test. The likelihood of having a medullary carcinoma >1 cm with calcitonin in this range is extremely low.

2.4 CT ≥ 10 and < 20 ng/L

Confounding factors should be evaluated. If drugs potentially affecting calcitonin can be discontinued safely, calcitonin can be repeated after a washout period. Gastrin levels return to the normal range by ~ 10 days after stopping proton pump inhibitors. No further actions are needed during the trial if the next calcitonin values remain below 20 ng/L.

If the subject is a screening failure or if the value is the last one taken in the trial, the subject should preferably be referred to a thyroid specialist for further evaluation.

These values may be found in ~ 2.5 to 4% of the trial population. Costante et al[1] had 216 patients in this category. 1/216 had a subsequent basal (unstimulated) calcitonin of 33 ng/L, and had C-cell hyperplasia at surgery, a lesion of unknown clinical significance. Two other studies used a cutoff of CT > 10 ng/L to screen for C-cell disease, but they do not provide sufficient information on patients with basal CT >10 and <20 ng/L to allow conclusions[2,3].

3 References

1 Costante G, Meringolo D, Durante C, Bianchi D, Nocera M, Tumino S et al. Predictive value of serum calcitonin levels for preoperative diagnosis of medullary thyroid carcinoma in a cohort of 5817 consecutive patients with thyroid nodules. J Clin Endocrinol Metab 2007; 92(2):450-455.

2 Verga U, Ferrero S, Vicentini L, Brambilla T, Cirello V, Muzza M et al. Histopathological and molecular studies in patients with goiter and hypercalcitoninemia: reactive or neoplastic C-cell hyperplasia? Endocr Relat Cancer 2007; 14(2):393-403.

3 Scheuba C, Kaserer K, Moritz A, Drosten R, Vierhapper H, Bieglmayer C et al. Sporadic hypercalcitoninemia: clinical and therapeutic consequences. Endocr Relat Cancer 2009; 16(1):243-253.

Global and country key Novo Nordisk staff

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

Content: Global key staff and Country key staff

Protocol Amendment

no 1
to Protocol, final version 2.0
dated 07 October 2014

Trial ID: NN9068-4166
DUAL™ II China

A trial comparing the efficacy and safety of insulin degludec/liraglutide and insulin degludec in combination with metformin in Chinese subjects with type 2 diabetes mellitus inadequately controlled with basal insulin therapy and metformin ± one other OAD

Trial phase: 3a

Applicable to China and Hong Kong

Amendment originator:

[redacted]

Table of Contents

1 Introduction including rationale for the protocol amendment

The CFDA approved the NN9068-4166 protocol version 2.0, dated 07 October 2014 on 06 June 2016. Since the preparation of the trial protocol in 2014, some of the Novo Nordisk standards and processes have evolved and updated, which is the reason for preparing the amendment and updating the protocol. This is in accordance with the feed-back received from CFDA; please refer to below text copied from the IDegLira IDL approval letter, optimization of the protocol is allowed:

"*Before the clinical trial operation, clinical research organization should further refine and optimize the protocol, pay attention to the exposed and potential safety risk of the product, and make a risk control and management plan.*"

While amending the protocol special attention has been on patient safety and reporting, data quality and GCP compliance. This means that minor refinements have been made throughout the protocol with the purpose of improving data quality and clarifying issues, where applicable. Additionally, typos and minor formatting corrections have been implemented throughout the protocol.

2 Changes

2.1.1 Changes to Protocol

2.1.2 Optimisation and standardisation of safety reporting

Rationale: Since IB version 6, the identified and potential risks included in the minimum mandatory safety text have been updated based on the clinical development of IDegLira**.** Additionally, standardisation and alignment with the current and future internal safety reporting processes within Novo Nordisk will result in a more systematic way of colleting safety data and improve the quality of data collected. Further, by updating the protocol, the safety processes and reporting will be simplified including reporting of medication error as AE requiring additional data rather than MESI.

Impact: The impact of the above is mentioned in sections below:

2.1.2.1 Introducing: "Medication error" and 'Adverse Events with additional data collection'

Impact: Section 12 updated with relevant sections, new sections 8.2.3.1 and 8.2.3.2 introduced and Appendix B updated.

2.1.2.2 Deletion of Medical event of special interest (MESI) definition and term

Impact: Throughout the protocol MESI has been deleted and medication errors are changed to AE requiring additional data collection.

2.1.3 Events in scope for adjudication added

Rationale: All coronary revascularisations (CR) occurring as a result of an Myocardial Infarction (MI) will be captured on the specific event form for the corresponding Acute Coronary Syndrome (ACS) event and source documents from the procedure will be reviewed by the Event Adjudication Committee (EAC) when adjudicating this ACS event.

Impact: Coronary revascularisation (CR) has been removed as event in scope for adjudication as only MIs and not the procedure itself will be adjudicated.

