Cover Page for Protocol

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Official title of study:	A double-blinded trial comparing the efficacy and safety of insulin degludec/liraglutide and insulin degludec both in combination with metformin in Japanese subjects with type 2 diabetes mellitus inadequately controlled with basal or premix/ combination insulin therapy and oral anti-diabetic drugs
Document date:	23 April 2018

16.1.1 Protocol and protocol amendments

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Redacted protocol
Includes redaction of personal identifiable information only.

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Protocol

DUAL™ II Japan

NN9068-4184

A double-blinded trial comparing the efficacy and safety of insulin degludec/liraglutide and insulin degludec both in combination with metformin in Japanese subjects with type 2 diabetes mellitus inadequately controlled with basal or pre-mix/combination insulin therapy and oral anti-diabetic drugs

Trial phase: 3a

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Insulin & Diabetes Outcomes, Clinical Operations

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List of abbreviations

ADA	American Diabetes Association
AE	adverse event
α-GI	alpha-glucosidase inhibitor
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BG	blood glucose
BMI	body mass index
CAS	completer analysis set
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CLAE	clinical laboratory adverse event
CV	coefficient of variation
DFU	direction for use
DUN	dispensing unit number
DPP-4	dipetidyl peptidase-4
DTR-QOL	Diabetes Therapy-Related QOL questionnaire
EAC	event adjudication committee
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EQ-5D-5L	EuroQol-5D-5L questionnaire
ET	end of treatment
FAS	full analysis set
FPFV	first patient first visit
FPG	fasting plasma glucose
FU	follow-up
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide-1

HbA_{1c}	glycosylated haemoglobin
hCG	human chorionic gonadotropin
HDL	high density lipoprotein
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IDeg	insulin degludec
IDegLira	insulin degludec/liraglutide
IMP	investigational medicinal product
IRB	institutional review board
IWRS	interactive web response system
LDL	low density lipoprotein
LLOQ	lower limit of quantification
LOCF	last observation carried forward
LPFV	last patient first visit
LPLV	last patient last visit
LSMeans	least square means
MEN 2	multiple endocrine neoplasia syndrome type 2
MI	myocardial infarction
MMRM	mixed model for repeated measurement
MTC	medullary thyroid carcinoma
NYHA	New York Heart Association
OAD	oral anti-diabetic drug
OD	once daily
PMDA	Pharmaceuticals and Medical Devices Agency
PRO	patient reported outcome
SAE	serious adverse event
SAS	safety analysis set
SD	standard deviation
SGLT2i	sodium glucose co-transporter 2 inhibitor

SIF	safety information form
SMBG	self-measured blood glucose
SU	sulfonylureas
SUSAR	suspected unexpected serious adverse reaction
T2DM	type 2 diabetes mellitus
TEAE	treatment emergent adverse event
TIA	transient ischemic attack
TMM	Trial Materials Manual
TSH	thyroid stimulating hormone
TZD	thiazolidinedione
T3	triiodothyronine
T4	thyroxine
UNL	upper normal limit
UNR	upper normal range
UTN	Universal Trial Number
VLDL	very low density lipoprotein

1 Summary

1.1 Objectives and endpoints

Primary objective

To confirm the superiority of insulin degludec/liraglutide (IDegLira) vs. insulin degludec (IDeg) in controlling glycaemia in Japanese subjects with type 2 diabetes mellitus (T2DM) after 26 weeks of treatment.

Secondary objective

To compare the general efficacy and safety of IDegLira and IDeg after 26 weeks of treatment in Japanese subjects with T2DM.

Primary endpoint

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

Key secondary endpoints

- Change from baseline in body weight after 26 weeks
- Change from baseline in fasting plasma glucose (FPG) after 26 weeks
- Number of treatment emergent severe or blood glucose (BG) confirmed hypoglycaemic episodes during 26 weeks of treatment

1.2 Trial design

This is a 26-week randomised, parallel two-arm, double-blinded, multi-centre, treat-to-target trial in Japanese subjects with T2DM inadequately controlled with basal insulin or pre-mix/combination insulin in combination with metformin with or without one of the following oral anti-diabetic drugs (OADs): sulphonylureas (SU), glinides, α-glucocidase inhibitors (α-GI), sodium-glucose co-transporter-2 inhibitors (SGLT2i) or thiazolidinediones (TZD).

The trial is designed to demonstrate superiority in HbA_{1c} of IDegLira as compared to IDeg with the dose capped at 50 units in subjects with T2DM as the maximum dose of IDegLira is 50 dose steps (50 units IDeg/1.8 mg liraglutide).

1.3 Trial population

A total of 210 Japanese subjects with T2DM inadequately controlled on insulin combined with metformin with or without one other OAD with HbA_{1c} in the range of 7.5-11.0% (both inclusive), and thus in need of treatment intensification to achieve or maintain glycaemic control, are planned to be randomised in the trial.

