Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT02501161
Sponsor trial ID:	NN9068-4228
Official title of study:	A 104 week clinical trial comparing long term glycaemic control of insulin degludec/liraglutide (IDegLira) versus insulin glargine therapy in subjects with type 2 diabetes mellitus (DUAL™ VIII)
Document date:	01 March 2019

16.1.1 Protocol and protocol amendments

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Redacted protocol
Includes redaction of personal identifiable information only.

.

Protocol

Trial ID: NN9068-4228

DUAL™ VIII – Durability

A 104 week clinical trial comparing long term glycaemic control of insulin degludec/liraglutide (IDegLira) versus insulin glargine therapy in subjects with type 2 diabetes mellitus

Trial phase: 3b

Protocol originator

[redacted]

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List of abbreviations

ABPI	Association of the British Pharmaceutical Industry	FU	follow-up
ADA	American Diabetes Association	GCP	Good Clinical Practice
AE	adverse event	GLP-1	Glucagon-like peptide-1
ALAT	Alanine aminotransferase	HbA_{1c}	glycosylated haemoglobin
ASAT	aspartate aminotransferase	hCG	human Chorionic Gonadotropin
BG	blood glucose	HDL	High density lipoprotein
BMI	body mass index	IB	Investigator's Brochure
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration	ICH GCP	International Conference on Harmonisation. Guideline for Good Clinical Practice
CRF	case report form	IDeg	insulin degludec
CTR	clinical trial report	IDegLira	insulin degludec/liraglutide
DPP-4	Dipeptidyl peptidase-4	IDMS	isotope-dilution mass spectrometry
DUN	dispensing unit number	IGlar	insulin glargine
EAC	Event Adjudication Committee	IRB/IEC	Institutional Review Boards/Independent Ethics Committees and regulatory
EASD	European Association for the Study of Diabetes	IWRS	interactive web response system
ECG	Electrocardiogram	LDL	Low-density lipoprotein
eCRF	electronic case report form	LLOQ	lower limit of quantification
EOT	end of treatment	LSFV	Last subjects first visit
FAS	full analysis set	MACE	major adverse cardiovascular events
FDA	U.S. Food and Drug Administration	MESI	medical event of special interest
FPG	fasting plasma glucose	MI	myocardial infarction
FSFV	first subject first visit	MMRM	mixed model for repeated measurement

NIMPs	non-investigational medicinal products
NYHA	New York Heart Association
OAD	oral antidiabetic drugs
Pre-disc	Premature discontinued from trial product
PRO	patient reported outcome
Px	Phone contacts for subjects premature discontinued from trial product
QD	quaque die (once daily)
SAE	serious adverse event
SAS	safety analysis set
s.c.	Subcutaneous
SF-36v2	Medical outcomes study 36-item short form version 2
SIF	safety information form
SMPG	self-measured plasma glucose
SUSAR	suspected unexpected serious adverse reaction
T2DM	type 2 diabetes mellitus
TEAEs	Treatment-emergent adverse events
TIA	transient ischemic attack
TMM	trial materials manual
Trim-D	Treatment related impact measure
TSH	thyroid stimulating hormone
UTN	Universal Trial Number
VLDL	very-low-density lipoprotein

1 Summary

Primary objective
To compare long-term glycaemic control of insulin degludec/liraglutide (IDegLira) versus insulin glargine (IGlar) in insulin naïve subjects with type 2 diabetes mellitus (T2DM) inadequately controlled on oral antidiabetic drugs (OAD[s]).

The secondary objective
To compare long-term efficacy and safety of IDegLira versus IGlar in insulin naïve subjects with T2DM inadequately controlled with OAD(s).

Primary endpoint
The following endpoint will be assessed up to 104 weeks. Time from randomisation to inadequate glycaemic control and need for treatment intensification, defined as a glycosylated haemoglobin (HbA_{1c}) of ≥ 7.0% at 2 consecutive visits from week 26, including week 26 if HbA_{1c} was ≥ 7% at week 12.

Key supportive secondary efficacy endpoints
- Time from randomisation to an HbA_{1c} > 6.5% at 2 consecutive visits from week 26
- Change from baseline after 26 weeks of treatment in:
  - HbA_{1c}
  - body weight
  - Fasting plasma glucose (FPG)
  - 9-point Self-measured plasma glucose (SMPG) profile (individual points in the profile)
- Insulin dose after 26 weeks of treatment
- Responder after 26 and 104 weeks of treatment (yes/no):
  - HbA_{1c} < 7.0%
  - HbA_{1c} ≤ 6.5%

Key supportive secondary safety endpoints
- Number of treatment-emergent severe or blood glucose confirmed symptomatic hypoglycaemic episodes during 26 and 104 weeks of treatment

Trial design
This is a 2-year, multinational, open-label, two-arm parallel, randomised trial with glycaemic target in subjects with T2DM inadequately controlled with OAD(s).
Inadequately controlled T2DM will be defined as an HbA_{1c} level of 7.0-11.0% (53-97 mmol/mol), both inclusive. A total of 1000 subjects will be randomised in a 1:1 manner using a centralised allocation via interactive web response system.

Subjects will be randomised to receive either once daily (QD) IDegLira or IGlar in combination with OAD(s) at randomisation. Dipeptidyl peptidase-4 (DPP-4) inhibitors and glinides must be discontinued at randomisation.

Trial population
Planned number of subjects to be randomised is 1000 (500 per arm).

Key inclusion criteria
- Male or female, age ≥18 years at the time of signing informed consent
- Subjects diagnosed with type 2 diabetes mellitus
- HbA_{1c} 7.0−11.0% (both inclusive) (53–97 mmol/mol) by central laboratory analysis
- Body mass index ≥20 kg/m^2
- Insulin naïve subjects; however short term insulin treatment for a maximum of 14 days prior to the day of screening is allowed, as is prior insulin treatment for gestational diabetes
- Stable daily dose(s) including any of the following antidiabetic drug(s)/regimens within 90 days prior to the day of screening:
  - Biguanides (metformin ≥1500 mg or maximum tolerated dose documented in the subject medical record)
  - Other OAD(s) allowed: sulphonylurea, glinides, pioglitazone, and DPP4-inhibitors (≥ half of the maximum approved dose according to local label or maximum tolerated dose as documented in subjects medical record)

Key exclusion criteria
- Screening calcitonin ≥50 ng/L
- Renal impairment estimated Glomerular Filtration Rate (eGFR) <60 ml/min/1.73 m^2 as per CKD-EPI value to be defined as listed in the classification CKD-EPI using IDMS for serum creatinine measurement on the day of screening
- Impaired liver function, defined as ALAT or ASAT ≥2.5 times upper limit of normal
- Family or personal history of Multiple Endocrine Neoplasia Type 2 or Medullary Thyroid Carcinoma
- History of pancreatitis (acute or chronic)
- Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria in a period of 90 days before the day of screening
- Anticipated initiation or change in concomitant medications for more than 14 consecutive days or on a frequent basis known to affect weight or glucose metabolism (e.g. orlistat, thyroid hormones, corticosteroids)

Assessments:
Key efficacy assessments:

- HbA_{1c}
- Body weight
- FPG
- SMPG

Key safety assessments:

- Hypoglycaemic episodes
- Adverse events

Trial products:
The investigational medicinal products used in this trial are:

- IDegLira 100 units/mL insulin degludec+ 3.6 mg/mL liraglutide, provided in a 3 mL pre-filled PDS290 pen injector for subcutaneous injection
- IGlar 100 units/mL solution provided in a 3 mL pre-filled Solostar® pen for subcutaneous injection

2 Flow chart

Trial Periods	Screening	Rand.	Treatment										EOT	FU1	FU2	Pre-disc[1]	
Visit number (V), Phone contact (P)[2]	V1	V2	P3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	P15	PX	V13A
Timing of visit (weeks)	≤ 2 weeks prior to V2	0	1	2	4	12	26	38	52	64	78	90	104	7 days after EOT	30 days after EOT	Every 3rd month	104
Visit window (days)			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	+3	±3	±3
SUBJECT RELATED INFO/ASSESSMENTS																	
Informed consent	X																
In/exclusion criteria	X	X															
Randomisation		X															
Pre-discontinuation of trial product			X	X	X	X	X	X	X	X	X	X	X				
Rescue criteria			X	X	X	X	X										
Withdrawal of consent			X	X	X	X	X	X	X	X	X	X	X	X	X[3]	X	
Demography[4]	X																
Concomitant illness	X																
Medical history	X																
Diagnosis of diabetes	X																
Diabetes treatment history	X																
Diabetes complications	X																
Family history of diabetes	X																
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X[5]	X[5]	X[6]	X[6]
Tobacco use (smoking status)	X																

[1] Subjects discontinuing trial product prematurely will be asked to attend the end of treatment visit and the 2 follow up visits after discontinuation corresponding to V13, V14 and P15. After the follow up period the subject should have phone contacts scheduled every 3rd month (PX) until the additional premature discontinuation follow up (V13A) visit performed at week 104. See section 8.1 for further details.
[2] A phone contact may be converted to a site visit if needed
[3] Only applicable for subjects discontinuing trial product prematurely
[4] Collection of sex and date of birth, race and ethnicity only if applicable by local law
[5] Only anti-diabetic medication for subjects that have prematurely discontinued trial product will be collected
[6] Only concomitant medication with the indication diabetes will be collected

Trial Periods	**Screening**	**Rand.**	**Treatment**										**EOT**	**FU1**	**FU2**	**Pre-disc**[1]	
Visit number (V), Phone contact (P)[2]	V1	V2	P3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	P15	PX	V13A
Timing of visit (weeks)	≤ 2 weeks prior to V2	0	1	2	4	12	26	38	52	64	78	90	104	7 days after EOT	30 days after EOT	Every 3rd month	104
Visit window (days)			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	+3	±3	±3
EFFICACY																	
Glucose metabolism																	
Fasting plasma glucose		X			X	X	X		X		X		X				
HbA_{1c}	X	X				X	X	X	X	X	X	X	X				X
Fasting C-peptide		X					X						X				
Fasting human insulin		X					X						X				
Lipids		X					X		X				X				
Body measurements																	
Height	X																
Body weight[7]	X	X			X	X	X		X		X		X				
BMI	X																
Self measured plasma glucose																	
QD[8]		X	X	X	X	X	X	X	X	X	X	X	X				
9-point profile[9]		X					X						X				
SAFETY																	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[10]	X[11]	X[11]
Hypoglycaemic episodes		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				
ECG	X												X[12]				

[7] Body weight should be measured fasting except for V1
[8] Subjects should measure QD Self measured plasma glucose (SMPG) fasting prior to breakfast. Diabetes medication should be withheld until after the SMPG measurement
[9] 9-point profile should be measured within 1 week prior to the site visit (on a day where unusual strenuous exercise is not anticipated)
[10] Only AE information for potential major adverse cardiovascular events (MACE) will be collected
[11] Only AE information for potential major adverse cardiovascular events (MACE) and SAE information will be collected
[12] ECG obtained within 2 weeks prior to V13 is acceptable if results are available for evaluation at V13

Trial Periods	**Screening**	**Rand.**	**Treatment**										**EOT**	**FU1**	**FU2**	**Pre-disc**[1]	
Visit number (V), Phone contact (P)[2]	V1	V2	P3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	P15	PX	V13A
Timing of visit (weeks)	≤ 2 weeks prior to V2	0	1	2	4	12	26	38	52	64	78	90	104	7 days after EOT	30 days after EOT	Every 3rd month	104
Visit window (days)			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	+3	±3	±3
Eye examination	X[13]												X[14]				
Physical examination	X												X				
Vital signs	X	X				X	X		X		X		X				
Biochemistry[15]	X	X					X		X				X				
Haematology[16]	X	X					X		X				X				
Hormones (calcitonin)	X	X				X	X	X	X	X	X	X	X				
Urinalysis (albumin:creatinine ratio)		X				X	X		X		X		X				
Pregnancy test[17]	X	(X)		(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	X				
OTHER ASSESSMENTS																	
Barriers in Diabetes Treatment		X															
PRO questionnaires																	
TRIM-D		X					X						X				
SF36v2		X					X						X				
TRIAL MATERIAL																	
Dispensing trial product		X		X	X	X	X	X	X	X	X	X					
IWRS call	X	X		X	X	X	X	X	X	X	X	X	X				
Drug accountability		X		X	X	X	X	X	X	X	X	X	X				
REMINDERS																	

[13] Eye examination performed within 12 weeks prior to V2 as part of routine practice may replace the screening assessment if results are available for evaluation at V2
[14] Eye examination performed within 2 weeks prior to V13 is acceptable if results are available for evaluation at V13
[15] Amylase, lipase, ALAT, albumin, alkaline phosphatase, ASAT, bilirubins total, calcium ionized, creatinine, potassium and sodium
[16] Erythrocytes, haematocrit, haemoglobin, leucocytes, thrombocytes, differential count (eosinophils, neutrophils, basophils, lymphocytes and monocytes)
[17] For women of childbearing potential a blood sample pregnancy test (serum hCG) must be performed at V1 and V13. Additionally, a urine pregnancy test must 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 will have to attend the site for an unscheduled visit as soon as possible to have a urine pregnancy test performed. If positive, a confirmatory serum hCG must be sent to the central laboratory. If required by local law, pregnancy test may be performed regularly

Trial Periods	**Screening**	**Rand.**	**Treatment**										**EOT**	**FU1**	**FU2**	**Pre-disc**[1]	
Visit number (V), Phone contact (P)[2]	V1	V2	P3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	P15	PX	V13A
Timing of visit (weeks)	≤ 2 weeks prior to V2	0	1	2	4	12	26	38	52	64	78	90	104	7 days after EOT	30 days after EOT	Every 3rd month	104
Visit window (days)			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	+3	±3	±3
Hand-out ID card	X																
Training in trial product and pen handling.		X		X	X												
Hand-out directions for use		X		X	X	X	X	X	X	X	X	X					
Hand-out and instruct in diary	X	X		X	X	X	X	X	X	X	X	X					
Collect and review diary		X		X	X	X	X	X	X	X	X	X	X	X			
Hand-out BG meter	X																
Instruct in BG meter use	X	X		X													
Attend visit fasting		X			X	X	X		X		X		X				
Make appointment for eye examination												X					
End of treatment													X				
Sign off Casebook															X[18]		X
End of trial (subject completion)															X[18]		X

[18] Not applicable for subjects that have prematurely discontinued trial product

3 Background information and rationale for the trial

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

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

3.1 Background information

Insulin degludec/liraglutide (IDegLira) is a combination product of insulin degludec (IDeg) and liraglutide. It is to be initiated and titrated to achieve adequate glycaemic control in a similar way as basal insulin therapy. The basal insulin and glucagon-like peptide-1 (GLP-1) analogue combination provides complimentary effects of the two compounds on fasting and postprandial glycaemic control in a single injection. IDegLira is available on the market as Xultophy® and has been approved for use in EU and Switzerland. IDegLira is indicated for the treatment of adults with type 2 diabetes mellitus (T2DM) to improve glycaemic control in combination with oral glucose-lowering medicinal products when these alone or combined with basal insulin do not provide adequate glycaemic control. Efficacy and safety of IDegLira has been demonstrated in previous randomised clinical trials (NN9068-3697, -3912, - 3851, - 3951 and -3952) and is currently (2nd quarter 2015) being evaluated in the randomised clinical trials NN9068-4119 (DUAL intensification) and NN9068-4056 (once weekly titration). In all finalised clinical trials, IDegLira has shown improved glycaemic control, less weight gain and a lower rate of hypoglycaemic episodes compared to basal insulin and improved glycaemic control and less gastrointestinal side effect compared to liraglutide. No unexpected safety issues were identified. For more information, see the IDegLira Investigator's Brochure (IB) current version[3] and any updates hereof.

IDeg is a long-acting basal insulin and is available on the market as Tresiba® which is approved for use in amongst others EU and Japan. For more details on IDeg see current IB[4], any updates hereof and locally approved labelling in countries where it is available.

Liraglutide is a native (human) GLP-1 receptor agonist and available on the market as Victoza®, which is approved for use amongst others in Australia, Canada, China, EU, Japan and US for the treatment of adults with T2DM to achieve glycaemic control. For more details on liraglutide, please see the local approved labelling for Victoza®.

The basal insulin and GLP-1 analogue combination brings complementary effects of the two compounds on fasting (IDeg and liraglutide) and postprandial (liraglutide) glycaemic control. The addition of liraglutide to IDeg reduces the requirement of exogenous insulin (i.e. insulin sparing effect) hence minimising the risk of hypoglycaemia and weight gain often associated with insulin treatment. The inherent weight reducing effect of liraglutide further contributes to the favourable

weight profile of the combination drug compared to basal insulin treatment. Furthermore, given the glucose dependent effect of liraglutide, liraglutide reduces postprandial glucose excursions while reducing the risk of unwanted lowering of inter-prandial or fasting glucose.

Insulin Glargine (IGlar) is a long-acting insulin analogue, on the market as Lantus®, indicated for treatment of diabetes mellitus in combination with oral antidiabetic drugs (OAD) and as part of a basal-bolus insulin regimen. For further details, please refer to the Summary of Product Characteristics[5] for IGlar and the local approved label information.

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

3.2 Rationale for the trial

Given the progressive nature of T2DM and despite the importance of glycaemic control early in the disease trajectory, lack of attainment of appropriate glycaemic targets is widespread. Current antidiabetic therapies, including treatment with basal insulin, may not provide adequate or sustained glycaemic control. In addition, these therapies are often complicated and difficult for subjects to adhere to.

According to consensus guidance from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)[6] treatment intensification should be considered for subjects with T2DM who do not reach the ADA/EASD HbA_{1c} target of 7% within 3–6 months of treatment[7], or the American Association of Clinical Endocrinologists target of HbA_{1c} ≤ 6.5%.[8]

This trial generates clinical evidence on durability, efficacy and safety of IDegLira in subjects inadequately controlled on OAD therapy. IDegLira has previously shown benefits compared to intensification with basal insulin and liraglutide in terms of glycaemic control (HbA_{1c}), percentage of subjects reaching target of HbA_{1c} <7% and weight in 26 and 52 weeks trials. Compared to basal insulin IDegLira has shown less hypoglycaemia. Furthermore, due to slower titration rate of liraglutide component in IDegLira compared to treatment with liraglutide alone, a lower rate of gastrointestinal side effects were also observed.[9, 10]

4 Objectives and endpoints

4.1 Objectives

Primary objective
To compare long-term glycaemic control of IDegLira versus IGlar in insulin naïve subjects with T2DM inadequately controlled with OAD(s).

Secondary objective
To compare long-term efficacy and safety of IDegLira in insulin naïve subjects with T2DM inadequately controlled with OAD(s).

4.2 Endpoints

4.2.1 Primary endpoint

The following endpoint will be assessed up to 104 weeks. Time from randomisation to inadequate glycaemic control and need for treatment intensification, defined as $HbA_{1c} \geq 7.0\%$ at 2 consecutive visits from week 26 (including week 26, if HbA_{1c} was $\geq 7\%$ at week 12).