2.1.4 Reporting of adverse events

Rationale: This is in order to align with the new Novo Nordisk processes for reporting of adverse events.

Impact: Protocol sections 8 and 12 updated.

2.1.5 Extra follow-up visit added at the end of trial

Rationale: In line with current FDA guidance, an additional follow-up visit (30 days after last dose on trial product) was added at the end of trial in order to collect further safety information on subject reported SAEs and concomitant antidiabetic treatment.

Impact: This will increase the trial duration with approximately 3 weeks – which has been updated in protocol where applicable (e.g. also figure 5.1 updated). Further, the terms 7-days follow up visit (FU1) and 30-days follow-up visit FU2 (Phone contact 30) have been introduced throughout the protocol – especially Sections 1, 2, 5 and 8.

2.1.6 Collection of data describing 'severe hypoglycaemic episodes'

Rationale: The protocol was written in 2014 based on SOP 110079 ed. 7.0. Since then the hypoglycaemia episode form has been updated to capture additional structured information on severe hypoglycaemia symptoms and resource use. Therefore a number of additional questions was added to the subject diaries.

Impact: The severe hypoglycaemia data being collected in the diaries has been added to protocol Sections 8.2.15 and other text corrections made to comply with current standards and improve narrative quality.

2.1.7 Hypoglycaemia unawareness

Rationale: Since the protocol was written in 2014 a new section "Hypoglycaemia unawareness" has been included in the protocol SOP 110079 edition 9.0. Because this trial does not exclude inclusion of subjects with impaired hypoglycaemia awareness the information about hypoglycaemia unawareness will be collected at the screening visit.

Impact: A new section 8.2.5 has been added to the protocol.

2.1.8 Smoking habits

Rationale: The protocol was written in 2014 based on SOP 110079 ed. 7.0. Since then section "8.2.6 Smoking habits" has been renamed to "Tobacco use" and the question about when the subject stopped smoking has been deleted.

Impact: Flowchart and section 8.2.6 updated.

2.1.9 Eye examination and ECG

Rationale: To be aligned with the global DUAL II trial collection of details of an abnormality of eye examination and ECG will be collected.

Impact: Section 8.2.11 and 8.2.12 updated.

2.1.10 Laboratory analysis

2.1.10.1 Fasting insulin

Rationale: In line with other DUAL trials the fasting insulin results will not be provided to the investigator as these are not used for clinical evaluation during the trial. Instead they will be included in an analytical report after end of trial and retained at Novo Nordisk. Also, fasting insulin is measured at a special lab and samples are stored until final CTR.

Impact: Section 8.3.1 updated, new section 8.3.4 added and section 24.2 updated.

2.1.10.2 Pregnancy test

Rationale: The text from flowchart foot note i was not mentioned anywhere else in the protocol. The text reads: "*For females of child-bearing potential a urine pregnancy test should be performed at site, if pregnancy is suspected or if a menstrual period is missed. If the subject reports missing menstrual at a phone contact, the subject must attend the site for an unscheduled visit as soon as possible to have a urine test done. If positive, a confirmatory serum hCG sample should be sent to the central laboratory*"

Impact: Section 8.3.1 updated.

2.1.11 Calcitonin

Rationale: The Calcitonin section in the protocol including an additional withdrawal criteria #7 and the Appendix D have been updated to align with the monocomponent of liraglutide based on minutes from liraglutide safety committee (SC) Mar 2015 and the IDegLira SC agreed on May-2015 that:

MTC monitoring set-up (no RET tests will be performed, deletion of the external CMC which is replaced by a guideline in the protocol and training of the investigators on handling of elevated calcitonin values consistent with the current guideline developed by the CMC) will be implemented in the DURABILITY trial (NN9068-4228) and other future NN9068 trials.

Impact: Sections 6.4, 8.3.2 and Appendix D updated.

2.1.12 Data on effect of time point for dosing

Rationale: To be able to provide data on the effect of time point for dosing being the same whatever medication is taken morning or evening which if we are asked to make analysis of this post hoc (we were asked from FDA about this).

Impact: Section 8.6 updated with additional bullet point for what to collect in diary.

2.1.13 Trial product details

Rationale: Since the protocol was written in 2014 product information concerning IDegLira, IDeg and liraglutide has been updated. Therefore the references to Investigator's Brochures and local labelling have been updated to the most updated editions.

Impact: References updated throughout the protocol.

2.1.14 IWRS

Rationale: Since the protocol was written in 2014 the IWRS system has been upgraded to Config. 3.1 to improve drug accountability and drug destruction. Further, dispensing verification has been included following introduction of the barcode scanner.

Impact: Updated section 9 and 10.