1.4 Key inclusion criteria

- Male or female Japanese subjects, age ≥ 20 years at the time of signing informed consent
- T2DM subjects (diagnosed clinically) ≥ 6 months prior to screening
- HbA_{1c} 7.5-11.0% [58 mmol/mol-97 mmol/mol] (both inclusive) by central laboratory analysis
- Subjects on stable daily insulin doses for at least 90 days prior to screening administered once or twice daily, either as basal insulin (e.g. IDeg, insulin glargine, insulin detemir, NPH insulin) or pre-mix/combination insulin (e.g. biphasic insulin aspart, insulin degludec/insulin aspart). Total daily insulin dose in the previous 90 days should be within 20-50 units, both inclusive, and on the day of screening, but fluctuations of ± 10% within the 90 days prior to screening are acceptable. The specified insulin treatment should be administered in combination
    - with a stable daily dose of metformin within current approved Japanese label for at least 90 days prior to screening,
    - additionally, the anti-diabetic treatment can be with or without a stable daily dose of one of the following other OADs: SU, glinides, α-GI, SGLT2i or TZD within current approved Japanese label for at least 90 days prior to screening
- Body Mass Index (BMI) ≥ 23 kg/m^2

1.5 Key exclusion criteria

- Receipt of any investigational medicinal product (IMP) within 30 days before screening
- Use of any anti-diabetic drug in a period of 90 days before screening (except pre-mix/combination or basal insulin, metformin, SU, glinides, α-GI, SGLT2i, or TZD) or anticipated change in concomitant medication, which in the investigators opinion could interfere with glucose metabolism (e.g. systemic corticosteroids or bolus insulin)
- Previous treatment with glucagon-like peptide-1 (GLP-1) receptor agonists
- Treatment with dipetidyl peptidase-4 (DPP-4) inhibitors during the last 90 days prior to screening
- Impaired liver function, defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 2.5 times upper limit of normal
- Renal impairment estimated Glomerular Filtration Rate (eGFR) < 60mL/min/1.73m^2 as per Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)
- Screening calcitonin ≥ 50 ng/L
- History of pancreatitis (acute or chronic)
- Personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia type 2 (MEN 2)
- Subjects presently classified as being in New York Heart Association (NYHA) Class IV

1.6 Assessments

1.6.1 Key efficacy assessments

- HbA_{1c}
- Body weight
- FPG

1.6.2 Key safety assessments

- Hypoglycaemic episodes
- Adverse events (AEs)

1.7 Trial products

- Insulin degludec/liraglutide, 100 units/mL + 3.6 mg/mL, 3 mL pre-filled PDS290 pen injector
- Insulin degludec, 100 units/mL, 3 mL pre-filled PDS290 pen injector.

2 Flow chart

Screening (SC) **Randomisation (RAN)** **Site visit (V)** **Phone contact (P)**[1] **End of Treatment (ET)** **Follow-up (FU)**	SC V	RAN V	P	V	P	V	P	V	P	V	P	V	P	V	P	V	P	ET V	FU P
Number	1	2	3	4	5	6	7 8 9	10	11 12 13	14	15 16 17	18	19 20 21	22	23 24 25	26	27 28 29 30 31	32	33
Time of V or P (week)	- 2	0	0,5[2]	1	1,5[2]	2	2,5[2] 3 3,5[2]	4	5 6 7	8	9 10 11	12	13 14 15	16	17 18 19	20	21 22 23 24 25	26	27
Visit window (days)			±1	±1	±1	±1	±1	±1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3
SUBJECT RELATED INFO/ASSESSMENTS																			
Informed consent	x																		
In/exclusion criteria	x	x																	
Randomisation[3]		x																	
Withdrawal criteria[4]			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Demography[5]	x																		
Diagnosis of diabetes	x																		
Diabetes treatment history	x																		

[1] A phone contact may be converted to a site visit.
[2] Corresponding to previous visit/contact date plus three days.
[3] Randomisation (V2) should take place as soon as all screening (including laboratory) results are available, reviewed and the subject is confirmed eligible and no later than 14 days after the screening (V1).
[4] If a subject is withdrawn from the trial, the investigator must aim to undertake procedures similar to those for the end of treatment (V32) as soon as possible and to perform the follow-up (P33).
[5] Collection of birth date, sex and race.

Screening (SC) **Randomisation (RAN)** **Site visit (V)** **Phone contact (P)**[1] **End of Treatment (ET)** **Follow-up (FU)**	SC V	RAN V	P	V	P	V	P	V	P	V	P	V	P	V	P	V	P	ET V	FU P
Number	1	2	3	4	5	6	7 8 9	10	11 12 13	14	15 16 17	18	19 20 21	22	23 24 25	26	27 28 29 30 31	32	33
Time of V or P (week)	- 2	0	0,5[2]	1	1,5[2]	2	2,5[2] 3 3,5[2]	4	5 6 7	8	9 10 11	12	13 14 15	16	17 18 19	20	21 22 23 24 25	26	27
Visit window (days)			±1	±1	±1	±1	±1	±1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3
Family history of diabetes	x																		
Diabetes complications	x																		
Concomitant illness	x																		
Medical history	x																		
Concomitant medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Tobacco use	x																		
EFFICACY																			
Pre-breakfast SMBG[6]			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
9-point SMBG profile[7]		x										x						x	
Body weight	x	x						x				x						x	
Waist circumference		x						x				x						x	
Blood pressure (systolic and diastolic)	x	x						x				x						x	
HbA_{1c}	x	x						x		x		x		x		x		x	
Fasting plasma glucose		x						x		x		x		x		x		x	

[6] Daily pre-breakfast SMBG should be recorded. Anti-diabetic medication should be withheld until after the SMBG measurement.
[7] 9-point SMBG profiles must be started in the morning on two consecutive days preferably in the week prior to the site visit where the subject has not been anticipating unusual strenuous exercise. Measurements are to be performed before and after (90 min after the start of the meal) breakfast, lunch, dinner, at bedtime, at 4 am and before breakfast on the following day.