4.2.2 Secondary endpoints

4.2.2.1 Supportive secondary endpoints

Supportive secondary efficacy endpoints

- Time from randomisation to $HbA_{1c} > 6.5\%$ at 2 consecutive visits from week 26* (including week 26, if HbA_{1c} was $> 6.5\%$ at week 12)
- Change from baseline in HbA_{1c} after 26 weeks of treatment*
- Change from baseline in body weight after 26* and 104 weeks of treatment
- Insulin dose after 26* and 104 weeks of treatment
- Responder after 26 and 104 weeks of treatment (yes/no):
  - $HbA_{1c} < 7.0\%$*
  - $HbA_{1c} < 7.0\%$ without weight gain
  - $HbA_{1c} < 7.0\%$ without treatment-emergent severe or blood glucose (BG) confirmed symptomatic hypoglycaemic episodes during the last 12 weeks of treatment
  - $HbA_{1c} < 7.0\%$ without treatment-emergent severe or BG confirmed symptomatic hypoglycaemic episodes during the last 12 weeks of treatment and without weight gain
  - $HbA_{1c} \leq 6.5\%$*
  - $HbA_{1c} \leq 6.5\%$ without weight gain
  - $HbA_{1c} \leq 6.5\%$ without treatment-emergent severe or BG confirmed symptomatic hypoglycaemic episodes during the last 12 weeks of treatment
  - $HbA_{1c} \leq 6.5\%$ without treatment-emergent severe or BG confirmed symptomatic hypoglycaemic episodes during the last 12 weeks of treatment and without weight gain

- Change from baseline after 26 weeks of treatment in:
  - Fasting plasma glucose (FPG)*
  - 9-point Self-measured plasma glucose (SMPG) profile:
    - 9-point profile (individual points in the profile)*
    - Mean of the 9-point profile
    - Prandial plasma glucose increments (from before meal to 90 min after breakfast, lunch and dinner). The mean increment over all meals will be derived as the mean of all available meal increments

- Change from baseline after 104 weeks of treatment in:
  - FPG
  - 9-point SMPG profile:
    - 9-point profile (individual points in the profile)
    - Mean of the 9-point profile
    - Prandial plasma glucose increments (from before meal to 90 min after breakfast, lunch and dinner). The mean increment over all meals will be derived as the mean of all available meal increments

- Change from baseline after 26 and 104 weeks of treatment in:
  - Blood pressure (systolic and diastolic)
  - Fasting C-peptide and fasting human insulin
  - 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)

Supportive secondary safety endpoints

- Number of treatment-emergent severe or BG confirmed symptomatic hypoglycaemic episodes during 26 and 104 weeks of treatment*
- Number of treatment emergent hypoglycaemic episodes according to ADA definition during 26 and 104 weeks of treatment
- Number of treatment-emergent nocturnal severe or BG confirmed symptomatic hypoglycaemic episodes during 26 and 104 weeks of treatment
- Number of treatment-emergent adverse events (TEAEs) during 26 and 104 weeks of treatment
- Change from baseline in clinical evaluation after 104 weeks of treatment:
  - Eye examination – fundus photography/dilated fundoscopy
  - Electrocardiogram (ECG)
  - Urine albumin/creatinine ratio
- Change from baseline after 26 and 104 weeks of treatment:
  - Pulse
- Change from baseline in laboratory assessments after 26 and 104 weeks of treatment:
  - Biochemistry

- Haematology
- Calcitonin

Supportive secondary health economics endpoints

- Change from baseline in patient reported outcomes (PRO) after 26 and 104 weeks of treatment:
  - Medical outcomes study 36-item short form version 2 (SF-36v2)
  - Treatment related impact measure (TRIM-D)

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

5 Trial design

5.1 Type of trial

This is a 2-year (104-week), multinational, open-label, two-arm parallel, randomised trial with glycaemic target in subjects with T2DM inadequately controlled with OAD(s).

Inadequately controlled T2DM will be defined as an HbA_{1c} level of 7.0-11.0% (53-97 mmol/mol), both inclusive. A total of 1000 subjects will be randomised in a 1:1 manner using a centralised allocation via an interactive web response system (IWRS).

Subjects will be randomised to receive either IDegLira or IGlar once daily (QD) in combination with OAD(s) at randomisation. Dipeptidyl peptidase-4 (DPP-4) inhibitors and glinides must be discontinued at randomisation.

The total trial duration will be approximately 110 weeks, consisting of a 2-week screening period, a 104-week treatment period, and 2 follow-up contacts (FU1 and FU2). FU1 is scheduled 7 days (+ 3 days) after last dose of trial product, and FU2 is scheduled 30 days (+ 3 days) after last dose of trial product. The purpose of FU1 is to collect all TEAEs and the purpose of FU2 is to collect potential major adverse cardiovascular events (MACE) occurring in the period between the 2 follow-up contacts.

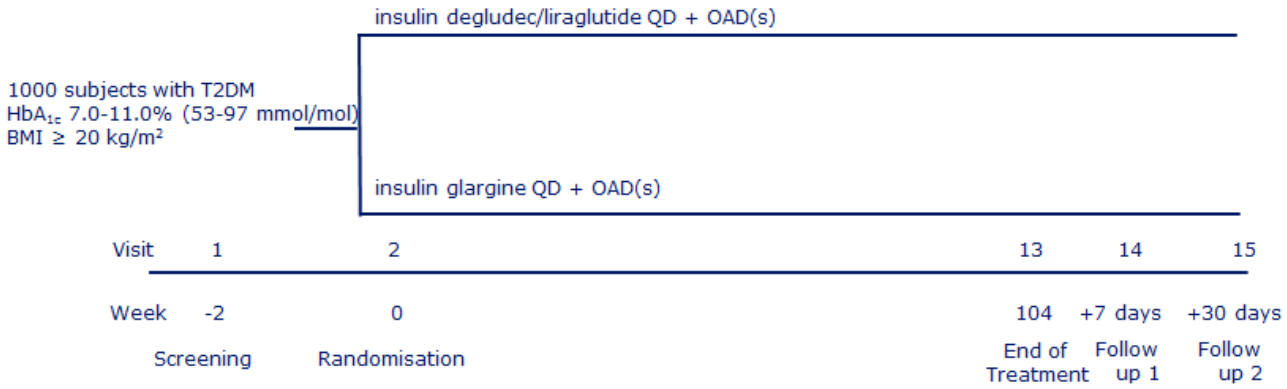


Figure 5–1 Trial design

5.2 Rationale for trial design

The overall rationale for the trial design is to demonstrate the long-term glycaemic control on IDegLira compared to IGlar in a 104-week treatment period. By using the present trial design a longer treatment duration of IDegLira in a setting more in alignment with clinical practice than previous randomised IDegLira trials will be investigated.

The open-label trial design and the visit schedule are chosen to align with clinical practice in order to ensure insulin titration based on SMPG values and to ensure the improvement in glycaemic control which could be expected in the clinic. The titration is in accordance with a predefined treatment algorithm. Please see Table 8–1.

5.3 Treatment of subjects

Subjects with T2DM with OAD(s) in accordance with the inclusion and exclusion criteria are eligible for the trial. When randomised, the subjects will receive one of the treatments described below:

- IDegLira added to OAD(s) treatment. IDegLira will be given s.c. QD. The recommended starting dose of IDegLira is 10 dose steps (10 units IDeg/0.36 mg liraglutide), and will be titrated according to a predefined titration algorithm twice weekly (see section 8.1) to a maximum dose of 50 dose steps (50 units IDeg/1.8 mg liraglutide) aiming to reach FPG target between 4.0–5.0 mmol/L (72–90 mg/dL)
- IGlar added to OAD(s) treatment. IGlar will be given s.c. QD at a starting dose of 10 units and will be titrated according to a predefined titration algorithm twice weekly (see section 8.1), with no predefined maximum dose, aiming to reach FPG target between 4.0−5.0 mmol/L (72−90 mg/dL)

All subjects will continue with the pre-trial OAD(s) except DPP-4 inhibitors and glinides which will be discontinued at randomisation. When trial product (IDegLira or IGlar) is added to sulphonylurea therapy, a reduction in the dose of sulphonylurea should be considered based on glycaemic response.

The dose and frequency of OAD(s) should not be changed during the trial except for safety reasons. The unchanged OAD doses should be confirmed at each visit and recorded in the subject's medical record and in the electronic case report form (eCRF) to verify compliance. Dose change in OAD(s) for a maximum duration of 14 days is allowed for safety reasons based on the Investigator's judgement. If a change in OAD dose has occurred, the duration and reason for the change should be recorded in subject's medical records and in the eCRF.

The trial products are described in section 9.

The treatment duration with trial products for individual subjects is planned for 104 weeks. Subjects discontinuing trial product due to inadequate control as defined in section 6.4 should be treated as described in section 5.4 and perform visit procedures as described in section 8.1.8.

5.4 Treatment after discontinuation of trial product

When discontinuing trial products the subject should be transferred to a suitable marketed product at the discretion of the investigator.

5.5 Rationale for treatment

In general, patients are be treated with basal insulin as first injectable (or as add on to ongoing GLP-1 treatment). Basal insulin will not be effective in all patients and some will need higher doses which could results in risk of hypoglycaemia and weight gain. In addition, these therapies are often complicated and difficult for patients to adhere to. In this trial the overall rationale is to demonstrate long-term efficacy of IDegLira compared to IGlar. IGlar has been chosen as it is currently the most widely used basal insulin in many countries.

The start dose of IDegLira corresponds to the starting dose of insulin treatment in type 2 diabetes population in clinical practice and as recommended in the IDegLira label.

Both IDegLira and IGlar will be titrated twice weekly following the same titration algorithm (see section 8.1).

All subjects, in both arms, will continue on metformin and pioglitazone at pre-trial dose. DPP-4 inhibitors and glinides must be discontinued at randomisation prior to administration of trial product. Reduction in sulphonylurea dose should be considered when trial product is added in order to decrease the risk of hypoglycaemia.

The treatment period of 104 week was chosen to demonstrate long-term efficacy and safety of the trial products.

6 Trial population

6.1 Number of subjects

Number of subjects planned to be screened: 1200
Number of subjects planned to be randomised: 1000
Mexico: 90 subjects are planned to be randomised/started on trial product in Mexico

Number of subjects expected to complete the trial (on trial product): 500

6.2 Inclusion criteria

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

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial
2. Male or female, age ≥ 18 years at the time of signing informed consent
3. Subjects diagnosed (clinically) with type 2 diabetes mellitus prior to the day of screening
4. HbA_{1c} 7.0−11.0% (both inclusive) (53–97 mmol/mol) by central laboratory analysis
5. Body mass index (BMI) ≥ 20 kg/m^2
6. Insulin naïve subjects; however short term insulin treatment for a maximum of 14 days prior to the day of screening is allowed, as is prior insulin treatment for gestational diabetes
7. Stable daily dose(s) including any of the following antidiabetic drug(s)/regimens within 90 days prior to the day of screening:
   - Biguanides (metformin ≥ 1500 mg or maximum tolerated dose documented in the subject medical record)
   - Other OAD(s) allowed: sulphonylurea, glinides, pioglitazone, and DPP4-inhibitors (≥ half of the maximum approved dose according to local label or maximum tolerated dose as documented in subject medical record)

6.3 Exclusion criteria

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

1. Known or suspected hypersensitivity to trial products or related products
2. Previous participation in this trial. Participation is defined as signed informed consent. Re-screening is not allowed
3. Female who is pregnant, breast-feeding or intend to become pregnant or of child-bearing potential not using adequate contraceptive methods (adequate contraceptive measures as required by local regulation or practice)

Brazil: For women who expressly declare free of the risk of pregnancy, either by not engaging in sexual activity or by having sexual activity with no birth potential risk, use of contraceptive method will not be mandatory.
United Kingdom: Adequate contraceptive measures are defined as established use of oral, injected or implanted hormonal methods of contraception, placement of an intrauterine device or intrauterine system, barrier methods of contraception (condom or occlusive cap with spermicidal foam/gel/film/cream/suppository), female sterilisation, male sterilisation (where partner is sole partner of subject), or true abstinence (when in line with preferred and usual lifestyle).

4. Receipt of any investigational medicinal product within 90 days prior to screening
   Brazil: Participation in other trials within 1 year prior to screening visit (visit 1) unless there is a direct benefit to the research subject at the investigator's discretion.
5. Any disorder which in the opinion of the investigator might jeopardise subject's safety or compliance with the protocol
6. Screening calcitonin ≥ 50 ng/L
7. Renal impairment estimated Glomerular Filtration Rate (eGFR) < 60 ml/min/1.73 m^2 as per CKD-EPI value to be defined as listed in the classification CKD-EPI using IDMS for serum creatinine measurement on the day of screening[11]
8. Impaired liver function, defined as ALAT or ASAT ≥ 2.5 times upper limit of normal
9. Acute decompensation of glycaemic control requiring immediate intensification of treatment to prevent severe metabolic dysregulation (e.g. diabetes ketoacidosis) in the previous 90 days prior to the day of the screening
10. Family or personal history of Multiple Endocrine Neoplasia Type 2 or Medullary Thyroids Carcinoma
11. History of pancreatitis (acute or chronic)
12. Any of the following: myocardial infarction, stroke or hospitalization for unstable angina and/or transient ischaemic attack within the past 180 days prior to the day of screening
13. Subjects presently classified as being in NYHA Class IV
14. Planned coronary, carotid or peripheral artery revascularisation
15. Inadequately treated blood pressure as defined as Class 2 hypertension or higher (systolic ≥ 160 mmHg or diastolic ≥ 100 mmHg) at screening
16. Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria in a period of 90 days before the day of screening
17. Anticipated initiation or change in concomitant medications for more than 14 consecutive days or on a frequent basis known to affect weight or glucose metabolism (e.g. orlistat, thyroid hormones, corticosteroids)
18. Proliferative retinopathy or maculopathy requiring acute treatment as verified by fundus photography or dilated fundoscopy performed within 90 days prior to randomisation
19. History or presence of malignant neoplasms within the last 5 years (except basal and squamous cell skin cancer and in-situ carcinomas)

6.4 Premature discontinuation of trial product

All efforts should be made to keep the subjects on trial product. In case a subject stops taking the trial product the subject should be encouraged to re-commence the treatment.

The trial product must be discontinued if the subject meets rescue criteria or if following applies:

- Investigator suspect acute pancreatitis. All drugs suspected to relate to this condition must be discontinued until confirmatory tests have been conducted and appropriate treatment should be initiated

The trial product must be permanently discontinued if the following applies:

- Included in the trial in violation of the inclusion and/or exclusion criteria
- HbA_{1c} is $\geq$ 7% measured at 2 consecutive visits from week 26 (including week 26 if HbA_{1c} was $\geq$ 7% at week 12)
- Pregnancy
- Intention of becoming pregnant
- Participation in another clinical trial throughout the trial
- In case the calcitonin value is $\geq$ 50 ng/L. Please see Appendix B
- Initiation or significant change in concomitant medications (in excess of 14 days) which in the investigator's opinion could affect weight or glucose metabolism
- Subjects that are diagnosed with acute pancreatitis (as a minimum 2 of 3: characteristic abdominal pain, amylase and/or lipase > 3x upper normal range or characteristic findings on ultrasound, computerised axial tomography/magnetic resonance imaging)

Permanent premature discontinuation of treatment with trial product will not lead to subject withdrawal from the trial. Trial product may be permanently discontinued at the investigator's discretion in case of a safety concern, unacceptable intolerability, or if a subject is judged to be non-compliant with trial procedures.

6.4.1 Rescue criteria

If the fasting SMPG values taken on 3 consecutive days or if any of the FPG samples analysed by the central laboratory exceeds the limit of:

- 15.0 mmol/L (270 mg/dL) from baseline to week 6,
- 13.3 mmol/L (240 mg/dL) from week 7 to week 12,
- 11.1 mmol/L (200 mg/dL) from week 13 to week 26,

and if no treatable intercurrent cause for the hyperglycaemia has been identified, the subject must be called for a confirmatory FPG measurement as soon as possible. A confirmatory FPG must be obtained and analysed by the central laboratory. If this FPG exceeds the limits described above, the subject must discontinue treatment with trial product.

See procedures for premature discontinuation further described in section 8.1.

6.5 Withdrawal of consent

The subject may withdraw at will at any time.

A subject who agrees to provide information concerning morbidities which are relevant for the assessments of cardiovascular outcomes or other serious adverse events (SAE) at the planned end of the trial is not to be considered withdrawn from the trial. These subjects should be followed as "premature discontinued of trial product", see section 6.4.

Only subjects who decline any further contact with the site in relation to the trial, and hence do not agree to report information which is relevant for the assessments of cardiovascular outcomes or other SAEs at the EOT should be considered as withdrawn from the trial.

Subjects who consider withdrawing informed consent should as a minimum be encouraged to have procedures performed according to EOT visit 13 and the 2 follow up contacts (see section 2).

Please see section 8.1 for procedure to be performed in case of subject withdrawal.

6.6 Subject replacement

Subjects who are withdrawn or permanently discontinue trial product will not be replaced.

6.7 Rationale for trial population

Subjects with T2DM which have inadequate glycaemic control with metformin ± other OAD(s) in need of treatment intensification to achieve glycaemic control are the target population for inclusion in the trial.

Eligible subjects will have an HbA_{1c} level of 7.0-11.0% (53-97 mmol/mol), both inclusive in order to include a T2DM population with OAD(s) who are not optimally controlled on their current treatment. These subjects may benefit from a treatment regimen with anticipated less risk of hypoglycaemia and weight gain, when IDegLira treatment is added.

Stable diabetes treatment for 90 days prior to trial enrolment in combination with inadequately controlled diabetes ensures that subjects are in need for treatment intensification. In addition, this is chosen in order to avoid previous change in medication that can influence the glucose metabolism during the first weeks of the trial.

The BMI limit of ≥ 20 kg/m^2 is chosen to include as broad a population as possible representative of a T2DM population.

7 Milestones

Planned duration of recruitment period (i.e. first subject first visit (FSFV) – last subject first visit (LSFV)): 32 weeks.

End of trial is defined as last subject last visit.

Recruitment:
Recruitment will be closed as soon as the total number of planned subjects to be randomised is achieved, taking the number of screened subjects and the screening failure rate into account.

The screening and randomisation rate will be followed closely via IWRS in order to estimate when to stop screening. All investigators will be notified immediately when the recruitment period ends, after which no further subjects may be screened and the IWRS will be closed for further screening. All subjects included in the screening period and eligible for randomisation can be randomised.

Trial registration:
Information of the trial will be disclosed at clinicaltrials.gov and novonordisk-trials.com. According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure[12], it will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE)[13], the Food and Drug Administration Amendment Act (FDAAA)[14], European Commission Requirements[15, 16] 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

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

8.1 Visit procedures

Investigator assessments

Review of diaries, questionnaires, laboratory reports, ECGs, eye examinations, physical examinations etc. must be documented with the investigator´s dated signature either on the front page of the documents and/or in the subject´s medical record. The signed documents must be retained at the trial site as source documentation.

Visit schedule

It is the responsibility of the investigator to ensure that all site visits and phone contacts occur according to the flow chart (section 2). A phone contact may be converted to a site visit, if needed.

All visit dates are calculated in relation to visit 2 (randomisation) except for visit 14 (FU1) which should take place 7 days (+ 3 days) after last dose of trial product. Likewise visit 15 (FU2) should take place 30 days (+ 3 days) after last dose of trial product.

8.1.1 Fasting requirements

Fasting is defined as at least 8 hours without food and drink intake, except for water and other prescribed medication. Trial product and other glucose lowering agents should be withheld on the day of the visit until blood sampling, fasting SMPG and body weight (if applicable) have been performed. Any other prescribed medication should be taken as usual. If the subject attends a fasting visit in a non-fasting state the blood sampling and body weight procedures should be re-scheduled within the visit window.

8.1.2 Screening (visit 1)

Informed consent process

Before screening, the investigator must provide the subject with verbal and written information about the trial. Informed consent must be obtained before any trial related activity, see section 18.2. The date of informed consent must be transcribed into the eCRF for all screened subjects.

Screening

Screening of subjects will be registered using IWRS (see section 10). Each subject will be assigned a unique 6-digit subject number which will remain the same throughout the trial. The first three digits in the subject ID number will consist of the site number and the last three digits of the subject ID number will indicate the individual subject number.

All inclusion and exclusion criteria must be reviewed and if any 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 the randomisation of the subject.

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

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

Screening failures

If a screened subject for any reason is not eligible the subject will be considered a screening failure. A screening failure session must be made in the IWRS. The case book must be signed.

For screening failures the screening failure form in the eCRF must be completed with the reason for not continuing in the trial. Serious and non-serious adverse events (AEs) from screening failures must be transcribed by the investigator into the eCRF. Follow-up of SAEs must be carried out according to section 12. Screening failures experiencing an AE that would otherwise qualify for adjudication will not be adjudicated as no trial product has been administered (See section 12).