2.1.15 Monitoring procedures more clearly specified

Rationale: In order to comply with current edition of SOP 110079 and to ensure subject safety and GCP compliance as early as possible at trial sites, the protocol will be updated to define the maximum allowed time (4 weeks) from FPFV until the first monitoring at site and 12 weeks for subsequent monitoring visits.

Impact: Updated Section 14 Monitoring Procedures.

2.1.16 Statistical considerations

Rationale: To be compliant with the updates made in other sections of the protocol the statistical considerations have been updated accordingly. Main update is related to hypoglycaemia definitions.

Impact: Section 17 updated.

2.1.17 Ethics

Rationale: In order to comply with current edition of SOP 110079 and to ensure subject safety and GCP compliance the protocol has been updated with the mandatory SOP template text. Section 18 of the protocol has been updated to include benefit-risk assessment section, which has previously been provided as a separate benefit-risk assessment document. The text in section 18 has been updated to align with updates from liraglutide and IDegLira programme

Impact: Section 18 updated**.**

2.1.18 Reports and publications

Rationale: In order to comply with current edition of SOP 110079 the protocol has been updated to reflect resent disclosure requirements.

Impact: Section 23 updated.

2.1.19 Retention of human biosamples

Rationale: In order to comply with current edition of SOP 110079 and to ensure subject safety and GCP compliance the protocol has been updated to more clearly describe which blood samples are exported out of China and for how long the samples will be stored.

Impact: Section 24.2 and SI/IC updated**.**

2.1.20 Flow Chart updates

Rationale: Based on above mentioned changes related to additional FU2 the flowchart has been updated displaying what procedures are to be performed at FU1 and FU2. Additionally, the flowchart is updated with tobacco use and hypoglycaemia unawareness as described previously.

Impact: Flow chart and footnotes updated accordingly.

2.1.21 List of abbreviations

Rationale: Since protocol preparation back in 2014, new standard abbreviations have been implemented and the following terms will be modified throughout the protocol. Also a few new terms have been added, refer to below.

Impact: IV/WRS replaced by IWRS, ASAT replaced by AST and ALAT replaced by ALT throughout the protocol. Additionally, MESI and SmPC have been deleted throughout the protocol.

2.2 Changes to the SI/IC

2.2.1 Adhering to local regulations and legal requirement

Rationale: Below sections have been added based on experience with EC requested information.

2.2.1.1 Blood sample handling & exportation

Impact: Section 1.7 named Information about antibody sampling and exportation added.

2.2.1.2 Funding of research

Impact: Section 4.1 is updated.

2.2.1.3 Liability information

Impact: Section 4.2 updated.

2.2.1.4 Subject re-imbursement fee

Impact: Section 4.3 updated.

2.2.2 Trial product market availability

Rationale: The description about cardiovascular safety is already included in the market launch information for the trial products in section 2.1.

Impact: Last part of section 1.2 about trial product market availability is deleted.

2.2.3 Text describing cardiovascular safety and DEVOTE

Rationale: In order to present the most recent status on the CV outcome trial initiated based on FDA request the below section has been updated.

Impact: The previous text in section 2.2.16 has been replaced by updated text in section 2.1.13.

2.2.3.1 Signal of increased cardiovascular risk

Impact: The previous text in safety section 2.0 about CV has been updated.

2.2.4 Update of section 2.3 If you become pregnant

Rationale: Section 2.3 has been updated based on the updated Minimum Mandatory Safety text from IDegLira.

2.2.5 Other SI/IC updates

Rationale: Based on updates made to the trial protocol

2.2.5.1 30 days follow up visit (FU 2) named phone contact 35, added

Impact: Section 1.1, 1.3, 1.4, 1.5.3 and 3.1 updated.

2.2.5.2 Extra SI/IC version to male partners

Impact: The version and date is updated to be aligned with the main SI/IC. Section 3 and 5 updated.

2.2.5.3 Extra SI/IC version for genetic testing obsolete

Impact: The SI/IC for genetic testing is no longer applicable for IDegLira trials. Therefore it will not be resubmitted.

Protocol Amendment

no 2
to Protocol, final version 2.0
dated 07 October 2014

Trial ID: NN9068-4166
DUAL™ II China

A trial comparing the efficacy and safety of insulin degludec/liraglutide and insulin degludec in combination with metformin in Chinese subjects with type 2 diabetes mellitus inadequately controlled with basal insulin therapy and metformin ± one other OAD

Trial phase: 3a

Applicable to China and Hong Kong

Amendment originator:

[redacted]

Introduction including rationale for the protocol amendment

During the approval process of amendment 01 the below refinement related to improved data quality has been discussed in the Biostatistics department. We therefore apply for approval of the below updates to section 17.4.2.2 to be made in the NN9068-4166 protocol. The reasons for the update are:

- More clearly addresses whether as to an endpoint is of continuous or categorical nature (i.e. summary statistics will be on the form {N,mean(SD),min,max,median} or {N,percentage})
- Specifies scatter plots that are better suited to detect unwanted anti body development

Current text to be deleted in section 17.4.2.2:

~~**Antibodies towards trial product**~~

~~Anti-insulin degludec antibodies including anti-human insulin antibodies, anti-liraglutide antibodies, anti-liraglutide antibodies cross reacting with native GLP-1 and *in vitro* neutralising effect of anti-liraglutide antibodies will be summarised and tabulated. The correlation between change from baseline after 26 weeks of treatment in anti-insulin degludec and anti-human insulin antibodies respectively, to insulin dose after 26 weeks of treatment, HbA_{1c} after 26 weeks of treatment and change from baseline after 26 weeks of treatment in HbA_{1c} will be illustrated using scatter plots.~~

~~For the liraglutide component of IDegLira and liraglutide, the number of subjects (N) and the percentage of subjects (%) with positive, cross-reacting to native GLP-1 and neutralising antibodies will be summarised.~~

~~Listing with subjects with liraglutide positive antibody formation will be produced. These listings should include efficacy information as minimum HbA_{1c} and body weight over time.~~

New text to be inserted in section 17.4.2.2:

17.4.2.2 Safety endpoints

Insulin and GLP-1 antibodies

Insulin antibodies (IDeg specific, cross-reacting to human insulin and total) will be summarised with arithmetic mean, standard deviation (SD), median, and minimum and maximum value by treatment and treatment week, and their mean over time will be plotted. Correlations will be explored graphically as follows. Insulin antibodies (IDeg specific, cross-reacting to human insulin and total) will be plotted against HbA_{1c} after 26 weeks, HbA_{1c} change from baseline after 26 weeks, and dose after 26 weeks. Change from baseline to FU1 in insulin antibodies (IDeg specific, cross-

reacting to human insulin and total) will be plotted against HbA_{1c} after 26 weeks, HbA_{1c} change from baseline after 26 weeks, and dose after 26 weeks.

GLP-1 antibodies (liraglutide specific, cross-reacting to native GLP-1, liraglutide in vitro neutralising and in vitro neutralising to native GLP-1) will be summarised by number of subjects (N) and percentage of subjects (%) with positive and negative samples.

Antibody measurements will be listed by subject and visit together with associated age, sex, BMI, HbA_{1c} and dose

Protocol Amendment

no 3
to Protocol, final version 2.0
dated 07 October 2014

Trial ID: NN9068-4166
DUAL™ II China

A trial comparing the efficacy and safety of insulin degludec/liraglutide and insulin degludec in combination with metformin in Chinese subjects with type 2 diabetes mellitus inadequately controlled with basal insulin therapy and metformin ± one other OAD

Trial phase: 3a

Applicable to China and Hong Kong

Amendment originator:

[redacted]

1 Changes to protocol

Section 8.4 subject diaries

Rationale: In the diary we collect the date, dose, injection site and exact clock time for injection from the previous 3 days of dosing. This was not included in the original protocol, but was added with amendment 1 for the purpose of being able to provide data on the effect of time point for dosing being the same whatever medication is taken morning or evening. The protocol text describing this procedure was copied from the NN9068-4148 protocol. However, in trial NN9068-4148 the purpose of this text is to register data prior to PK sampling. When copying the text from NN9068-4148 to NN9068-4166 too much of the text was included ("Date, dose, injection site and exact clock time for injection from the previous three days of dosing and on the day of the visit"). The text which describes collecting the information "and on the day of the visit" does not apply to NN9068-4166 where the purpose is to document the dosing time and not register data prior to PK sampling. There is no PK sampling in NN9068-4166. Therefore the text in the protocol should be updated as follows:

Current text: Date, dose, injection site and exact clock time for injection from the previous three days of dosing and on the day of the visit.

Updated text: Date, dose, injection site and exact clock time for injection from the previous three days of dosing.

Impact: Updated section 8.4.

2 Changes to SI/IC

At the IDegLira safety committee meeting on 30-Aug-2016, it was endorsed to update the MMST with the below stated text for the SI/IC.

Current text to be deleted in section 2.2.5:

~~**2.1.1 Gallstone disease**~~

~~**Cases of gallstones (cholelithiasis) and inflammation of the gallbladder (cholecystitis) have been reported from long-term clinical trials with liraglutide (component of IDegLira). These events may lead to hospitalisation and removal of the gallbladder. If you experience recurring upper abdominal pain, you should contact your trial doctor, who will decide whether you should discontinue trial product and/or undergo additional diagnostic procedures.**~~

New text to be inserted in section 2.2.5:

Gallstone disease

Cases of gallstones (cholelithiasis) and inflammation of the gallbladder (cholecystitis) have been reported from clinical trials with IDegLira. These events may lead to hospitalisation and removal of the gallbladder. If you experience recurring upper abdominal pain, you should contact your trial doctor who will decide whether you should discontinue trial medication and/or undergo additional diagnostic procedures

New text to be inserted as section 2.2.17

2.2.17 Other adverse events

Feeling tired has been reported with IDegLira in 1 to 10 out of 1000 patients in clinical trials.