Screening (SC) **Randomisation (RAN)** **Site visit (V)** **Phone contact (P)**[1] **End of Treatment (ET)** **Follow-up (FU)**	SC V	RAN V	P	V	P	V	P	V	P	V	P	V	P	V	P	V	P	ET V	FU P
Number	1	2	3	4	5	6	7 8 9	10	11 12 13	14	15 16 17	18	19 20 21	22	23 24 25	26	27 28 29 30 31	32	33
Time of V or P (week)	- 2	0	0,5[2]	1	1,5[2]	2	2,5[2] 3 3,5[2]	4	5 6 7	8	9 10 11	12	13 14 15	16	17 18 19	20	21 22 23 24 25	26	27
Visit window (days)			±1	±1	±1	±1	±1	±1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3
Lipids		x						x				x						x	
SAFETY																			
Adverse events		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Technical complaints		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Eye examination[8]	x																	x	
ECG[9]	x																	x	
Pulse	x	x						x				x						x	
Physical examination	x																	x	
Hypoglycaemic episodes		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Haematology	x											x						x	
Biochemistry	x											x						x	
Calcitonin	x											x						x	

[8] Eye examination will be performed as fundoscopy/fundus photography. If performed within 90 days prior to randomisation (V2) as part of routine practice, it may replace the screening assessment, if results are available for evaluation at V2. Eye examination obtained within 14 days prior to end of treatment (V32) is acceptable, if results are available for evaluation at V32.

[9] ECG obtained within 14 days prior to randomisation (V2), as part of routine practice, may replace the screening assessment and ECG obtained within 14 days prior to end of treatment (V32) is acceptable, if results are available for evaluation at the respective visits.

Screening (SC) **Randomisation (RAN)** **Site visit (V)** **Phone contact (P)**[1] **End of Treatment (ET)** **Follow-up (FU)**	SC V	RAN V	P	V	P	V	P	V	P	V	P	V	P	V	P	V	P	ET V	FU P
Number	1	2	3	4	5	6	7 8 9	10	11 12 13	14	15 16 17	18	19 20 21	22	23 24 25	26	27 28 29 30 31	32	33
Time of V or P (week)	- 2	0	0,5[2]	1	1,5[2]	2	2,5[2] 3 3,5[2]	4	5 6 7	8	9 10 11	12	13 14 15	16	17 18 19	20	21 22 23 24 25	26	27
Visit window (days)			±1	±1	±1	±1	±1	±1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3
Pregnancy test[10]	x	(x)		(x)		(x)		(x)		(x)		(x)		(x)		(x)		x	
OTHER ASSESSMENTS																			
Height	x																		
DTR-QOL[11]		x										x						x	
EQ-5D-5L[11]		x										x						x	
TRIAL MATERIAL																			
IWRS session	x	x						x		x		x		x		x		x	
Dispensing visit		x						x		x		x		x		x			
Drug accountability (IWRS)		x						x		x		x		x		x		x	
REMINDERS																			
Attend visit fasting[12]		x						x		x		x		x		x		x	
Discontinue OADs except for metformin		x																	

[10] For females of childbearing potential: A serum pregnancy test must be performed at screening (V1) and at end of treatment (V32). Urine pregnancy test should be performed at site if a menstrual period is missed, or if pregnancy is suspected, indicated by (x).
[11] PRO questionnaires should be completed by subject and reviewed by investigator.
[12] Fasting is defined as having consumed no food and drink except for water for the last 8 hours prior to visit. No diabetes treatment is allowed during fasting but other concomitant medication should be taken as usual. If a subject attend site visit in a non-fasting condition, blood sampling should be re-scheduled, preferably within the visit window.

Screening (SC) **Randomisation (RAN)** **Site visit (V)** **Phone contact (P)**[1] **End of Treatment (ET)** **Follow-up (FU)**	SC V	RAN V	P	V	P	V	P	V	P	V	P	V	P	V	P	V	P	ET V	FU P
Number	1	2	3	4	5	6	7 8 9	10	11 12 13	14	15 16 17	18	19 20 21	22	23 24 25	26	27 28 29 30 31	32	33
Time of V or P (week)	- 2	0	0,5[2]	1	1,5[2]	2	2,5[2] 3 3,5[2]	4	5 6 7	8	9 10 11	12	13 14 15	16	17 18 19	20	21 22 23 24 25	26	27
Visit window (days)			±1	±1	±1	±1	±1	±1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3
Handout ID card	x																		
Handout directions for use of trial product[13]		x						(x)		(x)		(x)		(x)		(x)			
Training in trial product and pen handling[14]		x	(x)	x	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)		
Handout and instruct in BG meter use	x																		
Handout and instruct in diary	x	x		x		x		x		x		x		x		x		x	
Collection of diary[15]		x		x		x		x		x		x		x		x		x	x
Instruction in titration algorithm		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Make appointment for eye examination																x			
End of treatment																		x	
End of trial[16]																			x
Sign of casebook																			x

[13] Handout direction for use only in case needed by subject during trial is indicated by (x).
[14] Training in trial product and pen handling should be performed at randomisation (V2) and one week after (V4). At other site visits and at phone contacts training will be at the investigator's discretion based on subject needs, indicated by (x).
[15] Diary data collected from end of treatment (V32) to follow-up (P33) will be collected per phone as notes written down by the investigator based on an interview.
[16] Due to the long half-life of insulin degludec, the follow-up (P33) procedures should be undertaken minimum 7 days after end of treatment (V32).