Re-sampling or re-screening is not allowed if the subject has failed one of the inclusion or exclusion criteria. Exception to this is if the initial blood samples are lost or haemolysed and analysis is not possible at the central laboratory.

8.1.3 Randomisation (visit 2)

Randomisation must not take place more than 14 calendar days after visit 1. All results from screening assessments, including laboratory results, ECG and eye examination must be available and reviewed by the investigator and the inclusion/exclusion criteria must be carefully reviewed to ensure the subject is eligible prior to the randomisation.

Randomisation of subjects will be done using the IWRS (see section 10).

At visit 2 the trial product must be dispensed to the subject and the directions for use given orally and in writing. For further information on trial product and direction for use please see section 9. The subject should take the first dose of trial product at visit 2 after randomisation is done, if possible or on the day after randomisation. The date of the first dose of trial product should be recorded in the eCRF.

DPP-4 inhibitor and glinides must be discontinued at the day of randomisation.

8.1.4 Treatment initiation and titration

To optimise and maintain glycaemic control, the investigator should throughout the trial be in contact with the subject every 3rd month. After randomisation there will be a phone contact after 1 week and visits to the site after 2 and 4 weeks to assist the subjects in initiating the new treatment.

Treatment regimen

All subjects will start on 10 dose steps (10 units of IDeg and 0.36 mg of liraglutide) or 10 units of IGlar QD. Maximum dose for IDegLira is 50 dose steps (50 units of IDeg and 1.8 mg of liraglutide). There is no predefined maximum dose of IGlar.

Injection area

IDegLira or IGlar should be injected s.c. into the thigh, upper arm (deltoid area) or the abdomen. It is recommended that the chosen region is the same throughout the trial. Rotation of injection sites within a given region is preferable.

Time of injection

IDegLira or IGlar should be injected QD at any time of the day, but preferably at the same time of day throughout the trial.

Titration

Dose will be adjusted twice weekly by the subject 3-4 days apart. The investigator will evaluate the diary and prescribe dose at all contacts.

Titration should be performed based on the mean of 3 pre-breakfast SMPG values, measured on the day of the titration and the 2 previous days. Titration should preferably be performed on the same days of the week throughout the trial (E.g., Mondays and Thursdays). The dose adjustment will be performed according to Table 8–1.

Table 8–1 Twice weekly titration algorithm for trial products

Mean of 3 pre-breakfast plasma glucose mmol/L (mg/dL)	Twice weekly adjustments: IDegLira (dose steps) IGlar (units)
< 4.0 (< 72)	-2
4.0-5.0 (72-90)	No adjustment
> 5.0 (> 90)	+2

8.1.5 Diaries

At each site visit the subjects will be provided with a new diary. The diary must be collected at the next site visit, and retained at the site as source data in accordance with section 14. The investigator is only allowed to record the following data in the diary:

- Subject ID number
- Date and time of next visit or phone contact
- Prescribed dose of trial product
- Data from SMPG measurements from previous diary, if required to complete next dose adjustment
- Review signature

The subject must record the following information in the diary:

- Date, time and value of the daily fasting SMPG measurements
- Date, time and dose of trial product each day
- Date, time and value of the 9-point SMPG profile prior to visits 2, 7 and 13
- Hypoglycaemic episodes (see section 8.4.1)
- Any medical issues
- Any new/change in medication
- Work absence due to a medical issue

The diary must be reviewed by the investigator to ensure that AE´s, including medical issues and concomitant medication, are reported (see section 8.2.1 and 12).

The purpose of having the subject record date, time and value of the fasting SMPG measurements and date, time and dose of trial product daily is to secure optimal titration. All these daily data must be reviewed by the investigator who must consider whether the reported values from the SMPG measurements must be reported as hypoglycaemic episodes (see section 8.4.1). Only date, time and value of the fasting SMPG measurements and date, time and dose of trial product for the last 3 days prior to the visit/phone contact should be transcribed into the eCRF. All other data entered by the subject in the diary should be transcribed into the eCRF.

The investigator should transcribe the diary data to the eCRF as soon as possible, preferably within 5 calendar days after each site visit or phone contact. Safety data from the diaries must be handled

according to the timelines described in Figure 12–1 . If data is obtained via phone and a discrepancy is later detected, the values in the eCRF should be corrected according to the diary.

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

Laboratory assessments

The laboratory analyses will be handled by a central laboratory. Descriptions of assay methods, laboratory supplies and procedures for obtaining samples, handling, transportation and storage of biological samples and information regarding who will perform the assessments, will be described in a trial specific laboratory manual, provided by the central laboratory (for central laboratory details, see Attachment I).

Laboratory samples not drawn on the day of the actual visit should preferably be drawn on another day within the visit window (flow chart section 2). For some of the samples drawn during the trial the subject must be fasting, see the flow chart section 2 and fasting requirements in section 8.1.

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

The laboratory equipment may provide analyses not requested in the protocol but produced automatically in connection with the requested analyses according to specifications in the laboratory standard operating procedures. Such data will not be transferred to the trial database, but abnormal values will be reported to the investigator.

Brazil: All laboratory results from Brazilian subjects must be provided to the investigator.

Laboratory results will be provided by the central laboratory to the investigator on an ongoing basis. For laboratory results outside the normal range the investigator must specify an evaluation on the laboratory report. The evaluation must follow the categories:

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

The investigator must review all laboratory results for concomitant illnesses and AEs and report these according to this protocol (see section 8.2.1 and section 12). The review of laboratory reports must be documented either on the documents and/or in the subject's medical record. The laboratory report must be evaluated as soon as possible and signed and dated by the investigator on the day of evaluation. The signed report must be retained at the site as source documentation.

The investigator should ensure that all laboratory samples for the subject are shipped to the laboratory immediately after the samples from visit 1 and visit 13 (or visit 13A for prematurely discontinued subjects) have been collected.

All samples will be destroyed on an ongoing basis after the analysis or at the latest at the completion of the clinical trial report (CTR).

8.1.6 Follow up visits (visit 14 and 15)

FU1 should be scheduled 7 days (+ 3 days) after last dose of trial product and FU2 should be scheduled 30 days (+ 3 days) after last dose of trial product. At FU1 information on antidiabetic treatment, any AEs and hypoglycaemic episodes occurring since visit 13 must be collected and recorded in the eCRF. At FU2 information on antidiabetic treatment and any MACE occurring since visit 13 must be collected and recorded in the eCRF.

8.1.7 Unscheduled visits

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

- An AE occurs that needs further attention
- Additional laboratory samples are needed due to an AE requiring special forms in the eCRF (see section 12.2)
- A confirmatory pregnancy test is needed
- A blood re-sampling related to a specific visit (if not possible to schedule the re-sampling within the visit window). Only if initial blood sample for some reason was not able to be analysed
- Confirmatory FPG test for rescue criteria evaluation

For 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 trial site 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 the data must be entered to the eCRF for the corresponding visit. Also, additional trial product dispensing or auxiliary supply dispensing does not require the use of the unscheduled visit form. An additional dispensing session should be made in the IWRS prior to additional trial product dispensing.

8.1.8 Premature discontinuation of trial product

Subjects discontinuing trial product prematurely due to any of the criteria for premature discontinuation of trial product (see section 6.4) will be called in for an EOT visit corresponding to visit 13 as soon as possible after discontinuation of trial product (i.e., day of last dose of trial product). Subject will be asked to bring the current diary and all dispensed trial product. FU1 and FU2 should be performed as described in section 8.1.6.

Once FU1 and FU2 are completed a phone contact should be performed every 3rd month. Information of antidiabetic treatment and any SAEs occurring since last contact must be collected and recorded in the eCRF. Phone contact must be documented in the medical record and eCRF. The subject must finally come in for a visit 13A at week 104 to report antidiabetic medication, SAEs and have a blood sample taken to measure HbA_{1c}.

Final drug accountability must be done once the subject has discontinued the trial product and the premature discontinuation must be recorded in the IWRS through a treatment discontinuation session.

The reason for the premature discontinuation of trial product must be recorded in the eCRF.

8.1.9 Withdrawal of consent

If a subject decides to withdraw from the trial, the investigator should aim to undertake procedures similar to those for visit 13, FU1 and FU2 (see section 8.1.6) as soon as possible after the last dose of trial product.

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

8.2 Subject related information

Demography

Demography consists of:

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

8.2.1 Concomitant illness and medical history

A **concomitant illness** is any illness that is present at the start of the trial (i.e. at visit 1) or found as a result of a screening procedure. Concomitant illness includes any pre-planned procedures, surgery and any intermittent illness (e.g. allergies) that may not be apparent at the time of screening. T2DM should not be recorded as concomitant illness. 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.

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.

Diagnosis of diabetes is an account in the eCRF of the date of diagnosis of diabetes.

Diabetes treatment history/diabetes complication is an account in the eCRF where information about current diabetes treatment, dose of current diabetes treatment, start date of current diabetes treatment is collected. It is also an account in the eCRF of medical events and complications related to diabetes i.e. diabetic retinopathy/neuropathy/nephropathy and macro angiopathy (including peripheral vascular disease). Details of all relevant diabetes complications must be recorded at trial entry (i.e. at screening visit). The information collected for diabetes complications should include diagnosis and date of onset.

Family history of diabetes is an account in the eCRF where information about the family history of diabetes is collected.

8.2.2 Concomitant medication

A **concomitant medication** is any medication, other than IDegLira or IGlar which is taken during the trial, including the screening and follow-up periods.

Details of any concomitant medication must be recorded at visit 1. Changes in concomitant medication must be recorded at each visit as they occur.

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

If a change is due to an AE, then this must be reported according to section 12. If the change influences the subject's eligibility to continue in the trial, the monitor must be informed. Please see section 6.4.

8.2.3 Smoking status (Tobacco use)

Details of smoking status must be recorded at visit 1. 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.

8.3 Assessments for efficacy

Body measurements

Height
Height is measured without shoes in centimetres (cm) or inches (inch) and rounded to the nearest cm or inch.

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

Body Mass Index (BMI)
BMI will be automatically calculated in the eCRF once height and weight are entered.

8.3.1 Self-measured plasma glucose

At visit 1 the subjects will be provided with a BG meter including lancets, plasma-calibrated test strips and control solutions as well as instructions for use. The subjects will be instructed in how to use the device and the instruction will be repeated as necessary during the trial.

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

Subjects should be instructed in how to record the results of the SMPG values in the diaries.

Quaque die
Subjects should perform QD SMPG measurements in a fasting state. For definition of fasting state see section 8.1. Diabetes medication (including trial products) should be withheld until after the measurement.

9-point profile
Subjects should perform SMPG measurements and record the obtained values for a 9-point profile within a week prior to visit 2, 7 and 13 on a day where the subject does not anticipate unusual strenuous exercise.
The SMPG values obtained from the measurements should be recorded in the diary (including clock time and date for the measurement) at the following time points, always starting with the pre-breakfast measurement:

- Before breakfast (this will be the SMPG of that day)
- 90 min after the start of the 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 (this will be the SMPG of that day)

8.4 Assessments for safety

Adverse events (AEs)
All AEs must be collected and reported according to the procedures described in section 12.

Adverse Events requiring special forms in the eCRF
For some AEs the investigator must fill in special forms in the eCRF. The AEs that require special forms in the eCRF are:

- Cardiovascular events
- Pancreatitis
- Neoplasms
- Thyroid disease

In case any of these events fulfil the criteria for a SAE, please report accordingly. See section 12.2.

Cardiovascular events
Cardiovascular events that are suspected as being related to one of the three categories below should be reported on the designated form in the eCRF:

1. Acute coronary syndrome
All types of myocardial infarction (MI) or hospitalisation for unstable angina, for further information (see Appendix A). If an event of acute coronary syndrome is observed during the trial, this must be recorded as an AE and on a specific acute coronary syndrome form in the eCRF. The following information must be reported if available:

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

2. Cerebrovascular events, e.g., stroke or transient ischemic attack (TIA)

If a cerebrovascular event is observed during the trial, this must be recorded as an AE and on a specific cerebrovascular event form in the eCRF. The following information must be reported if available:

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

3. Heart failure

If an event of heart failure requiring hospitalisation (admission to an in-patient unit or a visit to an emergency department that results in at least a 24 hour stay) is observed during the trial, this must be recorded as an SAE and in addition on a specific cardiovascular event form in the eCRF.
The following information must be reported if available:

- Signs and symptoms of heart failure
- NYHA Class
- Supportive imaging
- Supportive laboratory measurements
- Initiation or intensification of treatment for this condition

Pancreatitis

If a subject is diagnosed with pancreatitis during the trial, this must be recorded as an AE and on a specific pancreatitis event form in the eCRF. The following information must be reported if available:

- Signs and symptoms of pancreatitis
- Specific laboratory test supporting a diagnosis of pancreatitis:
  - Amylase
  - Lipase
  - ALAT and ASAT
  - Bilirubins, total
  - Alkaline Phosphatase
- Imaging performed and consistency with pancreatic disease.
- Complications to the event
- Relevant risk factors for pancreatic disease including:
  - History of gall-stones
  - History of pancreatitis
  - Family history of pancreatitis
  - Trauma

Neoplasm

All events of neoplasm (excluding thyroid neoplasm, but including malignant neoplasm, in situ neoplasm and benign neoplasm) must be recorded as an AE and on a specific neoplasm event form in the eCRF. The following information must be reported if available:

- Type of neoplasm
- Symptoms leading to identification of event
- Diagnostic imaging
- Pathological examination results
- Treatment for the event
- Participation in screening programs
- Risk factors associated to the event

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. If an event of thyroid disease, including any thyroid neoplasms observed during the trial, this must be recorded as an AE and on a specific thyroid disease event form in the eCRF. The following information must be reported if available:

- History of thyroid disease
- Signs and symptoms leading to investigations of thyroid disease
- Specific laboratory tests describing thyroid function including:
  - Thyroid stimulating hormone (TSH)
  - Total and free triiodothyronine (T3) and thyroxine (T4) and Free Thyroid Index
  - Calcitonin
  - Thyroid Peroxidase antibodies
  - Thyroglobulin and Thyroglobulin antibody
  - TSH receptor antibody
- Diagnostic imaging performed and any prior imaging supporting the disease history
- Pathologic examinations
- Treatment given for the condition
- Risk factors identified
- Family history of thyroid disease

8.4.1 Hypoglycaemic episodes

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

All plasma glucose values:

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

should be reported in the diary according to the instructions below throughout the trial from visit 2 to visit 14.

Upon onset of a hypoglycaemic episode the subject is recommended to measure plasma glucose every 15 minutes until the SMPG value is > 3.9 mmol/L (70 mg/dL) or symptoms have been resolved in accordance to current guidelines.[17]

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

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

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

The record should include the following information:

- Start date and time of hypoglycaemic episode
- The plasma glucose level before treating the episode (if available) and any follow up measurements
  The lowest value measured during the hypoglycaemic episode will be reported as the plasma glucose value for the episode, the remaining values will be kept as source data
- Whether the episode was symptomatic (Yes/No)
  A hypoglycaemic episode starting without symptoms should be updated to symptomatic if the subject experiences symptoms later during the episode.
- Whether the subject was able to treat him/herself
  If the severity of a hypoglycaemic episode aggravates, only one hypoglycaemic episode should be reported reflecting the most severe degree of hypoglycaemia.
- Date, time and dose of last IDegLira/IGlar administration prior to the episode
- Date and time of last main meal (not including snacks) prior to the episode
- Whether the episode occurred in relation to physical activity
- Worsening of any concomitant illness (pre-existing illness)
- Any sign of fever or other acute disease
- Whether the subject was asleep when the episode occurred
  - If yes, whether the symptoms of the episode woke up the subject

The answer to the question: "Was the subject able to treat him/herself?" must be answered "No" for an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or

take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.[17]

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

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

- Who assisted in the treatment of the hypoglycaemic episode (i.e. medical person or non-medical person)
- Where the treatment was administered (in clinic/emergency room/ hospital or other. If the subject was treated in clinic/emergency room/hospital, whether they were transported in an ambulance or not)
- Type of treatment provided by other person (i.e. oral carbohydrates, glucagon, IV glucose or other)
- Were symptoms alleviated after administration of treatment?
- Factors contributing to the episode (i.e. physical activity, missed meal, diet changed, medication error (i.e. overdose, mix-up between products), miscalculation of insulin dose, other factors not listed or unknown)
- Did the subject experience seizure?
- Was the subject unconscious/comatose?
- Did the subject experience any of the following symptoms[18] (layman term used in the diary is specified in brackets if different from the protocol term)?
    - Autonomic: sweating, trembling, hunger or palpitations (rapid or irregular heart beat)
    - Neuroglycopenic: confusion, drowsiness, speech difficulty, visual disturbances, odd behaviour, impaired balance or incoordination (reduced ability to coordinate movement)
    - General malaise: headache or malaise (feeling discomfort/unease)
    - Other symptoms?

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

Low SMPG values for non-severe hypoglycaemic episodes not having a hypoglycaemic episode form completed within 7 days since the SMPG measurement should be reported on a hypoglycaemic episode form with as much information as possible. Novo Nordisk will not query for additional data except for the date, SMPG value and whether the subject was able to self-treat due to decreased validity of such data.[19, 20]

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

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

Please be aware that hypoglycaemic episodes should not be reported before any trial drug is given i.e., hypoglycaemic episodes should be reported from visit 2.

Technical compliants
Technical complaints must be collected and reported according to the procedures described in section 12.4

ECG (electrocardiogram)
A 12-lead ECG must be performed. The ECG must be interpreted, signed and dated by the investigator to verify that the data has been reviewed. The ECG at screening must be done at the latest at visit 2 and the results interpreted by the investigator prior to randomisation to determine the eligibility of the subject.
The evaluation must follow the categories:

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

An ECG performed within 2 weeks prior to visit 13 is acceptable, if results are available for evaluation at visit 13.

Eye examination
Eye examination (fundus photography/dilated fundoscopy) must be performed by the investigator, a local ophthalmologist or an optometrist according to local practise. Results of the eye examination must be interpreted, signed and dated by the investigator to verify that the data has been reviewed before randomisation and in order to determine the eligibility of the subject.
The evaluation must follow the categories:

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

If an eye examination has been performed within 12 weeks prior to visit 2 the procedure does not need to be repeated, if the results are available for evaluation at visit 2. If the eye examination is performed before the subject consented to participate in the trial, it must be stated in the subject's medical records that the procedure was not performed in relation to this trial.
If an eye examination has been performed within 2 weeks prior to visit 13 the procedure does not need to be repeated, if the results are available for evaluation at visit 13.

Physical examination

A 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

Vital Signs

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

At visit 1 the blood pressure must be measured 3 times and all 3 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).

8.5 Laboratory assessments

Blood and urine samples will be collected in accordance with the flow chart (section 2) and analysed by the central laboratory to determine levels of the laboratory parameters listed below:

Blood samples for efficacy

- Glucose metabolism: HbA_{1c}, fasting plasma glucose, beta cell function (fasting C-peptide and fasting human insulin). Note: Low FPG values reported by central laboratory should NOT be reported as hypoglycaemic episodes; however these should be reported as an AE related to the procedure (e.g. a FPG result of 2.9 mmol/L (52 mg/dL) should be reported as 'low plasma glucose of 2.9 mmol/L (52 mg/dL)')
- Fasting lipid profile**:** triglycerides, cholesterol, LDL cholesterol, HDL cholesterol, VLDL cholesterol, free fatty acids

Blood and urine samples for safety

- Haematology: Erythrocytes, haematocrit, haemoglobin, leucocytes, thrombocytes, differential count (eosinophils, neutrophils, basophils, monocytes and lymphocytes)
- Biochemistry: Amylase, lipase, ALAT, ASAT, alkaline phosphatase, albumin, bilirubins total, creatinine, potassium, sodium and calcium, ionized
- Hormones: Calcitonin. In case any calcitonin value at any time in the trial is ≥ 10 ng/L the algorithm in Appendix B must be followed
  Pregnancy test: Females of childbearing potential will have a human chorionic gonadotropin (hCG) serum pregnancy test performed. Urine pregnancy test using urine-sticks will be performed at site during the trial for females of childbearing potential if a menstrual period is missed or pregnancy is suspected. If a urine test is positive, a confirmatory serum-hCG test must be taken and sent to the central laboratory for analysis. It should be documented in the eCRF in an unscheduled visit, describing "pregnancy test" under "other"
- A urinalysis to determine the albumin/creatinine ratio. Urine will be collected at site and sent to the central laboratory for analysis

8.6 Other assessments

Questionnaires

The investigator is only allowed to fill in the headings of the questionnaires.