Non MMST related update to section 1.5 to be consistent with the protocol

Throughout the trial you must continue your metformin treatment. ~~at the same stable dose and frequency as before your trial participation~~. The dose ~~and frequency~~ should not be changed at any time during the trial until the end of treatment visit".

Protocol Amendment

no 4
to Protocol, final version 2.0
dated 07 October 2014

Trial ID: NN9068-4166
DUAL™ II China

A trial comparing the efficacy and safety of insulin degludec/liraglutide and insulin degludec in combination with metformin in Chinese subjects with type 2 diabetes mellitus inadequately controlled with basal insulin therapy and metformin ± one other OAD

Trial phase: 3a

Applicable to China and Hong Kong

Amendment originator:

[redacted]

Introduction including rationale for the protocol amendment

After finalisation of NN9068-4166 protocol version 3.0 dated 31-Aug-2016 the following changes have been identified why an amendment is needed:

1.1 Section 18.1.1.1 Important identified risks

Rationale: The IDegLira safety committee agreed on 30-Aug-2016 to classify 'acute gallstone disease' as an important identified risk. Section 18 in the protocol has been updated to include 'acute gallstone disease' as an important identified risk.

Acute gallstone disease

Although infrequent, cases of gallstones (cholelithiasis) and inflammation of the gallbladder (cholecystitis) have been reported from clinical trials with IDegLira. Both cholelithiasis and cholecystitis have possible clinical implications for the patients as the events might lead to hospitalisation and cholecystectomy. If cholelithiasis is suspected, treatment should be discontinued and gallbladder examination and appropriate clinical follow-up should be initiated. If acute gallstone disease is confirmed, the trial product must be permanently discontinued.

1.2 Figure 5.1

Rationale: In protocol version 3.0 the below table is included:

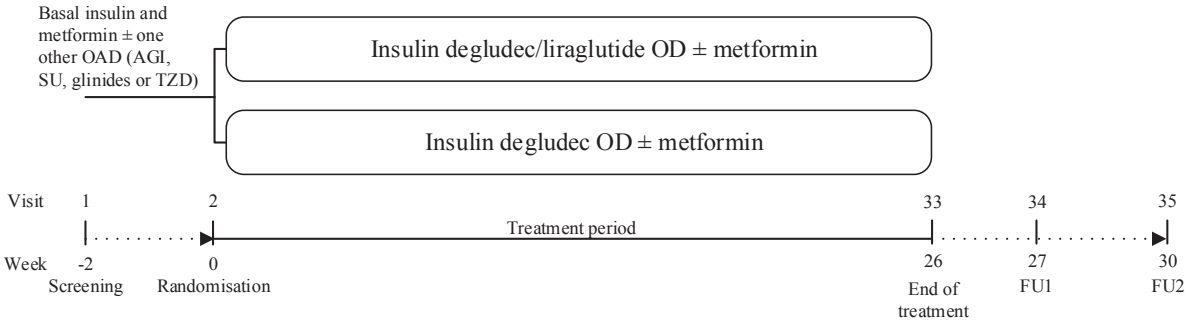

Figure 5.1 from protocol version 3.0 – to be replaced with figure below

This table mistakenly lists +/- metformin, which is not correct as all patients on both arms are to receive metformin +/- one other OAD. The figure has therefore been updated to include the 30-day FU2 visit based on the figure included in protocol version 2.0 as shown below:

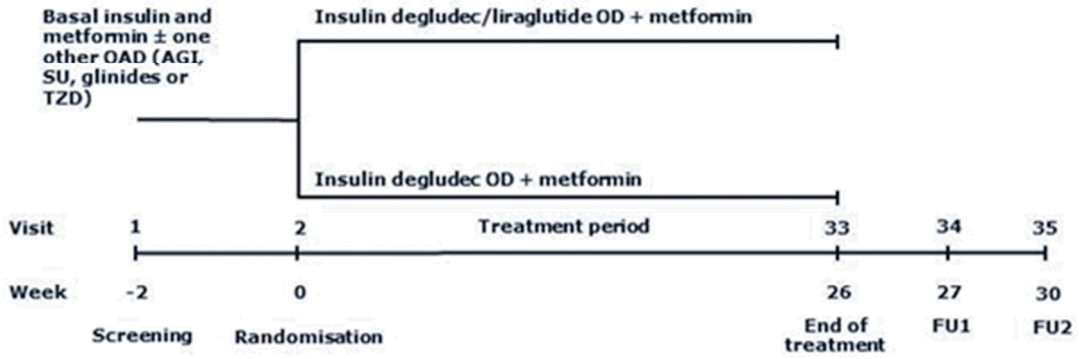

Figure 5.1 from protocol version 3.3 – to be inserted instead of figure above

1.3 Section 7 Milestones

Rationale: Topographical correction to be compliant with Protocol SOP 110079 version 9.0 template:

"Planned duration of recruitment period (First Subject First Visit – Last Subject *First*~~Last~~ Visit): 54 weeks. End of trial is defined as Last Subject Last Visit."