3 Background information and rationale for the trial

The trial will be conducted in compliance with this protocol, International Conference on Harmonisation Good Clinical Practice Guideline (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

T2DM is a progressive disorder characterised by insulin resistance and impaired insulin secretion. Landmark studies have demonstrated the importance of maintaining good glycaemic control to reduce the risk of long-term complications associated with diabetes[3, 4].

Given the progressive nature of T2DM, current anti-diabetic therapies with OADs and insulin often fail to provide sustained glycaemic control. The successful outcome of recent global trials combining basal insulin and GLP-1 treatment as separate injections has led to the inclusion of this treatment combination in the most recent guidelines from the Japanese Diabetes Society, the American Diabetes Association and in the European Association for the Study of Diabetes position statement on management of hyperglycaemia in T2DM[5-7].

Treatment guidance from the Japanese Diabetes Society suggests a stepwise approach comprising lifestyle changes followed by pharmacological intervention[7]. Initial OAD monotherapy is recommended, escalated with combination therapy with OADs combined with insulin, or GLP-1 receptor agonists, and combination of insulin and GLP-1 receptor.

Insulin degludec (IDeg)

IDeg is a long-acting basal insulin, marketed with the brandname Tresiba®, which has been approved in Japan, US, EU, and several other countries.

For more details on IDeg, see the current Investigator's Brochure (IB)[8] and any updates hereof as well as the latest Japanese approved labelling for Tresiba®.

Liraglutide

Liraglutide is an analogue native (human) GLP-1 receptor agonist and the active ingredient in Victoza®, which is approved in several countries e.g. Japan, Australia, Canada, China, EU and the US for the treatment of adults with T2DM to achieve glycaemic control. The approved maximum dose of liraglutide in Japan is 0.9 mg/day, in all other countries the approved dose is 1.8 mg/day. Furthermore 3.0 mg/day (maximum dose) of liraglutide for the treatment of obesity has recently been approved in the US and EU and is marketed as Saxenda®.

For more details on liraglutide, please see the current IB [9] and any updates hereof as well as latest Japanese approved labelling for Victoza®.

Insulin degludec/liraglutide (IDegLira)

IDegLira is a basal insulin (IDeg) and GLP-1 receptor agonist (liraglutide) combination solution for subcutaneous injection for treatment of T2DM with once daily use [10]. The combination brings complimentary effects of the two compounds (IDeg and liraglutide) on fasting and postprandial (liraglutide) glycaemic control. The addition of liraglutide to IDeg may reduce the requirement of exogenous insulin (i.e. insulin sparing effect), hence minimising the risk of hypoglycaemia and weight gain, often associated with basal 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. Moreover, given the glucose dependent effect of liraglutide, the liraglutide component reduces postprandial glucose excursions, while reducing the risk of unwanted lowering of inter-prandial or fasting glucose. IDegLira is to be initiated and titrated to achieve adequate glycaemic control in a similar way as basal insulin therapy. IDegLira is titrated in dose steps, one dose step equalling 1 unit of IDeg and 0.036 mg of liraglutide. The approved maximum dose of IDegLira is 50 dose steps, which equals 50 units of IDeg and 1.8 mg of liraglutide. Efficacy and safety of IDegLira has been demonstrated in previous randomised global clinical trials (NN9068-3697 DUAL™ I, NN9068-3912 DUAL™ II, which has formed the basis of the marketing authorisation application in EU among others. Marketing authorisation has been granted in several countries, e.g. in Switzerland and in EU. IDegLira is not approved in Japan.

In the global DUAL™ I and II, and all other finalised clinical trials in the IDegLira clinical development programme (including trials NN9068-3951, NN9068-3851 and NN9068-3952), IDegLira has shown to effectively improve the glycaemic control of the subjects, and no unexpected safety issues were identified. For an assessment of benefits and risks of the trial, see section 18.1.

For more information, see the current IB version of IDegLira[11], IDeg[8] and liraglutide[9] or any updates hereof.

3.2 Rationale for the trial

Current anti-diabetic therapies, including treatment with basal insulin may not provide adequate or sustained glycaemic control or may be associated with an unacceptable risk of hypoglycaemia and weight gain. In addition, these therapies are often complicated and difficult for subjects to adhere to. The combination of IDeg and liraglutide in IDegLira provides complimentary effects of the two compounds on glycaemic control, reduced risk of hypoglycemia, and reduced risk of weight gain, in a single daily injection.

Both IDeg and liraglutide are on the market in Japan. The present confirmatory trial (NN9068-4184 DUAL™ II Japan) in Japanese subjects with T2DM treated with insulin and OAD aims to confirm efficacy and safety of once daily treatment with IDegLira, as compared to treatment with once daily IDeg. To establish the contribution of the monocomponents in a combination product, and as the maximum daily dose of IDegLira is 50 dose steps (50 units of IDeg/1.8 mg of liraglutide); the IDeg dose in the comparator arm is capped at 50 units. Given that the trial is double-blinded, any difference between the two treatment arms will be attributable to the liraglutide component in IDegLira.