The investigator should check for empty fields in the questionnaires when returned by the subject. Review of the questionnaires must be documented either on the documents and/or in the subject's medical record.

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

All responses to the questionnaires must be transcribed into the eCRF.

Novo Nordisk baseline questionnaire

The Novo Nordisk baseline questionnaire: Barriers in Diabetes Treatment must be completed in accordance with the flowchart (section 2).

Patient reported outcomes

The following PRO questionnaires must be completed in accordance with the flowchart (section 2):

- SF-36v2[21]
- TRIM-D[22]

The PRO questionnaires should be completed at the same time point of the visit for all visits, e.g. before seeing the doctor.

8.7 Subject compliance

Throughout the trial, the investigator will remind the subjects to follow the trial procedures and requirements to ensure subject compliance. The investigator should assess the treatment compliance of the subject at each visit based on a review of glycaemic control, adherence of the visit schedule, completion of the subject diary including SMPG measurements. In addition, subject compliance will be assessed by monitoring of drug accountability. The unused amount of trial product will be assessed against the dispensed amount and, in case of discrepancies, the subject must be asked to clarify. If a subject is found to be non-compliant, the investigator will remind the subject of the importance of following the instructions given including taking the trial products as prescribed.

9 Trial supplies

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

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

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

9.1 Trial products

The following trial products are considered as investigational medicinal products and will be provided by Novo Nordisk A/S, Denmark:

Table 9–1 Investigational medicinal products

Investigational medicinal products	Strength	Dosage form	Route of administration	Container/ delivery device
Insulin Degludec/Liraglutide	100 units/mL + 3.6 mg/mL	Solution for injection	Solution for s.c. Injection	3 mL pre-filled PDS290 pen injector
Insulin Glargine	100 units/mL			3 mL pre-filled SoloStar®

Pre-trial OADs are considered as non-investigational medicinal products (NIMPs) and will not be supplied by Novo Nordisk, unless required by local law.
Slovakia: Pre-trial OADs and/or rescue medication used during the trial will not be supplied by Novo Nordisk, however these medications will be reimbursed by Novo Nordisk Slovakia s.r.o.
Argentina: NIMPs should be purchased or otherwise delivered to subjects in accordance with local health plans.

9.2 Labelling

The trial products will be labelled in accordance with Annex 13[23], local regulations and trial requirements.

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

The investigator must document that direction for use is given to the subject verbally and in writing at the first dispensing visit (visit 2). On all other dispensing visits the direction for use must be given in writing.

9.3 Storage

Storage and in-use conditions of the trial products are outlined in Table 9–2.

Table 9–2 Storage conditions for investigational medicinal products

Investigational medicinal products	Storage conditions (not-in-use)	In-use conditions	In-use time*
Insulin Degludec/Liraglutide	Store in refrigerator (2°C-8°C/36°F-46°F) Do not freeze Protect from light	Store below 30°C (86°F) Do not freeze Protect from light	Use within 3 weeks
Insulin Glargine		Do not store above 25°C US: Do not store above 30°C (86°F) Do not refrigerate Protect from light	Use within 4 weeks

* In-use time starts when the product is taken out of the refrigerator in the subject's home

The investigator must ensure the availability of proper storage conditions, and also 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 evaluated and approved for further use by Novo Nordisk. The investigator must take appropriate action to ensure correct storage.

9.4 Drug accountability and destruction

Drug accountability is the responsibility of the investigator.

Subjects must be 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) can be stored at room temperature and must be stored separately from non-allocated trial product. Drug accountability is performed by using the IWRS. Only dispensed DUNs returned by the subject (used/partly used or unused) are accounted for.

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

9.5 Auxiliary supplies

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

- Directions for Use for pen devices
- Needles for pen devices (needles used must not be longer than 8 mm)
- BG meters and BG meter auxiliaries

10 Interactive web response system

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

IWRS is used for:

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

It is important that the trial site dispenses the trial products allocated by IWRS in order to:

- Provide the correct trial product (correct DUN) according to randomisation and dispensing visits
- Secure available stock at site to cover the drug supply need for all enrolled subjects
- Ensure that no subjects receive trial product that will expire in between dispensing visits
- Secure that drug accountability is possible.

IWRS user manuals will be provided to each trial site.

11 Randomisation procedure and breaking of blinded codes

At the randomisation visit (V2) subjects will be randomised either to QD IDegLira or IGlar in combination with OAD(s). Dipeptidyl peptidase-4 (DPP-4) inhibitors and glinides must be discontinued at randomisation.

The randomisation will be carried out in a 1:1 manner using IWRS (500 subjects in each treatment arm).

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

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

- Pre-existing conditions, including those found as a result of screening procedures (pre-existing conditions should be reported as medical history or concomitant illness)
- Pre-planned procedures unless the condition for which the procedure was planned has worsened from the first trial related activity after the subject has signed the informed consent
- Non-serious hypoglycaemia is an AE, but is reported on a hypoglycaemic episode form instead of on an AE form, see section 8.4.1

The following three definitions are used when assessing an AE:

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

- **Causality**

Relationship between an AE and the relevant trial product(s):

  - **Probable** - Good reason and sufficient documentation to assume a causal relationship
  - **Possible** - A causal relationship is conceivable and cannot be dismissed
  - **Unlikely** - The event is most likely related to aetiology other than the trial product

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

Serious adverse event

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

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

A medical event of special interest (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 criteria.

1. Medication errors concerning trial products:

- Administration of wrong drug or use of wrong device
  Note: Use of wrong DUN is not considered a medication error unless it results in administration of wrong drug.
- Wrong route of administration, such as intramuscular instead of subcutaneous
- Administration of an overdose with the intention to cause harm (e.g. suicide attempt)
- 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 extent where clinical consequences for the trial subject were likely to happen as judged by the investigator, although they did not necessarily occur

When reporting a MESI (medication error), the following forms must be completed: the AE form, SIF and the specific medication error MESI form as described in section 12.2 and also illustrated in Figure 12–1.

Adverse events with additional data collection

AEs with additional data collection are AEs defined as critical for the evaluation of product safety. For these AEs the investigator must fill in additional forms in the eCRF. The AEs that require additional forms in the eCRF are:

- Cardiovascular events:
  - Acute coronary syndrome
  - Cerebrovascular event
  - Heart failure requiring hospital admission
- Pancreatitis
- Neoplasms
- Thyroid disease

For detailed information on AEs with additional data collection, see section 8.4.

Along with fatal events, certain events of interest will be adjudicated by an external independent Event Adjudication Committee (EAC) as described in section 12.7.2. For further information regarding definitions, rationales, and events that will be adjudicated see Appendix A.

Major Adverse Cardiovascular Event

A Major Adverse Cardiovascular Event (MACE) is any AE which can be categorised into the following groups:

- Cardiovascular Death
- Myocardial Infarction
- Hospitalization for Unstable Angina
- Transient Ischemic Attack and Stroke
- Heart Failure Event (requiring hospitalisation)
- Cardiac procedures
  - Interventional Cardiology
  - Peripheral Vascular Intervention
  - Stent Thrombosis

Technical complaints

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

- The physical or chemical appearance of trial products (e.g. discoloration, particles or contamination)
- 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 until the end of the post-treatment follow-up period. At FU1 all AEs must be collected. At FU2 potential MACE occurring in the period between visit 13 and FU2 must be collected.

Subjects discontinuing trial product prematurely (see section 6.4) will be contacted every 3rd month and asked for information about antidiabetic medication and serious adverse events (SAEs). These subjects should finally come in for a visit 13A at week 104, only to assess antidiabetic medication, SAEs and a blood sample to measure HbA_{1c}.
The events must be recorded in the applicable eCRF forms in a timely manner, see timelines below and Figure 12–1.

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

All AEs, 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: Current version of the Company Core Data Sheet or any updates hereof.
- IGlar: European Summary of Product Characteristics current version or any updates hereof.[5]

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

For AEs requiring additional information, a specific event form in addition to the AE form must be completed.

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

For AEs requiring adjudication, the event specific adjudication form must be completed.

The AE form for a non-serious AE not fulfilling the MESI or additional data collection criteria 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 SIF **within 5 calendar days** of the investigator's first knowledge of the SAE. SAEs with additional data collection: also the specific event form **within 14 calendar days** of the investigator's first knowledge of the AE. All forms must be signed **within 7 calendar days** from the date the information was entered in the eCRF
- **SAEs fulfilling the MESI criteria:** In addition to above, the MESI form **within 14 calendar days** of the investigator's first knowledge of the AE
- **Non-serious AE fulfilling the MESI criteria:** The AE form, and SIF and MESI form **within 14 calendar days** of the investigator's first knowledge of the event
- **Non –serious AEs with additional data collection:** The AE form and specific event form within **14 calendar days** of the investigator's first knowledge of the event
- **Events for adjudication**: Event Adjudication Document Collection Form must be completed **within 14 calendar days**. The investigator must provide the medical documentation **within 4 weeks** of event identification

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 enter the information on the appropriate forms in the eCRF.

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

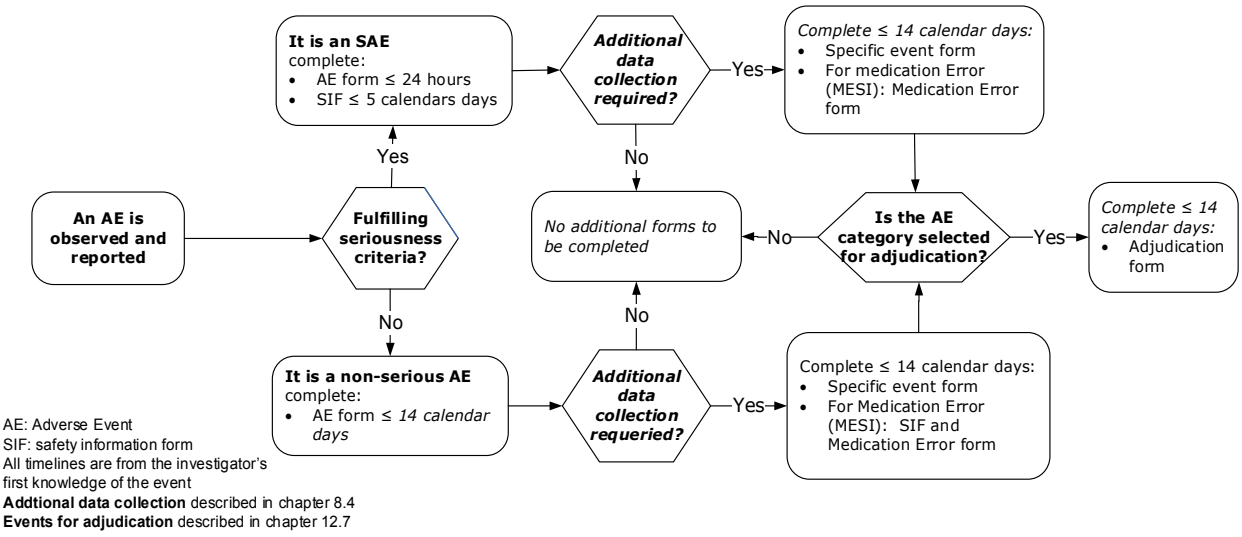


Figure 12–1 Initial reporting of AEs

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

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

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

12.3 Follow-up of adverse events

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

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

- **SAEs:** All SAEs must be followed until the outcome of the event is "recovered/resolved", "recovered/resolved with sequelae" or "fatal", and until all queries have been resolved. Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome "recovering/resolving" or "not recovered/not resolved". Cases can be closed with the outcome of "recovering/resolving" when the subject has completed the follow-up period and is expected by the investigator to recover. The SAE follow-up information should only include new (e.g. corrections or additional) information and must be reported **within 24 hours** of the investigator's first knowledge of the information. This is also the case for previously non-serious AEs which subsequently become SAEs

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

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

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

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

12.4 Technical complaints and technical complaint samples

12.4.1 Reporting of technical complaints

All technical complaints on any of the following products:
- IDegLira (100 units/mL + 3.6 mg/mL), 3 mL pre-filled PDS290 pen
- Novo Nordisk needles for prefilled pen
- IGlar (100 units/mL), 3 mL pre-filled Solostar®,

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. A technical complaint form for each batch or lot number or for each DUN must be completed.

The investigator must complete the technical complaint form in the eCRF within the following timelines of the trial site obtaining knowledge of the technical complaint:
- Technical complaint assessed as related to an SAE **within 24 hours**
- All other technical complaints within **5 calendar days**

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

12.4.2 Collection, storage and shipment of technical complaint samples

The investigator must collect the technical complaint sample and notify the monitor **within 5 calendar days** of obtaining the sample at trial site. The monitor must coordinate the shipment to Customer Complaint Center, Novo Nordisk 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 batch 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).

12.5 Pregnancies

12.5.1 Pregnancies in female subjects

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

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

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

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

1. **Reporting of pregnancy information**
   Information about the pregnancy and pregnancy outcome/health of the newborn infant(s) has to be reported on Maternal Form 1A and 1B, respectively.
   When the pregnancy outcome is abnormal (i.e. congenital anomalies, foetal death including spontaneous abortion and/or any anomalies of the foetus observed at gross examination or during autopsy), and/or when a congenital anomaly is diagnosed within the first month, further information has to be reported for the female subject on Maternal Form 2. In addition, information from the male partner has to be reported on the Paternal Form, after an informed consent has been obtained from the male partner.

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

2. Reporting of AE information

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

Forms and timelines for reporting AEs:

Non-serious AEs:

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

12.5.2 Pregnancies in female partners of male subjects (only applicable for US)

Male subjects must be instructed to notify the investigator if their female partner becomes pregnant during the trial, except in the screening period. At the last scheduled visit, male subjects must be asked if their female partner has become pregnant.

If a female partner has become pregnant during the trial, the investigator must follow-up on the pregnancy outcome and until the newborn infant is one month of age, irrespective of whether the trial is completed or not. The investigator must ask the male subject and assess, if the pregnancy outcome is normal or abnormal.

When the pregnancy outcome is **normal** this information is recorded in the subject's medical record only, no further information is collected and reported to Novo Nordisk. 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), the following must be reported by the investigator to Novo Nordisk electronically (e.g. in PDF format) or by fax:

1. **Reporting of pregnancy information**
   Information from the male subject has to be reported on the Paternal Form. Furthermore, information from the female partner (including information about the pregnancy outcome and health status of the infant until the age of one month) has to be reported on the Maternal Forms 1A, 1B and 2, after an informed consent has been obtained from the female 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 following AEs in the foetus and newborn infant have to be reported:
   - Non-serious AEs evaluated as possible/probably related to the father's treatment with the trial product(s)
   - SAEs in the foetus and newborn infant - whether or not related to the father's treatment with the trial product(s). This includes an abnormal outcome - such as foetal death (including spontaneous abortion) and congenital anomalies (including those observed at gross examination or during autopsy of the foetus)

Forms and timelines for reporting AEs:
Please see section 12.5.1, point 2, “Forms and timelines for reporting AEs”.

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 and death in worse case.

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 is flat and of somewhat longer duration than currently marketed long-acting insulin preparations. It may therefore take several hours more before stable normal BG is achieved after a hypoglycaemic episode when comparing to existing long acting insulin analogues.

Symptoms of minor hypoglycaemia should be treated with ingestion of carbohydrates. Severe hypoglycaemia resulting in loss of consciousness must be treated according to best medical practice (e.g. 25 mL of 50% dextrose solution given intravenously, or 0.5-1 mg of glucagon given s.c. or intramuscularly).

From clinical trials and marketed use of Victoza® 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 subjects 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[3] or any update hereof.

12.7 Committees related to safety

12.7.1 Novo Nordisk safety committee

Novo Nordisk has an internal IDegLira safety committee constituted to perform ongoing safety surveillance. The IDegLira 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 Event adjudication committee

An independent external EAC is established to perform qualitative validation of selected AEs according to pre-defined diagnostic criteria. The validation is based on review of pre-defined clinical data related to the specific AE. The events are reviewed by the EAC in a blinded manner.

The following AEs will be adjudicated in this trial:

- Fatal events
- Cardiovascular events:
  - Acute coronary syndrome
  - Cerebrovascular event
  - Heart failure requiring hospital admission
- Pancreatitis
- Neoplasms (all kinds of abnormal growth) excluding thyroid neoplasm
- Thyroid disease (thyroid neoplasm and/or thyroid disease requiring thyroidectomy)

Event adjudication will be performed for AEs in randomised subjects including AEs with an onset date during the screening period. Event adjudication will not be performed for AEs in screening failures.

The EAC is composed of permanent members who cover required medical specialities. The EAC members must disclose any potential conflicts of interest and must be independent of Novo Nordisk. The role of the EAC is solely to adjudicate events in a blinded manner. The EACs will have no authorisations to impact on trial conduct, trial protocol or amendments.

The EAC will review translated copies in English of medical documentation received in the adjudication packages (for example X-ray, ECGs, ultrasound images, discharge summaries, pathology reports, and death certificates). The EAC can evaluate an event, not initially reported as an AE for adjudication, to be adjudicated. The investigator must provide medical documentation as soon as possible, once the request from Novo Nordisk or the Event Adjudication vendor is received.

AEs for adjudication must be reported according to section 12.2. In addition the specific adjudication form should be completed **within 14 calendar days** of the investigator's first knowledge of the AE, and all relevant predefined documents provided according to instructions in the event adjudication site manual.

13 Case report forms

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

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

The following will be provided as paper CRFs:

- Pregnancy forms

In addition paper AE, technical complaint forms and SIF will be provided. These must be used when access to the eCRF is revoked or if the eCRF is unavailable.

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

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

13.1 Corrections to case report forms

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

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

13.2 Case report form flow

The investigator must ensure that data is recorded in the eCRF as soon as possible, preferably within **5 calendar days** after the visit. Once data has been entered, it will be available to Novo Nordisk for data verification and validation purposes. Queries will be generated on an on-going

basis and the investigator must ensure that queries are resolved as soon as possible, preferable within 5 calendar days.

The PRO questionnaires and the baseline questionnaire will be completed by the subjects on paper and data must be transcribed into the eCRF by the trial site staff.

At the end of trial the investigator must ensure that all remaining data have been entered into the eCRF no later than **24 hours** after the subject's last visit at the site. In addition, queries must be resolved immediately in order to ensure the planned lock of the database.

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 FSFV at the trial site and no later than 6 weeks after. The monitoring visit intervals will depend on the outcome of the remote monitoring of the CRFs, the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP, but will not exceed 12 weeks.

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 phone). 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.

The investigator is required to make a reasonable effort to obtain necessary additional information from external sources e.g. primary physician and other hospitals/departments to document the subjects' eligibility.

For SMPG measurements; only the values entered in the diary should be monitored as source data, although the BG meter can log a number of SMPG readings.

Source data generated by the trial site can be corrected by another person than the person entering the source data if accepted by local regulations; any correction must be explained, signed and dated by the person making the correction.The original diaries and questionnaires must be collected by the trial site and not be removed from the trial site.

The monitor will ensure that the CRFs are completed and that paper CRFs are collected. The following data will be source data verified for screening failures:

- Date for obtaining informed consent
- Screen failure reason

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

A follow-up letter (paper or electronic) will be sent to the investigator following each monitoring visit. This should address any action to be taken.