1.4 Section 8.2.13

Rationale: A 9-point SMPG is to be performed between visit1 to visit2 according to flow chart, so the BG-meter should be handed out to the subject at visit1 and not visit 2:

"At visit 1~~2~~, subjects will be provided with a BG-meter which must be used for all measurements during the trial. The subject should be supplied with oral and written directions for use of the device including the performance of regular calibrations according to the manufacturer's instructions. Sites should, as necessary, repeat the directions for use to the subject at subsequent visits.

1.5 Section 17 Statistical considerations

Rationale: The statistical models for the confirmatory secondary endpoints, hypoglycaemic episodes and dose, have been updated to be in alignment with the models for the global DUAL trials. In addition, clarifications around 1-sided versus 2-sided testing has been added and minor errors corrected.

<u>From section 17:</u>

"Unless otherwise specified, all continuous measurements will be summarised descriptively at each visit by treatment using observed data. After 26 weeks of treatment, descriptive statistics will be presented based both on observed and last observation carried forward (LOCF) imputed 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 *summarised by* ~~supplemented with~~ the geometric mean and coefficient of variation (CV)."

"Presentation of results from a statistical analysis will include the estimated mean treatment effects (Least Square Means [LSMeans]) for absolute values and change from baseline. In addition, estimated mean treatment difference (or ratio) will be presented together with the two-sided 95% confidence interval and corresponding two-sided ~~5%~~ p-value."

From section 17.1 Sample size calculation

"Superiority in the primary endpoint for IDegLira versus IDeg will be considered confirmed if the upper bound of the two-sided 95% confidence interval for the estimated mean treatment difference in change from baseline in HbA_{1c} (for IDegLira - IDeg) is strictly below 0% or equivalently if the p-value for the two-sided test of

$$H_0\ D=0 \text{ against } H_A\ D\neq 0,$$

is less than 5% and $D<0$, where D is the estimated treatment difference. 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% *(one-sided)*.

From section 17.4.1 Confirmatory secondary endpoints

The following two confirmatory endpoints will be tested for superiority of IDegLira vs. IDeg.

- Change from baseline in body weight after 26 weeks of treatment.
- Number of treatment emergent severe or BG confirmed hypoglycaemic episodes during 26 weeks of treatment.

The tests for superiority of the confirmatory secondary endpoints will be based on the FAS and will only be carried out if superiority of IDegLira vs. IDeg with regards to the primary endpoint is confirmed.

In order to control the overall type I error on a *two-sided* 5% level with regards to the secondary endpoints, a hierarchical testing procedure will be used. If superiority is confirmed with respect to change from baseline in body weight after 26 weeks of treatment the number of treatment emergent severe or BG confirmed hypoglycaemic episodes during 26 weeks of treatment will be tested for superiority.

Superiority for change from baseline in body weight will be considered confirmed if the upper bound of the two-sided 95% confidence interval for the estimated mean treatment difference (IDegLira minus IDeg) is strictly below zero or equivalently if the p-value for the one-sided test of

$$H_0\ D \geq 0.0\text{~~\%~~} \text{ against } H_A\ D < 0.0\text{~~\%~~},$$

is less than 2.5%, where D is the treatment difference.

The change from baseline in body weight after 26 weeks of treatment will be analysed using an ANCOVA model with treatment and previous OAD treatment (metformin ± one other OAD) as fixed factors and baseline weight as covariate.

Superiority for hypoglycaemic episodes will be considered confirmed if the upper bound of the two-sided 95% confidence interval for the estimated mean treatment ratio (IDegLira vs. IDeg) is strictly below one or equivalently if the p-value for the one-sided test of

$$H_0\ RR \geq 1.0 \text{ against } H_A\ RR < 1.0,$$

is less than 2.5%, where RR is the *treatment* ~~estimated~~ rate ratio.

Number of treatment emergent severe or BG confirmed hypoglycaemic episodes during 26 weeks of treatment will be analysed using a negative binominal regression model with a log-link function and the logarithm of the time period in which a hypoglycaemic episode is considered treatment emergent as offset. The model will include treatment and previous antidiabetic treatment as fixed factors ~~and baseline HbA_{1c} as covariate~~.