NN9068-4184 DUAL™ II Japan is a part of the Japanese IDegLira development programme, which also includes trials NN9068-4183 DUAL™ I Japan testing IDegLira against the monocomponents in OAD experienced T2DM subjects. In the three arm trial NN9068-4183 DUAL™ I Japan, IDegLira is tested against freely titrated IDeg and a maximum dose of 1.8 mg liraglutide, respectively, and safety and efficacy data of IDegLira combined with 6 different OADs will be collected in that trial. As such, the present trial in insulin experienced subjects with T2DM will together with NN9068-4183 be used for registration of IDegLira in Japan as agreed with the Pharmaceuticals and Medical Devices Agency (PMDA).

4 Objectives and endpoints

4.1 Objectives

4.1.1 Primary objective

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

4.1.2 Secondary objective

To compare the general efficacy and safety of IDegLira and IDeg after 26 weeks of treatment in Japanese subjects with T2DM.

4.2 Endpoints

4.2.1 Primary endpoint

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

4.2.2 Secondary endpoints

4.2.2.1 Supportive secondary endpoints

Supportive secondary efficacy endpoints:

- Daily insulin dose after 26 weeks
- Change from baseline in body weight after 26 weeks*
- Responder after 26 weeks (yes/no):
    - $HbA_{1c} < 7.0\%$
    - $HbA_{1c} < 7.0\%$ and without weight gain
    - $HbA_{1c} < 7.0\%$ without treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during the last 12 weeks of treatment
    - $HbA_{1c} < 7.0\%$ and without weight gain and without treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during the last 12 weeks of treatment
    - $HbA_{1c} \leq 6.5\%$
    - $HbA_{1c} \leq 6.5\%$ and 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
    - $HbA_{1c} \leq 6.5\%$ and without weight gain and without treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during the last 12 weeks of treatment

- Change from baseline after 26 weeks in:
    - FPG*
    - Waist circumference
    - Blood pressure (systolic and diastolic)
    - Self-measured blood glucose (SMBG) 9-point profile
        - 9-point profile (individual points in the profile)
        - Mean of the 9-point profile
        - Mean of postprandial 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
- Lipid profile after 26 weeks of treatment

Supportive secondary safety endpoints:

- Number of treatment emergent adverse events (TEAE) during 26 weeks of treatment
- Number of treatment emergent severe or BG confirmed hypoglycaemic episodes during 26 weeks of treatment*
- Number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during 26 weeks of treatment
- Number of treatment emergent hypoglycaemic episodes according to ADA definition during 26 weeks of treatment
- Number of treatment emergent nocturnal severe or BG confirmed symptomatic hypoglycaemic episodes during 26 weeks of treatment
- Change from baseline in clinical evaluation after 26 weeks of treatment:
    - Physical examination
    - Fundoscopy or fundus photography
    - Electrocardiogram (ECG)
    - Pulse
- Change from baseline in laboratory assessments after 26 weeks of treatment:
    - Biochemistry (including amylase and lipase)
    - Haematology
    - Calcitonin

Supportive secondary patient reported outcome endpoints:

- Change from baseline in patient reported outcomes (PROs) after 26 weeks of treatment:
    - Diabetes Therapy-Related QOL (DTR-QOL) questionnaire
    - EuroQol-5D (EQ-5D-5L) questionnaire

Key supportive secondary endpoints prospectively selected for disclosure (e.g. clinicaltrials.gov) are marked with an asterisk (*).

5 Trial design

5.1 Type of trial

This is a 26-week randomised, parallel two-arm, double-blinded, multi-centre, treat-to-target trial in Japanese subjects with T2DM inadequately controlled with basal insulin or pre-mix/combination insulin, combined with metformin with or without one of the following OADs: SU, glinides, α-GI, SGLT2i or TZD, hereafter collectively referred to as other OADs.

Inadequately controlled diabetes will be defined as HbA_{1c} level of 7.5-11.0 % both inclusive. A total of 210 subjects will be randomised in a 1:1 manner using an interactive web response system (IWRS) to either IDegLira once daily or IDeg once daily both in combination with metformin, see Figure 5–1. To ensure an even proportion of subjects on pre-trial basal or pre-mix/combination insulin in each treatment arm, the randomisation will be stratified with regards to these two different pre-trial insulin therapies combined with metformin with or without one other OAD (see section 11.2).

The duration of the trial from screening to follow-up will be approximately 29 weeks with a screening period of 2 weeks, a treatment duration of 26 weeks, and 1 week of follow-up. The trial will include a screening visit (V1) at which the eligibility of the subjects are assessed followed by a randomisation visit (V2), an end of treatment (ET) visit (V32) and a follow-up contact (P33) at end of trial (week 27).

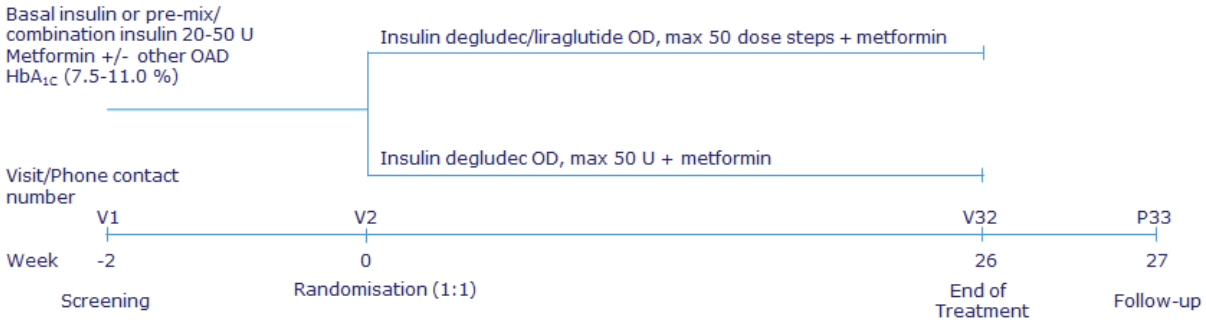


Figure 5–1 Trial design

5.2 Rationale for trial design

Based on prior experience from IDegLira trials, the treatment duration of 26 weeks is sufficient to reach a stable HbA_{1c} level and to obtain sufficient data for efficacy and safety evaluation.