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. In cases where data is transferred via non-secure electronic networks, data will be encrypted during transfer.

The subject and any biological material obtained from the subject will be identified by subject number and trial ID. Appropriate measures such as encryption or leaving out certain identifiers will be enforced to protect the identity of subjects in all presentations and publications as required by local, regional and national requirements.

16 Computerised systems

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

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

17 Statistical considerations

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).

All efficacy endpoints and PRO 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. Endpoints that are analysed untransformed and endpoints that are not formally analysed are summarised by the arithmetic mean, standard deviation, 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. Observed data will be used as the basis for plotting data if not otherwise specified. Change from baseline plots will be based on Least Square Means and SEs estimated from the mixed model for repeated measurement (MMRM). For endpoints that are analysed log-transformed, the geometric mean values will be plotted. In addition, plots will be made showing mean curves by time of treatment discontinuation. All descriptive summaries and plots will be based on on-treatment data unless otherwise specified.

Only endpoints derived after 26 and 104 weeks of treatment will be analysed statistically.

Subjects withdrawing from the trial or discontinuing treatment will contribute to the primary analysis as needing rescue therapy from the time of withdrawal/discontinuation.

For secondary endpoints, the expected percentage of missing data after 26 weeks of treatment is around 5%. Due to the nature of the trial design, the expected percentage of missing data after 104 weeks of treatment is 40% and 60% for IDegLira and IGlar respectively.

If an assessment has been made both at screening and randomisation, and if not otherwise specified, the value from the randomisation visit will be used as the baseline value. If the value measured at the randomisation visit is missing and the assessment also has been made at screening, then the screening value will be used as the baseline value.

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

A MMRM with an unstructured covariance matrix, with testing performed at week 26 and 104 will be applied for secondary continuous endpoints. The model includes treatment, visit, HbA_{1c} group, pre-trial diabetes medication and region as fixed factors and the corresponding baseline value as a

covariate. Interactions between visit and all factors and the covariate are also to be included in the model.

The factor "baseline HbA_{1c} group" is a dichotomised baseline HbA_{1c} variable with 2 categories: HbA_{1c} <8.5% or HbA_{1c} ≥8.5%.

The factor "previous OAD treatment" has 2 levels: OAD(s) + sulphonylurea or OAD(s).

The factor "region" has 5 levels: Europe (Norway, Israel, Russia, Turkey, Italy, UK, Slovakia, Hungary, Czech Republic and Poland), North America (US), South America (Mexico, Brazil and Argentina), Africa (South Africa), and Asia (India).

In the following, this model will be referred to as the standard MMRM model. This analysis will estimate the difference in change from baseline in the endpoint between IDegLira and IGlar assuming that subjects remain on trial product until week 26 and 104, respectively. In this model it is assumed that data are missing at random which is a reasonable assumption since most missing data will arise from subjects withdrawing due to inadequate glucose control as observed at the time of withdrawal.

Presentation of results from a statistical analysis will include the estimated mean treatment effects (Least Square Means) 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 p-value.

17.1 Sample size calculation

The primary objective of this trial is to compare long-term glycaemic control of IDegLira vs. IGlar in insulin naïve subjects with T2DM inadequately controlled with OAD(s). This is established by comparing the time from randomization to the need for treatment intensification for IDegLira and IGlar using a stratified log-rank test.

Formally, let D be the hazard ratio for time to treatment intensification. The null-hypothesis of no treatment difference will be tested against the alternative hypothesis as given by

H0: D =1 against HA: D ≠1

The need for treatment intensification is determined as the HbA_{1c} ≥ 7% at 2 consecutive visits from week 26 (including week 26, if HbA_{1c} was ≥ 7% at week 12). Subjects withdrawing from the trial or discontinuing treatment will contribute to the primary analysis as needing rescue therapy from the time of withdrawal/discontinuation. The data will inherently be interval censored, since HbA_{1c} is only measured at the scheduled visits while subjects may reach an HbA_{1c} ≥ 7.0% at any time between 2 visits.

The sample size is based on time from randomisation to the need of treatment intensification, a 1:1 randomisation scheme, a 5% significance level and exponential survival.

Based on experience from the phase 3a development program for IDegLira and IDeg, it is assumed that around 45% in the IDegLira arm will need treatment intensification compared with around 55% in the IGlar arm during the 2-year treatment period. Subjects withdrawing from the trial or discontinuing treatment are included in these proportions as needing treatment intensification. Table 17–1 shows power calculations for varying effect sizes.

Table 17–1 Power for varying treatment differences

Percentage of subjects needing treatment intensification before end of trial	IDegLira: 40% IGlar: 55% HR: 0.65	IDegLira: 45% IGlar: 55% HR: 0.75	IDegLira: 50% IGlar: 55% HR: 0.86	IDegLira: 55% IGlar: 65% HR: 0.72
800 subjects	99%	83%	31%	85%
1000 subjects	>99%	90%	37%	92%

HR: hazard ratio

From these assumptions the sample size is set to 500 subjects per treatment arm; in total 1000 subjects will be randomised. This will provide 90% power to detect a hazard ratio of 0.75 for IDegLira relative to IGlar (i.e., a 25% reduction in the risk of needing treatment intensification) using a two group log-rank test and a two-sided significance level of $\alpha = 0.05$.

17.2 Definition of analysis sets

The following analysis sets are defined in accordance with the ICH-E9 guidance[1]:

Full Analysis Set (FAS): includes all randomised subjects. In exceptional cases, subjects may be eliminated from the FAS. In such cases the elimination will be justified and documented.

The statistical evaluation of the FAS will follow the intention-to-treat principle and subjects will contribute to the evaluation “as randomised”.

Safety Analysis Set (SAS): includes all subjects receiving at least 1 dose of the investigational product or comparator. Subjects in the safety set will contribute to the evaluation “as treated”.

Randomised subjects who are lost to follow up and where no exposure information of the investigational product or 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 reason(s) for their exclusion will be

documented and signed by all parties. The documentation will be stored together with the remaining trial documentation.

17.3 Primary endpoint

The following endpoint will be assessed up to 104 weeks. Time from randomisation to inadequate glycaemic control and need for treatment intensification defined as an $HbA_{1c} \geq 7\%$ at 2 consecutive visits from week 26 (including week 26, if HbA_{1c} was $\geq$ to 7% at week 12).

Subjects withdrawing from the trial or discontinuing treatment will contribute to the primary analysis as needing rescue therapy from the time of withdrawal/discontinuation. The data will inherently be interval censored, since HbA_{1c} is only measured at the scheduled visits while subjects may reach an $HbA_{1c} \geq 7.0\%$ at any time between 2 visits (including week 26 if HbA1c was > to 7% at week 12).

The primary endpoint will be analysed using a stratified log-rank test where treatment, baseline HbA_{1c} group and previous OAD treatment will be included as strata in the model.

The variable "baseline HbA_{1c} group" is a dichotomised baseline HbA_{1c} variable with 2 categories: $HbA_{1c} < 8.5\%$ or $HbA_{1c} \geq 8.5\%$.

The variable "previous OAD treatment" is a categorical variable with 2 categories: OAD(s) + sulphonylurea or OAD(s).

Formally, let D be the hazard ratio for time to treatment intensification. The null-hypothesis of no treatment difference will be tested against the alternative hypothesis as given by

H0: D =1 against HA: D ≠1

Kaplan-Meier curves by treatment arm and strata from the model will be presented.

Sensitivity analysis

The following two sensitivity analysis will be carried out.

The first sensitivity analysis will take the interval censored nature of the data into account by using a semi-parametric proportional hazards regression model for interval censored data. The chosen model can be viewed as an extension of Turnbull's method[24] from a non-parametric model to a semi-parametric proportional hazards models as described in Alioum.[25]

The log-likelihood function of the data under the proportional hazards assumption can be expressed as:
$\Sigma_{i=1,\ldots,n} \log (\Sigma_{j=1,\ldots,m} \mu_{ij}(S(p_{j-1})^{\exp(\beta zi)} - S(p_j)^{\exp(\beta zi)}))$,
where:

- μ_{ij} is 1 if subject i's observed interval encompass the j^{th} Turnbull interval and 0 if this is not the case
- p_j is the right endpoint of the j^{th} Turnbull interval
- zi is the covariate vector for subject i and β is the corresponding vector of regression coefficients
- S is the survivor function for individuals with covariate vector zi = 0, based on the Turnbull method, i.e. a survivor function whose positive mass is restricted to the Turnbull intervals but which otherwise is free of constrictions (non-parametric)

Baseline HbA_{1c} group and previous OAD treatment will be included in the model by stratification, i.e. when expressing the model with regards to the integrated hazard using the identity - $\log(S(t)^{\exp(\beta z)}) = \Lambda(t,z)$, we have $\Lambda(t,z) = \Lambda_f(t)\exp(\beta z)$, where Λ_f is the integrated baseline hazard for baseline HbA_{1c} and previous OAD treatment stratum f, f = (HbA_{1c} < 8.5% and OAD(s), HbA_{1c} < 8.5% and OAD(s) + sulphonylurea , HbA_{1c} ≥ 8.5% and OAD(s), HbA_{1c} ≥ 8.5% and OAD(s) + sulphonylurea), while treatment and region will be included as factors in the model.

The test of no difference between treatment groups will be performed using a likelihood ratio test.

In the second sensitivity analysis the time to inadequate glycaemic control and need for treatment intensification will be compared between the IDegLira arm and the IGlar arm using a two-sided nonparametric test at a 5% significance level. The test will be a generalised log rank test for interval censored failure time data.[26] The analysis will not be based on any model assumptions such as proportional hazards. The possible failure times will be considered as a discrete set of time points corresponding to the scheduled visits. An alternative but technically equivalent model would be to view the failure time as a continuous variable which can only be observed to lie in the interval between the visit when treatment failure is established and the previous scheduled visit.

17.4 Secondary endpoints

17.4.1 Supportive secondary endpoints

17.4.1.1 Efficacy endpoints

Time from randomisation to HbA_{1c} > 6.5% at 2 consecutive visits from week 26.
Time from randomisation to HbA_{1c} > 6.5% at 2 consecutive visits from week 26 (including week 26 if HbA_{1c} was ≥ 6.5% at week 12).will be analysed and presented in the same way as the primary endpoint.

HbA_{1c}
Change from baseline in HbA_{1c} after 26 weeks of treatment will be analysed using the standard MMRM model.

Body weight
Change from baseline in body weight after 26 and 104 weeks of treatment will be analysed using the standard MMRM model.

Insulin dose after 26 and 104 weeks of treatment
The actual insulin dose will be summarised descriptively according to regimen as dose in units, and units/kg. The actual daily insulin dose will be analysed using the standard MMRM model.

HbA_{1c} responder after 26 and 104 weeks of treatment (yes/no)
Two dichotomous endpoints (responder/non-responder) will be defined based on whether a subject has met a specific target level after 26 and 104 weeks of treatment:

- HbA_{1c} target < 7.0%[7]
- HbA_{1c} target ≤ 6.5%[27]

Analysis of each of the four responder endpoints will be based on a logistic regression model with treatment, HbA_{1c} group, previous OAD treatment and region as fixed factors and baseline HbA_{1c} value as a covariate. Subjects withdrawing from the trial or discontinuing treatment will be imputed as being non-responder from time of withdrawal/discontinuation in line with the evaluation of the primary endpoint.

HbA_{1c} responder endpoints without weight gain
Responder for HbA_{1c} without weight gain after 26 and 104 weeks of treatment will be defined as HbA_{1c}<7.0% or ≤6.5% and change in body weight from baseline ≤ 0. Analysis of each of the 2 responder endpoints will be based on a logistic regression model with treatment, HbA_{1c} group, previous OAD treatment and region as fixed factors and baseline HbA_{1c} and baseline body weight as covariates. Subjects withdrawing from the trial or discontinuing treatment will be imputed as being non-responder from time of withdrawal/discontinuation in line with the evaluation of the primary endpoint.

HbA_{1c} responder endpoints without treatment-emergent severe or BG confirmed symptomatic hypoglycaemic episodes
Responder for HbA_{1c} without treatment-emergent severe or BG confirmed symptomatic hypoglycaemic episodes after 26 and 104 weeks of treatment will be defined as HbA_{1c} < 7.0% or ≤6.5% and without treatment-emergent severe or BG confirmed symptomatic hypoglycaemic episodes during the last 12 weeks of each treatment period. Analysis of each of the 2 responder endpoints will be based on a logistic regression model with treatment, HbA_{1c} group, previous OAD treatment and region as fixed factors and baseline HbA_{1c} values as a covariate. Subjects withdrawing from the trial or discontinuing treatment will be imputed as being non-responder from time of withdrawal/discontinuation in line with the evaluation of the primary endpoint.

HbA_{1c} responder endpoints without treatment-emergent severe or BG confirmed symptomatic hypoglycaemic episodes and without weight gain

Responder for HbA_{1c} without treatment-emergent severe or BG confirmed symptomatic hypoglycaemic episodes and without weight gain after 26 and 104 weeks of treatment will be defined as HbA_{1c} <7.0% or ≤6.5% without treatment-emergent severe or BG confirmed symptomatic during the last 12 weeks of each treatment period, and change in body weight from baseline ≤ 0. Analysis of each of the 2 responder endpoints will be based on a logistic regression model with treatment, HbA_{1c} group, previous OAD treatment and region as fixed factors and baseline HbA_{1c} values and baseline body weight as covariates. Subjects withdrawing from the trial or discontinuing treatment will be imputed as being non-responder from time of withdrawal/discontinuation in line with the evaluation of the primary endpoint.

Fasting plasma glucose

Change from baseline in FPG after 26 and 104 weeks of treatment will be analysed using the standard MMRM model.

9-point profile

The following 6 endpoints from the 9-point SMPG profile will be defined:

- 9-point profile (individual points in the profile)
- Mean of the 9-point profile, defined as the area under the profile (calculated using the trapezoidal method) divided by the measurement time
- Prandial plasma glucose 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 MMRM will be fitted to the 9-point profile data where measurements within subjects will be assumed correlated using an unstructured residual covariance matrix. The model will include treatment, visit, time, region and treatment by time interaction as fixed factors and baseline value corresponding to each time as covariate. Interactions between visit and all factors and covariates are also being included in the model.

Change from baseline in mean of the 9-point profile and prandial increment endpoints will be analysed separately using the standard MMRM model.

Blood pressure (systolic and diastolic)

Change from baseline in systolic and diastolic blood pressure will be analysed separately using the standard MMRM model.

Fasting C-peptide and fasting human insulin

These endpoints will be analysed separately using the standard MMRM model.

Fasting lipid profile
Cholesterol, LDL cholesterol, HDL cholesterol, VLDL cholesterol, triglycerides and free fatty acids will be analysed separately using the standard MMRM model. In these statistical analyses, the endpoint will be log-transformed and so will the corresponding baseline covariate.

17.4.1.2 Safety endpoints

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

A TEAE is defined as an event that has onset date on or after the 1st day of exposure to trial product and no later than 7 days after the last day of trial product. If the event has onset date before the 1st day of exposure on trial product 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. MACEs are considered treatment-emergent until 30 calendar days after the last day of trial product.

TEAEs are summarised descriptively, whereas non-TEAEs are presented in listings. TEAE data will be displayed in terms of the number of subjects with at least 1 event (N), the percentage of subjects with at least 1 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 treatment discontinuation or withdrawal.

Furthermore summary tables based on system organ class and preferred terms are made for:
- All TEAEs
- Serious TEAEs
- TEAEs possibly or probably related to trial product
- Severe, moderate and mild TEAEs
- TEAEs reported by safety areas of interest
- TEAEs with preferred term that are experienced by at least 5% (1%) of the subjects in any treatment arm or by at least 5% (1%) of all subjects

A listing for non-TEAEs with onset date before the first day of exposure to trial product will be presented. A listing will also be presented for non-TEAEs collected after the treatment-emergent period according to the definition of TEAE. All summaries will be prepared for TEAEs during 26 and 104 weeks of treatment separately.

Additional summaries will be displayed for MACEs collected between visit 13 and visit 13A for subjects who discontinue trial product prematurely.

Hypoglycaemic events
Data on treatment-emergent hypoglycaemic episodes are presented in terms of the number of subjects with at least 1 event (N), the percentage of subjects with at least 1 event (%), the number of events (E) and the event rate per 100 years (R).

Separate summaries are made by severity considering all severe or BG confirmed symptomatic hypoglycaemic episodes, nocturnal severe or BG confirmed symptomatic hypoglycaemic episodes and the ADA classification of hypoglycaemia. All summaries will be prepared for episodes during 26 and 104 weeks of treatment separately.

A negative binomial model with a log-link function and the logarithm of the time period in which a hypoglycaemic episode is considered treatment-emergent as offset will be used to analyse the number of treatment-emergent severe or BG confirmed symptomatic hypoglycaemic episodes during 26 and 104 weeks of treatment. The model will further include treatment, HbA_{1c} group, previous OAD treatment and region as fixed factors.

Number of treatment-emergent nocturnal severe or BG confirmed symptomatic hypoglycaemic episodes during 26 and 104 weeks of treatment will be analysed using the same model as used for the treatment-emergent severe or BG confirmed symptomatic hypoglycaemic episodes.

Clinical evaluation (eye examination, ECG and urine albumin/creatinine ratio)
Eye examination, ECG findings and urine albumin/creatinine ratio will be summarised descriptively, including:

- Summaries for each visit
- Change from baseline after 104 weeks of treatment

Pulse
Change from baseline in pulse will be analysed using the standard MMRM model.

Laboratory assessments (Biochemistry, Haematology and Calcitonin)
All laboratory parameters will be summarised descriptively.

The following tables will be presented:

- Shift tables from baseline to after 26 and 104 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. Summaries by visit and box plots will be based on data from scheduled visits. If a blood re-sample related to a specific visit is made, the first value will be used.

Shift and outlier tabulations as well as listings will include all recorded values, including values from unscheduled visits

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

- If the amylase or lipase baseline (at screening) value is > 3x upper normal range the information will be regarded as medical history for that subject

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 calendar days after the last day on trial product.

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

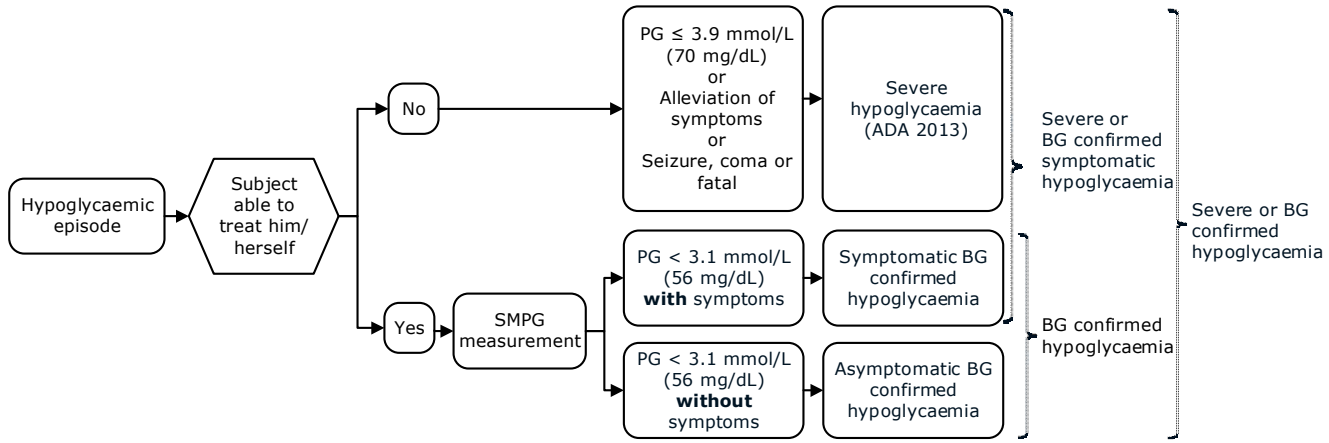
Hypoglycaemic episodes are classified according to the Novo Nordisk classification of hypoglycaemia (see Figure 17–1) and the ADA classification of hypoglycaemia (see Figure 17–2).