<u>From section 17.4.2.2 Safety endpoints, Calcitonin</u>

The distribution of all calcitonin measurements across treatment groups and time will be shown with *box plots* ~~histograms~~ and corresponding cumulative plots for actual levels of calcitonin and change from baseline. The plots will be presented by treatment group ~~(using~~ *at* EOT *using* ~~measurement~~ LOCF~~)~~ *imputed values* and within treatment group by week. Plots will be done by each gender, separately.

Protocol Amendment

no 5
to Protocol, final version 2.0
dated 07 October 2014

Trial ID: NN9068-4166
DUAL™ II China

A trial comparing the efficacy and safety of insulin degludec/liraglutide and insulin degludec in combination with metformin in Chinese subjects with type 2 diabetes mellitus inadequately controlled with basal insulin therapy and metformin ± one other OAD

Trial phase: 3a

Applicable to China and Hong Kong

Amendment originator:

[redacted]

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1 Introduction including rationale for the protocol amendment

After finalisation of NN9068-4166 protocol version 4.0 dated 28-Sep-2016 and the Subject information/informed consent form version 4.0 dated 08-Sep-2016 the following changes have been identified why an amendment is needed:

- To update with description of shipment of baseline antibody samples from [redacted] to Novo Nordisk, Denmark
- To update storage time for antibody samples
- To align where laboratory results will be reported
- To correct the starting dose of the liraglutide component
- To align withdrawal criteria #5
- To update SI/IC risk section with FDA approval of Xultophy

In this substantial protocol amendment global:

- Any new text is written in *italic*.
- Any text deleted from the protocol is written with a ~~strike through~~

2 Changes to Protocol version 4.0 dated 28-Sep-2016

2.1 Affected section 8.3.3: Baseline antibody samples shipped from [redacted] to Novo Nordisk Måløv, Denmark

Rationale: Analysis of in vitro neutralising activity of anti-drug antibodies (ADA) is a requirement from the health authorities (FDA, EMA, CFDA) (ref 1, 2, 3). According to the guidelines, antibody negative samples/baseline samples from the same population as is investigated for ADA development should be used for determining the cut point in the antibody analyses. Therefore, commercially obtained human serum samples should not be used to determine the cut point.

To comply with the recommendations, approximately 30 baseline (visit 2 samples) antibody samples will be shipped to a laboratory at Novo Nordisk, Måløv, Denmark to be used for the neutralising antibody cut point determination. These samples will consist of visit 2 antibody samples from the patients that are ADA positive at the follow up 1visit, as well as an additional number of antibody negative visit 2 samples randomly chosen among the antibody negative trial subjects. This procedure is in accordance with the previous global trials in the NN9068 phase 3 trial programme.

No results from the antibody negative visit 2 samples will be reported to the OC database or the investigator as these are only used for calculation of the neutralising cut point and not for any clinical relevant results. The only results to be reported in the CTR from the in vitro neutralising anti-liraglutide antibody analysis are the results of the antibody positive follow-up visit 1 samples.

1: FDA Draft guidance: Assay Development and Validation for Immunogenicity testing of Therapeutic Protein Products. Guidance for Industry. 2016
2: EMA Guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins draft 2015
3: CFDA Guideline for quality control of recombinant DNA products 2003

Updates text section 8.3.3 in protocol version 4.0:
FU1 samples positive for anti-liraglutide antibodies will in addition be analysed for in vitro neutralising effect in a cell based assay. In vitro neutralising effect will be analysed by Novo Nordisk. *Anti-liraglutide antibody positive FU1 samples and baseline (visit 2) samples belonging to the same subject will be forwarded by the special lab performing the antibody analysis to Novo Nordisk. Additionally, a number of baseline samples from subjects with antibody negative FU1 samples will also be forwarded to Novo Nordisk to set a cut point for the analysis.*

2.2 Affected section 24.2: Storage time for antibody samples

Rationale: To be aligned with previous trial NN5401-3598 conducted in China and OHGRA guidance on storage time for antibody samples the protocol text has been updated to be aligned with the 3598 study protocol section 8.5 (EN version 3.0, dated 27-Aug-2015).

In section 24.2 storage time for antibody samples and Fasting insulin samples are on purpose differently described. The long term storage for antibody samples is requested by the FDA but is not applicable for any other parameters or samples. There are no clear rules for retaining samples for biomarkers, so it has been decided that Fasting insulin samples are stored until final CTR. This is contrary to the regular safety samples at central laboratories which are discarded a few days after analysis. Reason for the difference is that sample results are released (and considered final) continuously from the central labs whereas the special labs release results at DBL due to limitations in the special lab LIMS systems. This keep the option for re-analysis open until biomarker data has been evaluated. So it will not be advisable to store the Insulin samples as long as the antibody samples.