The current trial is designed to demonstrate superiority in HbA_{1c} of IDegLira as compared to IDeg in subjects with T2DM. To enable an evaluation of the contribution of the liraglutide component of IDegLira to glycaemic control and secondary endpoints, the maximum dose of IDeg in the IDeg

arm is set to 50 units, i.e. equivalent to the maximum dose of the IDeg component in IDegLira (50 units of IDeg/1.8 mg of liraglutide).

Two types of insulin are allowed pre-trial (basal and pre-mix/combination insulin), since these may reflect different states of disease progression, the randomisation will be stratified with regards to pre-trial insulin therapy (see section 11.2).

The treat-to-target approach is used in both arms and has been chosen in order to ensure optimal titration based on pre-breakfast SMBG values and thereby to obtain improved HbA_{1c} results.

5.3 Treatment of subjects

Subjects with T2DM treated with 20 to 50 units of basal insulin or pre-mix/combination insulin given once or twice daily in combination with metformin with or without one other OAD are eligible for the trial. Apart from metformin, all other OADs will be discontinued at randomisation. Moreover, basal insulin or pre-mix/combination insulin will be discontinued at randomisation in favour of either IDegLira or IDeg. No other anti-diabetic treatment, or treatment which in the investigators opinion could interfere with weight, glucose or lipid metabolism should be initiated between screening and ET.

Hence, IDegLira and IDeg will be given as add-on to metformin therapy. The trial drugs will be double-blinded and should be injected subcutaneously once daily in the thigh, upper arm (deltoid region) or abdomen. Dosing can be done at any time of the day independent of meals, but should be approximately at the same time of the day throughout the trial for the individual subject. The injection area chosen should remain unchanged throughout the trial, although rotation within the area is recommended. Both trial drugs will be provided in a prefilled device. Titration should be performed twice weekly for both treatment arms (see Appendix A).

5.3.1 Insulin degludec/liraglutide

The recommended start dose of IDegLira is 10 dose steps (10 units IDeg/0.36 mg liraglutide), with the option of choosing up to 16 dose steps (16 units IDeg/0.6 mg liraglutide) at the investigator's discretion. The 0.36 mg of liraglutide contained in the recommended starting dose almost corresponds to the approved starting dose (0.3 mg) of Victoza® in Japan. IDegLira will be titrated twice weekly according to a predefined titration algorithm to a maximum of 50 dose steps (50 units insulin degludec/1.8 mg liraglutide) aiming to reach a FPG target between 4.0 mmol/L (72 mg/dL) and 5.0 mmol/L (90 mg/dL).

5.3.2 Insulin degludec

The recommended starting dose of IDeg is 10 units, with the option of choosing up to 16 units at the investigator's discretion. IDeg will be titrated twice weekly according to a predefined titration

algorithm with a maximum dose of 50 units of IDeg aiming to reach a FPG target between 4.0 mmol/L (72 mg/dL) and 5.0 mmol/L (90 mg/dL).

5.4 Treatment after discontinuation of trial product

When discontinuing trial products, either at the scheduled ET visit or if a subject is withdrawn, the subject should be recommended a suitable marketed product at the discretion of the investigator.

5.5 Rationale for treatment

IDegLira will be investigated to demonstrate efficacy and safety, when administered to insulin experienced subjects with T2DM, inadequately controlled on a stable dose of insulin combined with metformin with or without one other OAD. This is in line with clinical practice to escalate treatment in this setting with the initiation of a GLP-1 receptor agonist, basal insulin or a combination of basal insulin and a GLP-1 receptor agonist, such as IDegLira.

Pre-trial insulin and OAD treatment should be in accordance with current Japanese approved labelling. Subjects should be on at least 90 days of stable treatment (insulin and OADs) defined as unchanged medication and unchanged dose. To reduce the risk of hypoglycaemia all other OADs apart from metformin will be discontinued at randomisation. After randomisation metformin treatment should remain unchanged during the trial, however in case of safety concerns the dose may be reduced at the discretion of the investigator. To avoid impact on trial objectives, no other treatments affecting weight, glucose or lipid should be used, and certain drugs should not be used before the trial (see exclusion criteria no. 5, 6 and 7).

IDeg capped at a maximum dose of 50 units per day have been included as comparator in order to assess the additional effect of the liraglutide component in IDegLira as compared to treatment with IDeg alone at a similar dose.

For further information regarding dosing and treatment refer to Appendix A.

6 Trial population

Number of subjects

Planned number of subjects to be randomised: 210.
Expected number of subjects to complete the trial: 179.