Novo Nordisk classification of hypoglycaemia

In normal physiology, symptoms of hypoglycaemia occur below a plasma glucose level of 3.1 mmol/L (56 mg/dL).[28] Therefore, Novo Nordisk has included hypoglycaemia with plasma glucose levels below this cut-off point in the definition of BG confirmed hypoglycaemia.

Novo Nordisk uses the following classification in addition to the ADA classification:

- Severe hypoglycaemia according to the ADA classification[29]
- Symptomatic BG confirmed hypoglycaemia: An episode that is BG confirmed by plasma glucose value < 3.1 mmol/L (56 mg/dL) **with** symptoms consistent with hypoglycaemia
- Severe or BG confirmed symptomatic hypoglycaemia: An episode that is severe according to the ADA classification[29] or BG confirmed by a plasma glucose value < 3.1 mmol/L (56 mg/dL) **with** symptoms consistent with hypoglycaemia



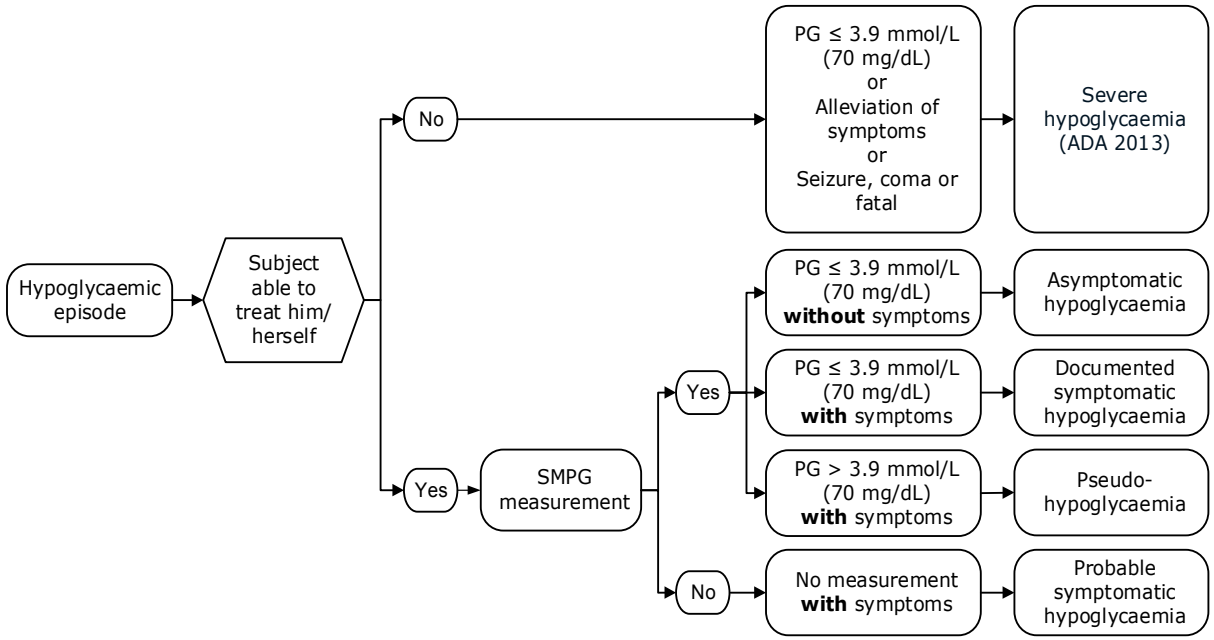
Note: Glucose measurements are performed with capillary blood calibrated to plasma equivalent glucose values

Figure 17–1 Novo Nordisk classification of hypoglycaemia

ADA classification[17] of hypoglycaemia

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

- Pseudo-hypoglycaemia: An episode during which the person with diabetes reports any of the typical symptoms of hypoglycaemia with a measured plasma glucose concentration > 3.9 mmol/L (70 mg/dL) but approaching that level
- Probable symptomatic hypoglycaemia: An episode during which symptoms of hypoglycaemia are not accompanied by a plasma glucose determination but that was presumably caused by a plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL)



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

Figure 17–2 ADA classification of hypoglycaemia

17.5 Health economics endpoints

The following questionnaires will be used to compare PROs between treatments:

- SF-36v2[21]
- TRIM-D[22]

For each questionnaire, the summary scores will be summarised descriptively by visit and the change from baseline in score will be analysed separately using the standard MMRM model.

18 Ethics

18.1 Benefit-risk assessment of the trial

IDegLira is a combination drug under development for treatment of T2DM, consisting of IDeg and liraglutide. IDegLira was developed to take advantage of the combined effects of a basal insulin and GLP-1 receptor agonist on glycaemic control through the complimentary actions on fasting glucose mediated by IDeg and liraglutide, and on postprandial glycaemic control mediated by liraglutide, in a single administration.

IDeg and liraglutide have shown to be effective in lowering BG levels. It can therefore be expected that the majority of subjects with insufficiently controlled BG, randomised to treatment with IDegLira or IGlar will experience an improved glucose control during the trial. In addition, the subjects treated with IDegLira may benefit from the effect of treatment on weight previously demonstrated for liraglutide.

The cumulative exposure to IDegLira from completed Novo Nordisk sponsored clinical trials is 1,881 subjects with T2DM and 97 healthy subjects.

Subjects who prematurely discontinue trial product will be offered the same visit schedule and an end of trial assessment. The subjects will have the right to withdraw from the trial at any time, without giving a specific reason. The subject and the investigator will decide on and initiate the best available treatment for the subject.

Randomised subjects will be treated with IDegLira or IGlar which are anticipated to be better than the OADs treatment they received prior to entering the trial, even though they will stop their DPP-4 inhibitors and glinides treatment at randomisation. All participating subjects will need to spend some extra time at the visits at the clinic, and some of the required tests performed during the trial are outside the normal practice.

Inclusion and exclusion criteria have been defined in order to ensure that subjects are eligible for trial participation at the time of enrolment. Furthermore, treatment discontinuation criteria are defined in order to adjust treatment if deemed necessary. The subject will be followed throughout the planned trial duration for safety reporting.

There is no information available today indicating that an overall risk associated with the use of IDegLira could exceed the risks associated with the use of the individual compounds.

The trial product may be associated with AEs, but relevant precautions have been implemented in the design and planned conduct of the trial in order to minimise the risks and inconveniences of participating in the trial. These precautions include thorough information regarding the correct administration of the trial product and gradual dose adjustment. Furthermore, subjects are fully

informed about possible AEs and inconveniences and will be instructed to contact the investigator in case of any concerns regarding the trial participation.

Clinical risk profile of IDegLira and risk mitigations for NN9068-4228

The following important potential and identified risks with IDegLira are derived from completed trials with IDegLira as well as from the development programmes of its individual components, IDeg and liraglutide, and all of which will be closely followed in this trial:

Identified risks

Hypoglycaemia

Hypoglycaemia is a pharmacological effect from insulin administration. The addition of liraglutide to IDeg has shown to reduce the requirement of exogenous insulin and hence minimise the risk of hypoglycaemia.

Immunogenicity (allergic reactions)

All peptide/protein based drugs have an inherent risk of allergic reactions. Allergic reactions are well known class effects for insulins and GLP-1 receptor agonists. Subjects with previous allergic reactions to IDeg or liraglutide will be excluded from the trial.

Pancreatitis

An association between the use of GLP-1 receptor agonists and pancreatitis has been suggested based on case reports received in clinical trials and during marketed use of drugs from this class. Even though a final conclusion regarding a causal relationship has not been established[30] a causal relationship is possible, and acute pancreatitis (acute or chronic) is therefore considered an identified risk for all GLP-1 receptor agonists. Subjects with history of pancreatitis will be excluded from the trial as a precaution.

There have been few clinical reported events of acute pancreatitis (inflammation of the pancreas) presenting with persistent severe abdominal pain (usually accompanied by vomiting) with liraglutide treatment. As a consequence of the known events of acute pancreatitis, Novo Nordisk will analyse blood samples for amylase and lipase during the trial to monitor the subjects' safety. Furthermore, participating subjects should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, IDegLira and other potentially suspected medicinal products will be discontinued.

Gastrointestinal adverse events

Gastrointestinal adverse events are considered class effects for GLP-1 receptor agonists and are among the most frequently reported events in patients treated with IDegLira. The gradual 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 NN9068-4228 is 0.36 mg, which is less than the starting dose of liraglutide when administered as the mono component (Victoza®).

Potential risks

Altered renal function

Dehydration due to known gastrointestinal effects associated with GLP-1receptor agonists may in rare cases be associated with renal impairment in predisposed subjects. Subjects treated with IDegLira should be advised of the potential risk of dehydration in relation to gastrointestinal side effects and take precautions to avoid fluid depletion. Furthermore, impaired renal function as defined in the protocol is an exclusion criterion in this trial. Monitoring of creatinine will be performed during the trial as part of standard safety laboratory surveillance.

Medullary thyroid cancer (C-Cell carcinogenicity)

Thyroid C-cell carcinogenicity has been reported in rats and mice treated with GLP-1 receptor agonists in non-clinical studies. Based on these findings, monitoring of serum calcitonin will be performed every 3rd month in the present trial. Subjects with thyroid disease will be closely monitored and in case of elevated calcitonin a recommendation for follow-up is included in Appendix B.

Neoplasm

Epidemiologic evidence suggests that subjects with T2DM are at higher risk for many forms of cancer. Moreover, evidence from observational studies indicates that some medications used to treat hyperglycaemia are associated with either increased or reduced risk of cancer. It is thus important to demonstrate, that new anti-diabetes therapies do not increase the inherent risk of neoplasms in the T2DM population. Neoplasms will be followed closely. All neoplasms will be adjudicated externally by an EAC.

Pancreatic cancer

Pancreatic cancer is included as a potential risk, due to the focus on the potential association with GLP-1-based therapies. There is currently no support from non-clinical investigations or clinical trials that GLP-1 receptor agonists increase the risk of pancreatic cancer.[31] GLP-1 receptor agonist treatment will be withdrawn in patients with suspicion of/diagnosed pancreatic cancer and appropriate treatment and monitoring will be initiated.

Epidemiologic evidence suggests that subjects with T2DM are at significantly higher risk for many forms of cancer.[32,33]

Cardiovascular disorders

T2DM is associated with an increased risk of cardiovascular disease, which is a major diabetic complication leading to death in this population. In the clinical development programme for

liraglutide and IDegLira, a mean increase in pulse (by 2-3 bpm) and a slight decrease in systolic blood pressure have been observed. The long-term clinical effects of the increase in pulse have not been established. Therefore, cardiovascular disorders are recognised as an important potential risk for IDegLira.

The following cardiovascular events will be followed closely: acute coronary syndrome, cerebrovascular event and heart failure requiring hospital admission. In addition, selected cardiovascular events and all cause death will be adjudicated by the EAC.

Lack of efficacy due to anti-IDeg or anti-liraglutide antibody formation

Consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals, subjects may develop anti-IDeg and anti-liraglutide antibodies following treatment with liraglutide and IDeg. Antibody formation seems to be of no consequence for the efficacy and the safety of liraglutide or current insulin preparations.

Medication errors, including errors with transfer from injectable diabetes therapy

Medication errors may occur due to lack of training before initiating IDegLira therapy, subjects unawareness of difference between IDegLira and other injectable diabetes therapy (insulin or GLP-1 receptor agonists) or distraction during preparation for injection. Mixing up IDegLira with different types of insulin may result in hypo- and/or hyperglycaemia. Mixing up IDegLira with a GLP-1 agonist may result in gastrointestinal disorders. Investigators should mitigate this risk by providing clear instructions of use and importance of not mixing two injectable treatments by understanding their difference in function.

In conclusion, no safety or tolerability issues of concern have been observed so far in the nonclinical and clinical programme for IDegLira that would prohibit further clinical development of this product. The development programme has not identified any risks associated with the use of IDegLira that are not already known from IDeg or liraglutide; for further information please see section 3.1. The benefits are therefore concluded to outweigh the risks, and the proposed use of IDegLira in trial NN9068-4228 is considered warranted.

Other

In reproduction and development toxicity studies liraglutide has been shown to be teratogenic in rats and rabbits including reduced growth and major abnormalities at systemic exposures below human exposure at the maximum recommended human dose of 1.8 mg/day. The US Victoza® Prescribing Information includes the Pregnancy Category C (US FDA Pharmaceutical Pregnancy Categories: “Animal reproduction studies have shown an adverse effect on the foetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks”). Due to this pregnant women and women with the intention to become pregnant, are excluded from the trial.

Dorsal skin sarcomas at the injection site were significantly increased in male mice at the highest liraglutide dose of 3 mg/kg/day. These fibrosarcomas were attributed to the high local concentration of drug near the injection site. The liraglutide concentration in the clinical formulation (6 mg/ml) is 10-times higher than the concentration in the formulation used in the carcinogenicity study (0.6 mg/ml). The observed increase in skin sarcomas in high-dose male mice is of unknown relevance for human safety.

Areas of special interest with regards to safety of trial product are described in detail in the IDeg IB[4] current version or any updates hereof, the liraglutide local approved labelling current version or any updates hereof and/or the IDegLira IB[3] current version or any updates hereof.

It is concluded that the potential benefits from participating in the trial outweigh the potential risks. The safety profile for the investigational medicinal products generated from the clinical and nonclinical development programme has not revealed any safety issues that would prohibit administration of those in accordance with the planned clinical trial.

18.2 Informed consent

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

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

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

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

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

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

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

In this trial additional informed consent must be obtained if:

- A female subject becomes pregnant during the trial, the male partner should be asked to sign a separate informed consent form (if abnormality is found in the foetus or new-born infant)
- A male subject report that his female partner has become pregnant during the trial, the female partner should be asked to sign a separate informed consent form (only applicable for the US)

In addition, all subjects will be asked to sign a separate informed consent form in order to give permission to collect cardiovascular information in case the subject withdraws. The subject will be asked to sign this additional informed consent when entering the trial and the cardiovascular information will be collected at the time of the initial planned EOT.

18.3 Data handling

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

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

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

18.4 Information to subject during trial

The subject may receive information provided to the site by Novo Nordisk, example of this may be a "thank you for your participation letter" after completion of the trial.

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

18.5 Premature termination of the trial and/or trial site

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

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

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

19 Protocol compliance

Deviations from the protocol should be avoided.

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

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

Documentation on protocol deviations must be kept in the investigator's trial master file and sponsor 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 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 (or a general assurance number/statement of compliance)
- Curricula vitae of investigator and sub-investigator(s) (current, dated and signed - must include documented GCP training or a certificate)
- Signed receipt of Investigator's Brochure or Summary of Product Characteristics
- Signed and dated Agreement on Protocol
- Signed and dated Agreement on Protocol Amendment, if applicable
- Contract, signed by the investigator and/or appropriate parties on behalf of the investigator's site and Novo Nordisk
- Source document agreement
- Central laboratory certification and normal ranges
- Insurance statement, if applicable
- Financial disclosure form from investigator and sub-investigator(s)

Only applicable for US trial sites:

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

FDA form 1572

For US sites:

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

For sites outside the US:

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

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

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

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

22 Responsibilities

The investigator is accountable for the conduct of the trial at his/her site. If any tasks are delegated, the investigator must maintain a log of appropriately qualified persons to whom he/she has delegated specified trial-related duties. The investigator must ensure that there is adequate 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 trial master file. The documents including the subject identification code list should be kept in a secure locked facility, so no unauthorized persons can get access to the data.

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

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

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

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

23 Reports and publications

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

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

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

One investigator will be appointed by Novo Nordisk to review and sign the clinical trial report (signatory investigator) on behalf of all participating investigators. The signatory investigator will be appointed based upon the criteria defined by the International Committee of Medical Journal Editors for research publications.[34]

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.[12]

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

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

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

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

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

23.1.1 Authorship

Authorship of publications should be in accordance with the Uniform Requirements of the International Committee of Medical Journal Editors[34] (sometimes referred to as the Vancouver Criteria).

23.1.2 Site-specific publications by investigators

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

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

23.2 Investigator access to data and review of results

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

Individual investigators will have their own research subjects' data.

24 Retention of clinical trial documentation

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

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

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

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

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

25 Institutional Review Boards/Independent Ethics Committees and regulatory authorities

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

During the trial, the investigator or Novo Nordisk, as applicable, must promptly report the following to the IRB/IEC, in accordance with local requirements: updates to 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 benefit-risk analysis in case it will have an impact on the planned follow-up of the subjects), annually written summaries of the trial status, and other documents as required by the local IRB/IEC.

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

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

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

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

26 Indemnity statement

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

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

Novo Nordisk accepts liability in accordance with:

Russia: Federal Law of 12 April 2010 No. 61-FZ "On Medicinal Drugs' Cerculation.

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

United Kingdom: The company sponsoring the research (the pharmaceutical company Novo Nordisk) carries product liability for its products. If products from Novo Nordisk cause bodily injury, legal liability will usually exist unless others have shown negligence. In the UK, compensation for any injury caused by taking part in this study will be in line with the guidelines of the Association of the British Pharmaceutical Industry (ABPI). Broadly speaking the ABPI guidelines recommend that the sponsor, Novo Nordisk, without legal commitment, should compensate you without you having to prove that it is at fault. This applies in cases where it is likely that an injury results from giving a new drug or any other procedure carried out in accordance with the protocol for the study. Novo Nordisk will not compensate you where injury results from giving a new drug or any other procedure in a manner which was not in accordance with the protocol for the study. Your right in law to claim compensation for injury where you can prove negligence is not affected. Copies of the ABPI guidelines are available on request.

27 References

1 International Conference on Harmonisation. ICH Harmonised Tripartite Guideline. Good Clinical Practice. 01 May 1996.

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11 KDIGO. 2012 Clinical Practive Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney International Supplements 2013; 3(1).

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Appendix A

Medical events of special interest, events with additional data collection and events requiring adjudication

Trial ID: NN9068-4228

DUAL™ VIII– Durability

A 104 week clinical trial comparing long term glycaemic control of insulin degludec/liraglutide (IDegLira) versus insulin glargine therapy in subjects with type 2 diabetes mellitus

Trial phase: 3b

1 Events with additional data collection and events requiring adjudication

Events with additional data collection and/or events requiring adjudication	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	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 • 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 unstable angina 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. **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

Events with additional data collection and/or events requiring adjudication	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
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)) Chronic pancreatitis will be defined by characteristic imaging finding (ultrasound, CT, MRI) with abnormal pancreatic function tests or characteristic histological findings.	Treatment with GLP-1 agonists has been associated with acute pancreatitis. Pancreatitis (including necrotising pancreatitis) is an identified risk according to the Company Core Data Sheet (CCDS) for liraglutide, a component of IDegLira. Novo Nordisk therefore monitors these events closely.	All events will be adjudicated

Events with additional data collection and/or events requiring adjudication	Definitions	Rationale	Event Adjudication Committee
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 a thyroid disease and should not be reported as a Neoplasm)	Neoplasm is an event we follow closely for GLP-1 analogues due to non-clinical findings in rats and mice treated with GLP-1 agonists.	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.	All thyroid neoplasms will be adjudicated. Thyroid disorders which require thyroidectomy will be adjudicated

2 Medical Events of Special Interest (MESI)

Medical Events of Special Interest	Definitions	Rationale	Event Adjudication Committee
Medication errors concerning trial products	1. Administration of wrong drug or use of wrong device. Note: Use of wrong DUN is not considered a medication error unless it results in administration of wrong drug. 2. Wrong route of administration, such as intramuscular instead of subcutaneous 3. Administration of an overdose with the intention to cause harm (e.g. suicide attempt) 4. 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 extent where clinical consequences for the trial subject were likely to happen as judged by the investigator, although they did not necessarily occur.	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

3 Reference

1 Hicks KA, Hung HMJ, Mahaffey KW, Mehran R, Nissen SE, Strockbridge NL et al. Standardized Definitions for Cardiovascular and Stroke End Point Events in Clinical Trials (DRAFT). 20 Aug 2014.