Updated text section 24.2 in protocol version 4.0:
Antibody samples will be stored ~~until after end of trial and~~ until marketing authorisation approval or until the research project terminates, ~~but no longer than 15 years from end of trial after which they will be destroyed~~. Fasting insulin samples will be stored until final CTR after which they will be destroyed.

2.3 Affected section 8.3: Reporting of laboratory results not provided to Investigator

Rationale: Based on guidance from the China Human Genetic Resources Administration Office (OHGRA) it is a concern that the protocol is not consistent as to where laboratory results that are not provided to the investigator will be published (antibody and fasting insulin). Because all results are summarised in the CTR the affected section is updated for consistency.

Updated text section 8.3.4 in protocol version 4.0:
Results from fasting insulin samples will not be provided to the investigator as these are not used for clinical evaluation during the trial. ~~Instead they will be included in an **analytical report** after end of trial.~~ *The results will be described in the **CTR** after end of trial.*

2.4 Affected section 18.1.1.1: Starting dose of liraglutide component

Rationale: The starting dose of the liraglutide component is correctly listed as 0.6 mg in section 5.5 Rationale for treatment but in section 18.1.1.1 Gastrointestinal adverse events it's mistakenly listed as 0.36 mg. This means that the starting dose of liraglutide is the same and not less than the starting dose of liraglutide when administered as the mono-component.

Updated text section 18.1.1.1 Gastrointestinal adverse events

Gastrointestinal adverse events are considered class effects for GLP-1 RAs and are among the most frequently reported events in patients treated with IDegLira. The titration of IDegLira is slow and has previously shown to result in a lower frequency of gastrointestinal adverse effects. The dose of the liraglutide component in the start dose of IDegLira in the present trial is ~~0.36~~ *0.6* mg, which is *the same as* ~~*less* than~~ the starting dose of liraglutide when administered as the mono-component (Victoza®).

2.5 Affected section 6.4 Withdrawal criteria#5

Rationale: The week intervals for withdrawal criteria #5 are not clearly defined and not similar to Global DUAL I protocol; week 6 and 12 were included in two intervals.

Updated text section 6.4 in protocol version 4.0:

1. If all pre-breakfast SMPG values taken on three consecutive days or if any FPG samples analysed by the central laboratory exceeds the limit of:
   15.0 mmol/L after baseline to week 6
   13.3 mmol/L from week *7*~~6~~ to week 12
   11.1 mmol/L from week 1*3*~~2~~ to last week prior to end of treatment

and given there is no intercurrent cause for the hyperglycaemia, a confirmatory FPG must be performed at the next scheduled visit, or if deemed necessary by the investigator at an unscheduled

3 Changes to Subject information/informed consent form version 4.0 dated 08-Sep-2016

3.1 Affected section 1.7: Baseline antibody samples shipped from [redacted] to Novo Nordisk Måløv, Denmark

Rationale: To be aligned with the update in the protocol.

Updated section 1.7 Information about laboratory sampling and exportation:
In order to standardise the sample analysis used in this trial, all serum antibody samples and fasting insulin samples including yours, will be shipped to ~~a~~ special laborator*ies*~~y~~ outside of China and Hong Kong. The antibody samples *will be shipped to* [redacted] *located in* [redacted] *and to Novo Nordisk, located in Denmark, for analysis.* ~~and~~ ~~f~~Fasting insulin samples will be shipped to [redacted] located in [redacted] By involving only *two* ~~one~~ special laborator*ies*~~y~~, comparability of results from subjects at all investigational sites involved in the trial will be ensured.

Further, the serum antibody samples must only be used in relation to this trial, and all samples will be destroyed as biological/medical waste at [redacted] *and Novo Nordisk*, after receiving marketing authorisation from the authorities and never shipped back to China or Hong Kong.

3.2 Affected section 3.3: Storage time for antibody samples

Rationale: To be aligned with the update in the protocol.

Updated section 3.3 Will my participation in the trial be kept confidential?
Antibody samples will be stored until *marketing authorisation approval or until the research project terminates.* ~~final feedback from the Chinese health authorities, but no longer than maximum 15 years from end of trial~~

3.3 Affected section 2.1: What are the possible risks if you participate in this trial

Rationale: Xultophy was approved by FDA on 21-Nov-2016. Adding this information to the SI/IC will ensure that patients receive the most updated safety information.

Updated section 2.1: What are the possible risks if you participate in this trial
You must inform the trial staff about any other medications (including over-the-counter drugs and herbal remedies) that you are using during the trial. If you are prescribed new medicines or start taking a new over-the-counter drug, you should inform the trial staff immediately.
IDegLira, which is approved in EU *and US* under the name*s* Xultophy® *and Xultophy® 100/3.6, respectively* , is well tolerated. In the clinical development programme IDegLira did not show increased incidence of side effects compared to its two monocomponents, Tresiba® (insulin degludec) and Victoza® (liraglutide).