6.1 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 Japanese subjects ≥ 20 years of age at the time of signed informed consent.
3. Type 2 diabetes mellitus subjects (diagnosed clinically) ≥ 6 months prior to screening.
4. HbA_{1c} 7.5-11.0% [58 mmol/mol-97 mmol/mol] (both inclusive) by central laboratory analysis.
5. Subjects on stable daily insulin doses for at least 90 days prior to screening administered once or twice daily according to current Japanese label, either as basal insulin (e.g. IDeg, insulin glargine, insulin detemir, NPH insulin), or pre-mix/combination insulin (e.g. biphasic insulin aspart, insulin degludec/insulin aspart). Total daily insulin dose in the previous 90 days should be within 20-50 units, both inclusive, and on the day of screening, but fluctuations of ± 10% within the 90 days prior to screening are acceptable. The specified insulin treatment should be administered in combination
    - with a stable daily dose of metformin within current approved Japanese label for at least 90 days prior to screening,
    - additionally, the anti-diabetic treatment can be with or without a stable daily dose of one of the following other oral anti-diabetic drugs: sulphonylureas (SU), glinides, α-glucocidase inhibitors (α-GI), sodium-glucose co-transporter-2 inhibitors (SGLT2i) or thiazolidinediones (TZD) within current approved Japanese label for at least 90 days prior to screening.
6. Body Mass Index (BMI) ≥ 23 kg/m^2.

Rational for inclusion criteria:

- Criterion 1 is applied through an ethical consideration, in accordance with the GCP [1]
- Criterion 2 is applied to exclude minors through an ethical consideration. Subjects aged 65 year or older are included in accordance with the ICH guideline: Studies in support of special populations: Geriatrics[12]
- Criteria 3 and 4 are chosen according to the objective of the trial. Being diagnosed for 6 months or more is required in order to ensure correct diagnosis and metabolic stabilisation. HbA_{1c} range

(7.5-11.0 %) is chosen to include subjects whose glycaemic control is not adequate on pre-trial treatment and intensification is considered possible. The upper limit of HbA_{1c} is chosen in order to exclude subjects with unacceptable glycaemic control who need a more intensive therapy.

- Criterion 5 is applied to ensure that the subject's glycaemic control is stabilised at randomisation. 90 days of unchanged pre-trial treatment are required.
- Criterion 6 is chosen in order to ensure a population allowing for exploring the full dose range of IDegLira, and to minimize the individual impact of any weight loss that may be associated with IDegLira treatment.

6.2 Exclusion criteria

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

1. Known or suspected hypersensitivity to trial product(s) or related products.
2. Previous participation in this trial. Participation is defined as signed informed consent.
3. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using adequate contraceptive methods (e.g., abstinence, diaphragm, condom [by the partner], intrauterine device, sponge, spermicide or oral contraceptives).
4. Receipt of any investigational medicinal product (IMP) within 30 days before screening.
5. Use of any anti-diabetic drug in a period of 90 days before screening (except pre-mix/combination insulin or basal insulin, metformin, sulphonylureas (SU), glinides, α-glucocidase inhibitors (α-GI), sodium-glucose co-transporter-2 inhibitors (SGLT2i), or thiazolidinediones (TZD) or anticipated change in concomitant medication, which in the investigators opinion could interfere with glucose metabolism (e.g. systemic corticosteroids or bolus insulin).
6. Previous treatment with glucagon-like peptide-1 (GLP-1) receptor agonist.
7. Treatment with dipetidyl peptidase-4 (DPP-4) inhibitors during the last 90 days prior to screening.
8. Impaired liver function, defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 2.5 times upper limit of normal (UNL).
9. Renal impairment estimated glomerular filtration rate (eGFR) <60ml/min/1.73m^2 as per Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI).
10. Screening calcitonin ≥ 50 ng/L.
11. History of pancreatitis (acute or chronic).
12. Personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN 2).
13. Subjects presently classified as being in New York Heart Association (NYHA) Class IV.
14. Within the past 180 days have had any of the following: myocardial infarction (MI), stroke or hospitalisation for unstable angina and/or transient ischemic attack (TIA) prior to screening.

15. Inadequately treated blood pressure as defined as Class 2 hypertension or higher (Systolic ≥ 160 mmHg or diastolic ≥ 100 mmHg) in accordance with National High Blood Pressure Education Program, 7th Joint National Committee and European Societies of Hypertension/Cardiology 2013 guidelines[13].
16. Proliferative retinopathy or maculopathy requiring acute treatment as verified by fundoscopy or fundus photography performed within 90 days prior to randomisation.
17. Diagnosis of malignant neoplasms within the last 5 years (except basal and squamous cell skin cancer, polyps and in-situ carcinomas) prior to screening.
18. Any condition that in the opinion of the investigator might jeopardise subject's safety or compliance with the protocol.

Rationale for the Exclusion Criteria:

- Criteria 1, 8-18 are chosen to ensure the safety of the subjects
- Criterion 2 is chosen in order to exclude subjects who were previously judged as ineligible, since such subjects may be in an unstable condition and at risk for drop-out
- Criterion 3 is chosen as it is standard requirement for clinical trials with new chemical and biological entities
- Criteria 4-7 are chosen to minimise factors that may influence the results

6.3 Withdrawal criteria

The subject may withdraw consent at will at any time. The subject's decision to withdraw from the trial must always be respected. See section 8.2 for procedures to be performed for subjects withdrawing consent.

The subject may also be withdrawn from treatment at any time at the discretion of the investigator due to a safety concern.