Appendix B

Monitoring of Calcitonin

Trial ID: NN9068-4228

DUAL™ VIII – Durability

A 104 week clinical trial comparing long term glycaemic control of insulin degludec/liraglutide (IDegLira) versus insulin glargine therapy in subjects with type 2 diabetes mellitus

Trial phase: 3b

1 Background

Treatment with GLP-1 receptor agonists has shown to be associated with thyroid C-cell changes in rodents but not in non-human primates. The human relevance of this finding is unknown. However, based on the findings in rodents, monitoring of serum calcitonin (a sensitive biomarker for C-cell activation) is currently being performed in clinical trials with insulin degludec/liraglutide (IDegLira).

While there is general agreement on the clinical interpretation of substantially elevated calcitonin levels (greater than 100 ng/L) as likely indicative of C-cell neoplasia, the interpretation of values between upper normal range (5.0 and 8.4 ng/L for women and men, respectively) and 100 ng/L is less clear with regards to indication of disease.

There are several known confounding factors affecting calcitonin levels, e.g.:

- renal dysfunction
- smoking
- autoimmune thyroiditis
- several drug classes (e.g. proton pump inhibitors, beta-blockers, H_2-blockers and glucocorticoids)

Physiology of C-cell activation in various clinical conditions and in different patient populations (i.e. with various co-morbidities) is poorly understood. There may be various clinical conditions not identified so far which mildly or moderately affect calcitonin secretion by C-cells.

2 Calcitonin monitoring

A blood sample will be drawn at pre-specified trial visits for measurement of calcitonin. Subjects with a calcitonin value ≥ 50 ng/L cannot be randomised according to protocol section 6.3. In case a subject has a calcitonin value ≥ 10 ng/L the algorithm outlined in Figure 1 and described below should be followed. The algorithm applies for all calcitonin values including screening values.

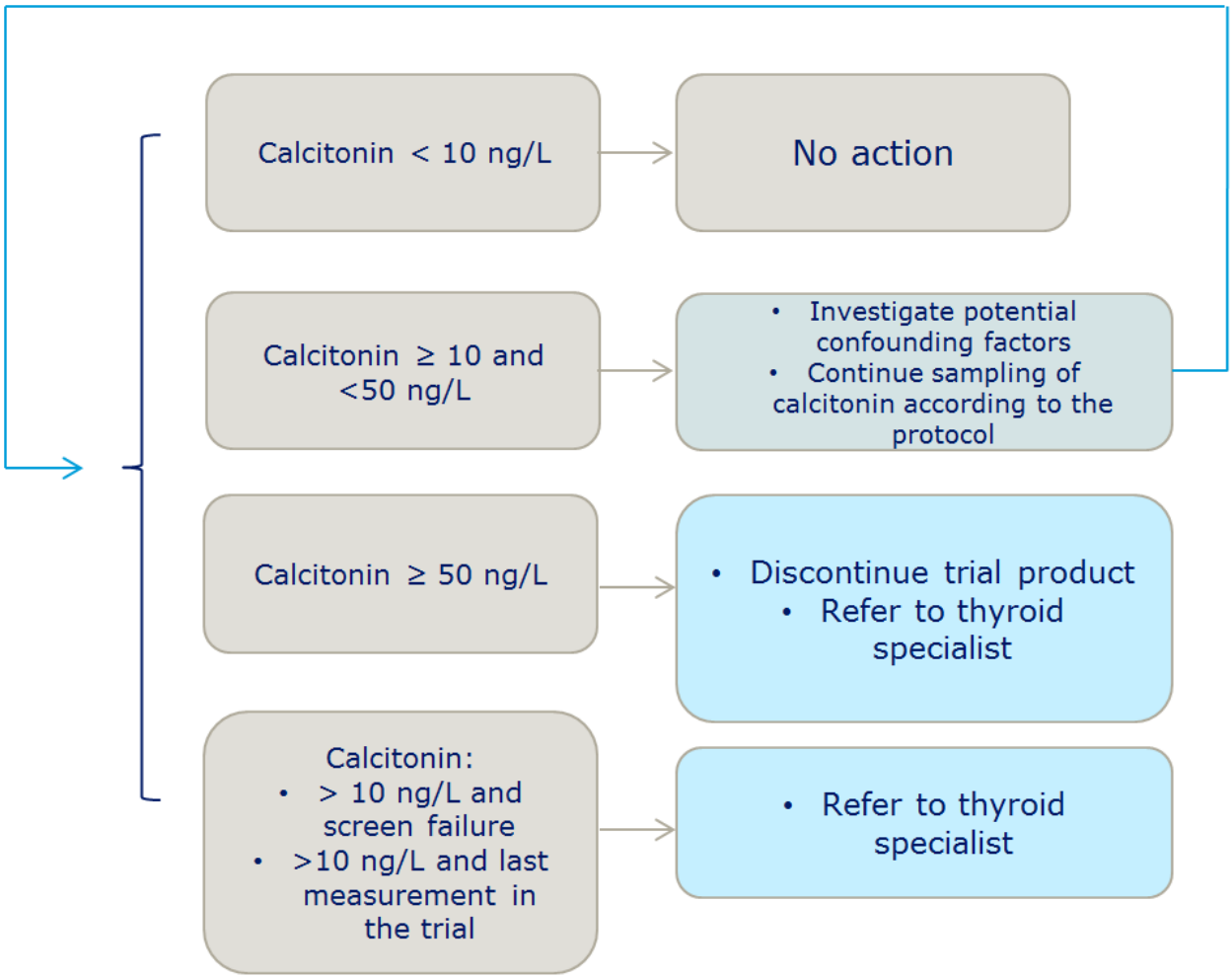

Figure 1 Flow of calcitonin monitoring

2.1 Calcitonin ≥ 100 ng/L

Action: The subject (even if a screen failure) must immediately be referred to a thyroid specialist for further evaluation and the trial product must be discontinued (see section 6.4 premature discontinuation of trial product). The subject can remain in the trial; however, all medications suspected to relate to this condition must be discontinued until diagnosis has been established.
Background: These values were found in 9 (0.15%) of a population of 5817 patients with thyroid

nodular disease[1]. All of these patients were diagnosed with MTC resulting in a positive predictive value of 100%.

Diagnostic evaluation should include:

- thyroid ultrasound examination
- fine needle aspiration of any nodules >1 cm
- potentially surgery with neck dissection

In case a subject is diagnosed with MTC, it is common clinical practice to explore the family history of MTC or MEN2 and perform a genetic test for RET proto-oncogene mutation.

2.2 Calcitonin ≥ 50 and < 100 ng/L

Action: The subject (even if a screen failure) should be referred to a thyroid specialist for further evaluation and the trial product should be discontinued. The subject can remain in the trial however; all medications suspected to relate to this condition should be discontinued until appropriate treatment has been initiated.

Background: These values were found in 8 (0.14%) of the population of 5817 patients with thyroid nodular disease [1]. Two of these subjects were diagnosed with MTC and two were diagnosed with C-cell hyperplasia, resulting in a positive predictive value of a C-cell anomaly of 50%.

Diagnostic evaluation should include:

- thyroid ultrasound examination
- if available no contraindication, a pentagastrin stimulation test. Subjects with positive pentagastrin stimulation tests should be considered to undergo surgery
- if pentagastrin is not available, thyroid ultrasound and fine needle aspiration biopsy may add important clinical information informing the need for surgery.

2.3 Calcitonin ≥ 10 and <50 ng/L

Action: The subject can continue in the trial on trial product. Continue sampling of calcitonin according to the protocol. If the subject is a screen failure or if the value is from the last sample taken in the trial, the subject should be referred to a thyroid specialist for further evaluation.

Background: Calcitonin values from 20-50 ng/L were found in up to 1% of subjects of the population of 5817 patients with thyroid nodular disease[1]. The predictive value of a C-cell anomaly for this calcitonin level was 8.3%. However, the likelihood of having a medullary carcinoma > 1 cm with calcitonin in this range is extremely low.
For calcitonin values 10-20 ng/L Costante et al[1] identified 216 (3.7%) patients. One patient out of the 216 had a subsequent basal (unstimulated) calcitonin of 33 ng/L, and had C-cell hyperplasia at surgery. Two other studies used a cut-off 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

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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 *1.0*
dated 10 July 2015

Trial ID:NN9068-4228

DUAL™ VIII – Durability

A 104 week clinical trial comparing long term glycaemic control of insulin degludec/liraglutide (IDegLira) versus insulin glargine therapy in subjects with type 2 diabetes mellitus

Trial phase: 3b

Applicable to *Mexico*

Amendment originator:

[redacted]

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Page

1 Introduction including rationale for the protocol amendment

The purpose of this amendment is to document clearly, objectively and explicitly guaranteed the gratuitous nature of the medical treatment for the Research Subject, and the compensation to which he/she will be entitled to in the event of suffering damages to his/her health directly attributable to the investigation, even in the event if he/she decides to withdraw or be withdrawn from such investigation.

The foregoing is supported in Articles 100, 101, 102 section IV, of the General Health Law; 14 sections I, VI, IX and X, 58 section III, 62 sections I, VIII and IX, and 115 of the Decree wherein there are amended, added and repealed several provisions contained in the Rulings of the General Health Law for Health Research Affairs; and numbers 4.6, 5.5, 5.7, 5.10, 6.2, 6.3.2.7, 7.2, 10.8, 11.1 and 11.2 of the NOM-012-SSA3-2012 providing criteria for execution of projects for health research in human beings.

In this protocol amendment:

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

2 Changes

2.1 Changes in Section 3 Background information and rationale for the trial

The following texts will be added to the protocol in page 15.

Mexico:

In the case of Mexico the above will include the following responsibilities for the head of the Institution/Health Care Establishment, Ethics, Research and, when applicable, Biosafety Committees and sponsor within their scope of responsibility:

a) *Investigation follow-up*

b) *Damages to health arising from the investigation development; as well as those arising from interruption or advanced suspension of treatment due to non-attributable reasons to the Subject;*

c) *Timely compliance of the terms in which the authorization of a research for health in human beings had been issued;*

d) *To present in a timely manner the information required by the Health Authority.*

2.2 Changes in Section 6.5 Withdrawal Consent

The following text will be added to the protocol in page 26.

For Mexico: should the subject his/her family members parents or legal representative decide to withdraw the consent for participation in the trial, the subject will be entitled to receive appropriate, free of charge medical care and/or trial drug during the follow up period of the protocol when it will be established with certainty that no untoward medical consequences of the subject´s participation in the research occurred.

2.3 Changes in Section 26 Indemnity statement

The following texts will be added to the protocol in page 92.

Novo Nordisk accepts liability in accordance with:

Mexico:

a) *Novo Nordisk carries product liability for its products assumed under the special laws, acts/and/or guidelines for conducting trials in any country, including those applicable provisions on the Mexican United States. If the subject feels that something goes wrong during the course of this trial, the subject should contact the trial staff in the first instance.*

b) *If during their participation in the trial the subject experiences a disease or injury that, according to the trial doctor and the sponsor, is directly caused by the study medication and/or a study procedure that otherwise would not have been part of his/her regular medical care, the subject will receive from the Institution or Medical Care Establishment and free of charge, the appropriate medical treatment as required. In this case, the costs resulting from such treatment as well as the costs of any indemnification established by law will be covered by the trial sponsor in accordance with the terms provided by all applicable regulations; even if the subject discontinues his/her participation in the study by his own will or by a decision from the investigator.*

c) *By signing the informed consent, the subject will not renounce to any compensation or indemnification he/she may be entitled to by law, nor will he/she will incur any additional expense as a result of his/her participation in the trial; any additional expense resulting from the subject's participation in the trial will be covered by the trial sponsor.*

Protocol Amendment

no *02*
to Protocol, final version *1.0*
dated 10-Jul-2015

Trial ID: NN9068-4228

A 104 week clinical trial comparing long term glycaemic control of insulin degludec/liraglutide (IDegLira) versus insulin glargine therapy in subjects with type 2 diabetes mellitus

Trial phase: 3b

Applicable to *Norway*

Amendment originator:

[redacted]

Table of Contents

1 Introduction including rationale for the protocol amendment

In this protocol amendment:

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

1.1 Rationale for the amendment

This amendment has been prepared in order to:

1. Clarify number of subjects.
2. Revise exclusion criterion no. 3 in order to follow CTFG[1] recommandations related to contraception and pregnancy testing in clinical trials (final version 2014-09-15).
3. Update risk benefit section with precautionary information about NYHA class III, inflammatory bowel disease and diabetic gastroparesis

2 Changes

2.1 Section 6.1 Number of subjects

Number of subjects planned to be screened: 1200
Number of subjects planned to be randomised: 1000
~~Mexico: 90 subjects are planned to be randomised/started on trial product in Mexico~~
Number of subjects expected to complete the trial (on trial product): 500

2.2 Section 6.3 Exclusion criteria

4. Female who is pregnant, breast-feeding or intend to become pregnant or of child-bearing potential not using ~~adequate~~ *highly effective* contraceptive methods (*highly effective* ~~adequate~~ contraceptive measures as required by local regulation or practice)

***Norway**: Highly effective methods are defined as established use of oral, injectable, transdermal, implantable or intravaginal hormonal methods of contraception associated with inhibition of ovulation, placement of an intrauterine device, female sterilisation, male sterilisation (where partner is sole partner of subject), or true abstinence (when in line with preferred and usual lifestyle).*

2.3 Section 18.1 Benefit-risk assessment for the trial

There is no information available today indicating that an overall risk associated with the use of IDegLira could exceed the risks associated with the use of the individual compounds. ***For Norway only:** Caution is advised when including patients with NYHA class III and the inclusion of patients with inflammatory bowel disease and diabetic gastroparesis is at the investigator's discretion.*

3 References

1 http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

Protocol Amendment

no *3*
to Protocol, final version 1.0
dated 10 July 2015

Trial ID:
NN9068-4228

DUAL™ VIII – Durability

A 104 week clinical trial comparing long term glycaemic control of insulin degludec/liraglutide (IDegLira) versus insulin glargine therapy in subjects with type 2 diabetes mellitus

Trial phase: 3b

Applicable to *all countries*

Amendment originator:

[redacted]

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Page

1 Introduction including rationale for the protocol amendment

In this protocol amendment:

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

1.1 Rationale for the amendment

This amendment has been prepared in order to:

1. In Section 5.3, remove the time constraint on the duration of OAD dose changes. The rationale for this is that it may be necessary to change the dose of OAD(s) for longer than 14 days due to safety reasons
2. Clarify inclusion criteria 7, concerning OAD treatment and which combinations are allowed in the trial
3. Replace the wording relating to the randomisation visit timeframe in section 8.1.3. The rationale for this change is that visit timeframes are specified in Section 2 Flowchart. In addition, an element of flexibility may be required to accommodate scenarios where an eligible patient is not able to attend for randomisation on day 14 due to force majeure
4. In section 6.4.1, remove sentence about rescue criteria as trial product should not be paused while awaiting the confirmatory FPG
5. Clarify the rescue criteria in order to make it clear that they apply after baseline visit meaning after initiation of treatment
6. In section 8.1.4, align with previous and current DUAL protocols, that titration should be based on the Investigators evaluation of the diary taking hypo-, hyperglycaemia etc. into consideration
7. Align wording in section 8.4.1 with the eCRF
8. Update that low FPG should be reported as Clinical Laboratory Adverse Event (CLAE) at the discretion of the investigator as per current protocol text
9. In section 8.6, align with the PRO Questionnaire that site staff can fill in the headings on the questionnaire forms not only the investigator
10. In section 12.1 update safety definition with current protocol template text
11. Remove time constraint in Figure 12 for reporting of non-serious AEs as per current protocol template text
12. Update drug accountability process to clarify accountability is to be performed on all trial products received at site as per new functionality in IWRS 3.1
13. Correct typographical errors

2 Changes

2.1 List of abbreviations

IRB/IEC Institutional Review Board~~s~~/Independent Ethics Committee~~s and regulatory~~

2.2 Section 2 Flowchart

Trial Periods	**Screening**	**Rand.**	**Treatment**										**EOT**	**FU1**	**FU2**	**Pre-disc[1]**	
Visit number (V), Phone contact (P)[2]	V1	V2	P3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	P15	PX	V13A
Timing of visit (weeks)	≤ 2 weeks prior to V2	0	1	2	4	12	26	38	52	64	78	90	104	7 days after EOT	30 days after EOT	Every 3rd month	104
Visit window (days)			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	+3	±3	±3
SUBJECT RELATED INFO/ASSESSMENTS																	
Informed consent	X																
In/exclusion criteria	X	X															
Randomisation		X															
Pre-discontinuation of trial product			X	X	X	X	X	X	X	X	X	X	X				
Rescue criteria			X	X	X	X	X										
Withdrawal of consent			X	X	X	X	X	X	X	X	X	X	X	X	X[3]	X	
Demography[4]	X																
Concomitant illness	X																
Medical history	X																
Diagnosis of diabetes	X																
Diabetes treatment history	X																
Diabetes complications	X																
Family history of diabetes	X																

[1] Subjects discontinuing trial product prematurely will be asked to attend the end of treatment visit and the 2 follow up visits after discontinuation corresponding to V13, V14 and P15. After the follow up period the subject should have phone contacts scheduled every 3rd month (PX) until the additional premature discontinuation follow up (V13A) visit performed at week 104. See section 8.1 for further details.
[2] A phone contact may be converted to a site visit if needed
[3] Only applicable for subjects discontinuing trial product prematurely
[4] Collection of sex and date of birth, race and ethnicity only if applicable by local law

Trial Periods	**Screening**	**Rand.**	**Treatment**										**EOT**	**FU1**	**FU2**	**Pre-disc[1]**	
Visit number (V), Phone contact (P)[2]	V1	V2	P3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	P15	PX	V13A
Timing of visit (weeks)	≤ 2 weeks prior to V2	0	1	2	4	12	26	38	52	64	78	90	104	7 days after EOT	30 days after EOT	Every 3rd month	104
Visit window (days)			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	+3	±3	±3
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X[5]	X5	X[6]	X6
Tobacco use (smoking status)	X																
EFFICACY																	
Glucose metabolism																	
Fasting plasma glucose		X			X	X	X		X		X		X				
HbA_{1c}	X	X				X	X	X	X	X	X	X	X				X
Fasting C-peptide		X					X						X				
Fasting human insulin		X					X						X				
Lipids		X					X		X				X				
Body measurements																	
Height	X																
Body weight[7]	X	X			X	X	X		X		X		X				
BMI	X																
Self measured plasma glucose																	
QD[8]		X	X	X	X	X	X	X	X	X	X	X	X				
9-point profile[9]		X					X						X				
SAFETY																	

[5] For subjects that have prematurely discontinued trial product only anti-diabetic medication will be collected
[6] Only concomitant medication with the indication diabetes will be collected
[7] Body weight should be measured fasting except for V1
[8] Subjects should measure QD Self measured plasma glucose (SMPG) fasting prior to breakfast. Diabetes medication should be withheld until after the SMPG measurement
[9] 9-point profile should be measured within 1 week prior to the site visit (on a day where unusual strenuous exercise is not anticipated)

Trial Periods	**Screening**	**Rand.**	**Treatment**										**EOT**	**FU1**	**FU2**	**Pre-disc[1]**	
Visit number (V), Phone contact (P)[2]	V1	V2	P3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	P15	PX	V13A
Timing of visit (weeks)	≤ 2 weeks prior to V2	0	1	2	4	12	26	38	52	64	78	90	104	7 days after EOT	30 days after EOT	Every 3rd month	104
Visit window (days)			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	+3	±3	±3
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[10]	X[11]	X11
Hypoglycaemic episodes		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				
ECG	X												X[12]				
Eye examination	X[13]												X[14]				
Physical examination	X												X				
Vital signs	X	X				X	X		X		X		X				
Biochemistry[15]	X	X					X		X				X				
Haematology[16]	X	X					X		X				X				
Hormones (calcitonin)	X	X				X	X	X	X	X	X	X	X				
Urinalysis (albumin:creatinine ratio)		X				X	X		X		X		X				
Pregnancy test[17]	X	(X)		(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	X				
OTHER ASSESSMENTS																	

[10] Only AE information for potential major adverse cardiovascular events (MACE) will be collected
[11] Only AE information for potential major adverse cardiovascular events (MACE) and SAE information will be collected
[12] ECG obtained within 2 weeks prior to V13 is acceptable if results are available for evaluation at V13
[13] Eye examination performed within 12 weeks prior to V2 as part of routine practice may replace the screening assessment if results are available for evaluation at V2
[14] Eye examination performed within 2 weeks prior to V13 is acceptable if results are available for evaluation at V13
[15] Amylase, lipase, ALAT, albumin, alkaline phosphatase, ASAT, bilirubins total, calcium ionized, creatinine, potassium and sodium
[16] Erythrocytes, haematocrit, haemoglobin, leucocytes, thrombocytes, differential count (eosinophils, neutrophils, basophils, lymphocytes and monocytes)
[17] For women of childbearing potential a blood sample pregnancy test (serum hCG) must be performed at V1 and V13. Additionally, a urine pregnancy test must 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 will have to attend the site for an unscheduled visit as soon as possible to have a urine pregnancy test performed. If positive, a confirmatory serum hCG must be sent to the central laboratory. If required by local law, pregnancy test may be performed regularly

Trial Periods	**Screening**	**Rand.**	**Treatment**										**EOT**	**FU1**	**FU2**	**Pre-disc[1]**	
Visit number (V), Phone contact (P)[2]	V1	V2	P3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	P15	PX	V13A
Timing of visit (weeks)	≤ 2 weeks prior to V2	0	1	2	4	12	26	38	52	64	78	90	104	7 days after EOT	30 days after EOT	Every 3rd month	104
Visit window (days)			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	+3	±3	±3
Barriers in Diabetes Treatment		X															
PRO questionnaires																	
TRIM-D		X					X						X				
SF36v2		X					X						X				
TRIAL MATERIAL																	
Dispensing trial product		X		X	X	X	X	X	X	X	X	X					
IWRS call	X	X		X	X	X	X	X	X	X	X	X	X				
Drug accountability		X		X	X	X	X	X	X	X	X	X	X				
REMINDERS																	
Hand-out ID card	X																
Training in trial product and pen handling.		X		X	X												
Hand-out directions for use		X		X	X	X	X	X	X	X	X	X					
Hand-out and instruct in diary	X	X		X	X	X	X	X	X	X	X	X	*X*				
Collect and review diary		X		X	X	X	X	X	X	X	X	X	X	X			
Hand-out BG meter	X																
Instruct in BG meter use	X	X		X													
Attend visit fasting		X			X	X	X		X		X		X				
Make appointment for eye examination												X					

Trial Periods	**Screening**	**Rand.**	**Treatment**										**EOT**	**FU1**	**FU2**	**Pre-disc[1]**	
Visit number (V), Phone contact (P)[2]	V1	V2	P3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	P15	PX	V13A
Timing of visit (weeks)	≤ 2 weeks prior to V2	0	1	2	4	12	26	38	52	64	78	90	104	7 days after EOT	30 days after EOT	Every 3rd month	104
Visit window (days)			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	+3	±3	±3
End of treatment													X				
Sign off Casebook															X[18]		X
End of trial (subject completion)															X18		X

66

[18] Not applicable for subjects that have prematurely discontinued trial product

2.3 Section 5.3 Treatment of subjects

The dose and frequency of OAD(s) should not be changed during the trial except for safety reasons. The unchanged OAD doses should be confirmed at each visit and recorded in the subject's medical record and in the electronic case report form (eCRF) to verify compliance. ~~Dose change in OAD(s) for a maximum duration of 14 days is allowed for safety reasons based on the Investigator's judgement.~~ If a change in OAD dose has occurred, the duration and reason for the change should be recorded in subject's medical records and in the eCRF.

2.4 Section 6.2 Inclusion criteria

7. Stable daily dose(s) including any of the following antidiabetic drug(s)/regimens within 90 days prior to the day of screening:

- Biguanides (metformin ≥ 1500 mg or maximum tolerated dose documented in the subject medical record)
- Other OAD(s) allowed: sulphonylurea, glinides, pioglitazone, and DPP4-inhibitors (≥ half of the maximum approved dose according to local label or maximum tolerated dose as documented in subject medical record)
    - *DPP4-inhibitors and glinides are not allowed as monotherapy and the combination of DPP4-inhibitors and glinides is not allowed. This is to ensure background OAD treatment as both DPP4-inhibitors and glinides are stopped before initiating trial product.*

2.5 Section 6.4 Premature discontinuation of trial product

The trial product must be discontinued if the ~~subject meets rescue criteria or if following applies: i~~Investigator suspects acute pancreatitis. All drugs suspected to relate to this condition must be discontinued until confirmatory tests have been conducted and appropriate treatment should be initiated

2.6 Section 6.4.1 Rescue criteria

If the fasting SMPG values taken on 3 consecutive days or if any of the FPG samples analysed by the central laboratory exceed the limit of:
15.0 mmol/L (270 mg/dL) ~~from~~ *after* baseline to week 6,
13.3 mmol/L (240 mg/dL) from week 7 to week 12,
11.1 mmol/L (200 mg/dL) from week 13 to week 26,
and if no treatable intercurrent cause for the hyperglycaemia has been identified, the subject must be called for a confirmatory FPG measurement as soon as possible. A confirmatory FPG must be obtained and analysed by the central laboratory. If this FPG exceeds the limits described above, the subject must discontinue treatment with trial product.

2.7 Section 8.1.3 Randomisation (visit 2)

The randomisation visit (visit 2) must take place no more than 2 weeks after the screening visit.
The subject should if possible take the first dose of trial product at visit 2 after randomisation is done or on the day after randomisation. The date *and dose* of the first dose of trial product should be recorded in the eCRF.

2.8 Section 8.1.4 Treatment initiation and titration

Titration
Dose will be adjusted twice weekly by the subject 3-4 days apart. The investigator will evaluate the diary and prescribe dose at all contacts. *It is important that other information, such as symptoms of hypo- or 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.*
Titration should be performed based on the mean of 3 pre-breakfast SMPG values, measured on the day of the titration and the 2 previous days. Titration should preferably be performed on the same days of the week throughout the trial (E.g., Mondays and Thursdays). The dose adjustment will be performed according to Table 8-1.

2.9 Section 8.4.1 Hypoglycaemic episodes

The record should include the following information:

- Start date and time of hypoglycaemic episode
- The plasma glucose level before treating the episode (if available) and any follow up measurements
- The lowest value measured during the hypoglycaemic episode will be reported as the plasma glucose value for the episode, the remaining values will be kept as source data
- Whether the episode was symptomatic (Yes/No)
- A hypoglycaemic episode starting without symptoms should be updated to symptomatic if the subject experiences symptoms later during the episode.
- Whether the subject was able to treat him/herself
- If the severity of a hypoglycaemic episode aggravates, only one hypoglycaemic episode should be reported reflecting the most severe degree of hypoglycaemia.
- Date, time and dose of last IDegLira/IGlar administration prior to the episode
- Date and time of last main meal (not including snacks) prior to the episode
- Whether the episode occurred in relation to physical activity
- *Change in* ~~Worsening of~~ any concomitant illness ~~(pre-existing illness)~~
- Any sign of fever or other acute disease

- Whether the subject was asleep when the episode occurred
    - If yes, whether the symptoms of the episode woke up the subject

2.10 Section 8.5 Laboratory assessments

Blood samples for efficacy

- Glucose metabolism: HbA_{1C}, fasting plasma glucose, beta cell function (fasting C-peptide and fasting human insulin). Note: ~~Low FPG values reported by central laboratory should NOT be reported as hypoglycaemic episodes; however these should be reported as an AE related to the procedure (e.g. a FPG result of 2.9 mmol/L (52 mg/dL) should be reported as 'low plasma glucose of 2.9 mmol/L (52 mg/dL)')~~ *A FPG result < 3.9 mmol/L (70mg/dL) should not be reported as a hypoglycaemic episode but as a clinical laboratory adverse event (CLAE) at the discretion of the investigator (see Section 12.1).*

2.11 Section 8.6 Other Assessments

Questionnaires

The investigator *or site staff* are only allowed to fill in the headings of the questionnaires.

The investigator should *review the questionnaires* ~~check~~ for empty fields *and potential adverse events* ~~in the questionnaires~~ when returned by the subject. Review of the questionnaires must be documented either on the documents and/or in the subject's medical record.

2.12 Section 9.4 Drug accountability and destruction

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

Subjects must be 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) can be stored at room temperature and must be stored separately from non-allocated trial product. Drug accountability is performed by using the IWRS. Only dispensed DUNs returned by the subject (used/partly used or unused) are accounted for.

2.13 Section 12.1 Definitions

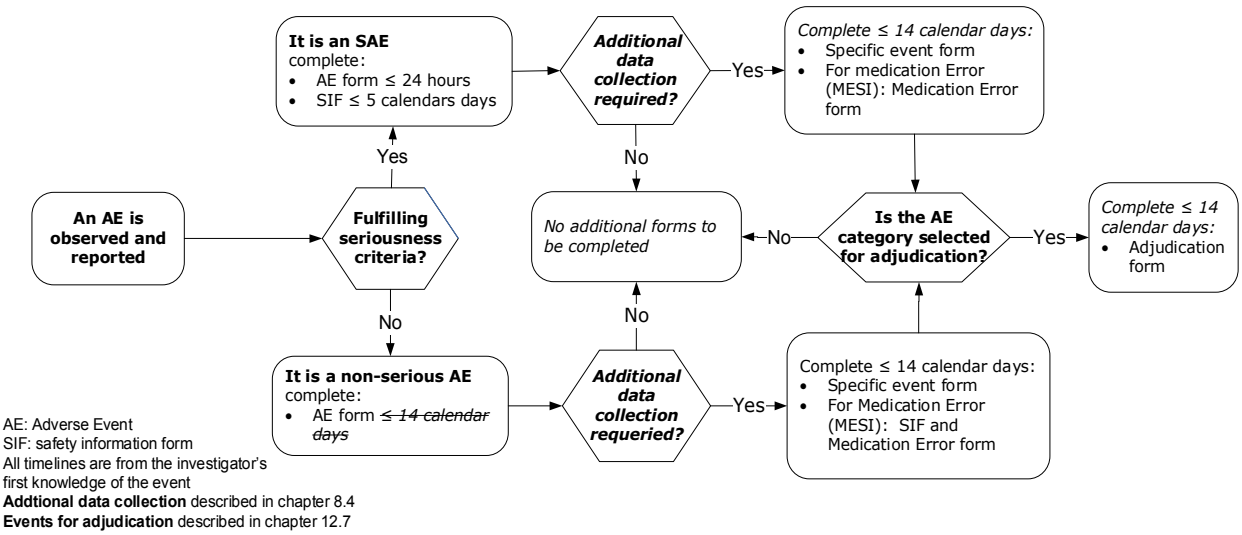
<u>Serious adverse event</u>

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

- *Suspicion of transmission of infectious agents via the trial product*

- *Risk of liver injury defined as alanine aminotransferase (ALAT) or aspartate aminotransferase (ASAT) >3 x UNL and total bilirubin >2 x UNL, where no alternative aetiology exists (Hy's law).*

Figure 12–1 Initial reporting of AEs



Protocol Amendment

no 4
to Protocol, final version 3.0
dated 30 June 2016

Trial ID: NN9068-4228

DUAL™ VIII – Durability
A 104 week clinical trial comparing long term glycaemic control of insulin degludec/liraglutide (IDegLira) versus insulin glargine therapy in subjects with type 2 diabetes mellitus

Trial phase: 3b

Applicable to all countries

Amendment originator:

[redacted]

Table of Contents

Page

1 Introduction including rationale for the protocol amendment

NN9068-4228 Protocol (Version 3.0, 30 June 2016) will be amended for the following reasons:

1. The '(x)' will be removed from the pregnancy testing row for visits 2-12 in the flowchart in section 2 as this is believed to be the root cause of a high number protocol deviations causing extra pregnancy testing.
2. The section on laboratory assessments on page 34 will be moved under section 8.5 Laboratory assessments to ensure all information on laboratory procedures are in one section.
3. In section 8.5 Laboratory assessments, the following changes will be implemented:
   - The section removed from page 34 concerning laboratory assessments will be moved into section 8.5 Laboratory assessments, it will be placed after the current text.
   - A sentence will be added to clarify the storage of haematology slides in cases where there is an abnormality.
   - It will be specified that fasting human insulin is not distributed to sites in the laboratory reports. Fasting human insulin is analysed in batches and results will not be reported to sites as they have no clinical significance.
   - An editorial correction will be made to the CLAE text, as equal to symbol is missing from '≤ 3.9 mmol/L (70 mg/dL)'.
4. The definition of Major Adverse Cardiovascular Event (MACE) will be clarified in section 12.1 to ensure it aligns with the FDA definition.
5. The core company safety sheet for IDegLira has been updated. This means the minimum mandatory safety text has been updated for IDegLira and needs to be included in the protocol section 18.1 Benefit-risk assessment of the trial.

In this protocol amendment:

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

2 Changes to the protocol

2.1 2 Flowchart

Trial Periods	**Screening**	**Rand.**	**Treatment**										**EOT**	**FU1**	**FU2**	**Pre-disc[1]**	
Visit number (V), Phone contact (P)[2]	V1	V2	P3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	P15	PX	V13A
Timing of visit (weeks)	≤ 2 weeks prior to V2	0	1	2	4	12	26	38	52	64	78	90	104	7 days after EOT	30 days after EOT	Every 3rd month	104
Visit window (days)			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	+3	±3	±3
SUBJECT RELATED INFO/ASSESSMENTS																	
Eye examination	X[13]												X[14]				
Physical examination	X												X				
Vital signs	X	X				X	X		X		X		X				
Biochemistry[15]	X	X					X		X				X				
Haematology[16]	X	X					X		X				X				
Hormones (calcitonin)	X	X				X	X	X	X	X	X	X	X				
Urinalysis (albumin:creatinine ratio)		X				X	X		X		X		X				
Pregnancy test[17]	X	~~(X)~~		~~(X)~~	~~(X)~~	~~(X)~~	~~(X)~~	~~(X)~~	~~(X)~~	~~(X)~~	~~(X)~~	~~(X)~~	X				

2.2 8.1.5 Diaries

~~Laboratory assessments~~

~~The laboratory analyses will be handled by a central laboratory. Descriptions of assay methods, laboratory supplies and procedures for obtaining samples, handling, transportation and storage of biological samples and information regarding who will perform the assessments, will be described in a trial specific laboratory manual, provided by the central laboratory (for central laboratory details, see Attachment I).~~

~~Laboratory samples not drawn on the day of the actual visit should preferably be drawn on another day within the visit window (flow chart section 2). For some of the samples drawn during the trial the subject must be fasting, see the flow chart section 2 and fasting requirements in section 8.1.~~

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

~~The laboratory equipment may provide analyses not requested in the protocol but produced automatically in connection with the requested analyses according to specifications in the laboratory standard operating procedures. Such data will not be transferred to the trial database, but abnormal values will be reported to the investigator.~~

~~**Brazil**: All laboratory results from Brazilian subjects must be provided to the investigator.~~

~~Laboratory results will be provided by the central laboratory to the investigator on an ongoing basis. For laboratory results outside the normal range the investigator must specify an evaluation on the laboratory report. The evaluation must follow the categories:~~

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

~~The investigator must review all laboratory results for concomitant illnesses and AEs and report these according to this protocol (see section 8.2.1 and section 12). The review of laboratory reports must be documented either on the documents and/or in the subject's medical record. The laboratory report must be evaluated as soon as possible and signed and dated by the investigator on the day of evaluation. The signed report must be retained at the site as source documentation.~~

~~The investigator should ensure that all laboratory samples for the subject are shipped to the laboratory immediately after the samples from visit 1 and visit 13 (or visit 13A for prematurely discontinued subjects) have been collected.~~

~~All samples will be destroyed on an ongoing basis after the analysis or at the latest at the completion of the clinical trial report (CTR).~~

2.3 8.5 Laboratory assessments

2.3.1 Editorial change

Blood and urine samples will be collected in accordance with the flow chart (section 2) and analysed by the central laboratory to determine levels of the laboratory parameters listed below:

Blood samples for efficacy

Glucose metabolism: HbA_{1C}, fasting plasma glucose, beta cell function (fasting C-peptide and fasting human insulin). Note: A FPG result ≤ 3.9 mmol/L (70 mg/dL) should not be reported as a hypoglycaemic episode but as a clinical laboratory adverse event (CLAE) at the discretion of the investigator (see Section 12.1).

2.3.2 Text moved from 8.1.5 Diaries and including new text on haematology and fasting human insulin

The laboratory analyses will be handled by a central laboratory. Descriptions of assay methods, laboratory supplies and procedures for obtaining samples, handling, transportation and storage of biological samples and information regarding who will perform the assessments, will be described in a trial specific laboratory manual, provided by the central laboratory (for central laboratory details, see Attachment I).

Laboratory samples not drawn on the day of the actual visit should preferably be drawn on another day within the visit window (flow chart section 2). For some of the samples drawn during the trial the subject must be fasting, see the flow chart section 2 and fasting requirements in section 8.1.

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

The laboratory equipment may provide analyses not requested in the protocol but produced automatically in connection with the requested analyses according to specifications in the laboratory standard operating procedures. Such data will not be transferred to the trial database, but abnormal values will be reported to the investigator.

***Brazil**: All laboratory results from Brazilian subjects must be provided to the investigator.*

Laboratory results (except fasting human insulin) will be provided by the central laboratory to the investigator on an ongoing basis. For laboratory results outside the normal range the investigator must specify an evaluation on the laboratory report. The evaluation must follow the categories:

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

The investigator must review all laboratory results for concomitant illnesses and AEs and report these according to this protocol (see section 8.2.1 and section 12). The review of laboratory reports must be documented either on the documents and/or in the subject's medical record. The laboratory report must be evaluated as soon as possible and signed and dated by the investigator on the day of evaluation. The signed report must be retained at the site as source documentation.

The investigator should ensure that all laboratory samples for the subject are shipped to the laboratory immediately after the samples from visit 1 and visit 13 (or visit 13A for prematurely discontinued subjects) have been collected.

All samples will be destroyed on an ongoing basis after the analysis or at the latest at the completion of the clinical trial report (CTR). However, in case of abnormal haematology analysis test results, part of the sample may be kept for up to 2 years.

2.4 12 .1 Definitions

Major Adverse Cardiovascular Event

~~A Major Adverse Cardiovascular Event (MACE) is~~ Any *cardiovascular* AE ~~which can be~~ categorised into the following groups *will be evaluated as a potential Major Adverse Cardiovascular Event (MACE):*

- Cardiovascular Death
- Myocardial Infarction
- Hospitalization for Unstable Angina
- Transient Ischemic Attack and Stroke
- Heart Failure Event (requiring hospitalisation)
- Cardiac procedures
  - Interventional Cardiology
  - Peripheral Vascular Intervention
  - Stent Thrombosis

A MACE is defined as:

- *Cardiovascular Death*
- *Non-fatal Myocardial Infarction*
- *Non-fatal Stroke*

2.5 18.1 Benefit-risk assessment of the trial

Gastrointestinal adverse events

Gastrointestinal adverse events are considered class effects for GLP-1 receptor agonists and are among the most frequently reported events in patients treated with IDegLira. The gradual 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 NN9068-4228 is 0.36 mg, which is less than the starting dose of liraglutide when administered as the mono component (Victoza®).

Gallstone disease

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.