The subject must be withdrawn from the trial treatment if the following applies:

1. Included in the trial in violation of the inclusion and/or exclusion criteria and/or randomised in error.
2. Withdrawal of consent to proceed in the trial.
3. Pregnancy.
4. Intention of becoming pregnant.
5. Initiation of any systemic treatment with products which in the investigator's opinion could interfere with subject's weight, or glucose or lipid metabolism (e.g. systemic corticosteroids).
6. Any of the calcitonin samples analysed by the central laboratory are ≥ 50 ng/L (see Appendix D).
7. Subjects diagnosed with acute pancreatitis (see section 8.5.2).
8. Simultaneous participation in another clinical trial of an approved or non-approved IMP.

9. If the pre-breakfast self-measured blood glucose (SMBG) values taken on three consecutive days or if any of the fasting plasma glucose (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

   Given there is no intercurrent cause for the hyperglycaemia, action is to be taken by the investigator as soon as possible to obtain a confirmatory FPG from central laboratory. If there is no intercurrent cause for the hyperglycaemia, and FPG exceeds the limits stated above, the subject must be withdrawn.

Rationale for the Withdrawal Criteria:

- Criterion 1 is applied to withdraw the subjects enrolled or randomised in error
- Criterion 2 is applied since subjects can withdraw at will at any time
- Criteria 3 and 4 are applied as it is standard requirement for clinical trials with new chemical and biological entities
- Criterion 5 is applied to minimise any factors influencing the results of efficacy and safety in the trial
- Criteria 6-8 are applied for general safety concerns
- Criterion 9 is applied to withdraw subjects who have persistently unacceptable poor glycaemic control from an ethical and safety viewpoints

6.4 Subject replacement

Withdrawn subjects will not be replaced.

6.5 Rationale for trial population

Subjects with T2DM treated with insulin, but in need of treatment intensification to achieve or maintain glycaemic control is the target population for inclusion in the trial.

More specifically Japanese subjects with T2DM inadequately controlled on once or twice daily basal or pre-mix/combination insulin with metformin with or without one other OAD with HbA_{1c} in the range of 7.5-11.0% (both inclusive), and eligibility for treatment intensification based on the investigators discretion, will be randomised to treatment. The rationale for this specific trial population is to ensure inclusion of subjects reflecting a population of insulin treated T2DM subjects that require additional treatment, which will allow for exploration of the higher dose range of IDegLira in order to substantiate the superior effect of IDegLira compared to IDeg. Additionally, a lower limit of BMI (≥ 23 kg/m2) will minimize the individual impact of weight loss that has been observed in global trials with IDegLira.

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

7 Milestones

Planned duration of recruitment period (first patient first visit (FPFV) – last patient first visit (LPFV):16 weeks.
End of trial is defined as last patient last visit (LPLV).

7.1 Recruitment

Recruitment will be done according to agreements with the individual investigational sites. In order to secure recruitment timelines, the agreed distribution of subjects between sites may be changed.

The screening and randomisation rate will be followed closely via the 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.

7.2 Trial registration

Information of the trial will be disclosed at clinicaltrials.gov, novonordisk-trials.com and at the Clinical Trials Information/JapicCTI site (clinicaltrials.jp). According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure[14], it will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors [15], the Food and Drug Administration Amendment Act[16], European Commission Requirements[17, 18] 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. These are also included in the flow chart (see section 2).

8.1 Visit procedures

It is the responsibility of the investigator to ensure that all site visits and phone contacts including procedures occur according to the flow chart. A phone contact may be converted to a site visit, if needed, while a site visit cannot be converted to a phone contact.

8.1.1 Investigator's assessment

Review of diaries, PROs, laboratory reports, ECGs, eye examination (fundoscopy/fundus photography), physical examination 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 investigator site as source documentation.

If clarification of entries or discrepancies in the diary or PRO 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.

At screening visit (V1) any abnormal clinically significant findings (laboratory reports, ECGs, eye examination, physical examination etc.) must be recorded in the medical history/concomitant illness form in the electronic case report form (eCRF). At subsequent visits' any clinically significant change or new clinically significant finding must be reported as an AE according to section 12.2.

8.1.2 Fasting requirements

The subject should attend some visits fasting. Fasting is defined as at least 8 hours prior to visit without food and drink intake, except for water. Trial product and metformin should be withheld on the day of the visit until blood sampling has been performed. Other prescribed concomitant medication can be taken as usual.

If the subject attends a fasting visit in a non-fasting condition, blood sampling should be rescheduled, preferably within the visit window.

8.1.3 Informed consent process

Informed consent must be obtained before any trial-related activity, see section 18.2. Accordingly, before any screening (V1) procedure takes place, the investigator must provide the subject with verbal and written information about the trial. The date of informed consent must be transcribed to the eCRF.

8.1.4 Screening

Screening will be carried out by using IWRS (see section 10). Each subject will be assigned a unique 6-digit subject number which will remain the same throughout the trial.

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

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

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 the eye examination is missing, the investigator must ensure these are obtained for assessment of eligibility prior to the randomisation of the subject.

8.1.4.1 Screening failures

For screening failures the screening failure form in the eCRF must be completed with the reason for not continuing in the trial. Serious adverse events (SAEs) from screening failures must be transcribed by the investigator into the eCRF. Follow-up on SAEs must be carried out according to section 12. A screening failure session must be made in the IWRS. The case book must be signed.

Re-screening is NOT allowed if the subject has failed one of the inclusion or exclusion criteria; this includes re-sampling (unless samples are lost or unsuitable for analysis e.g. haemolysed).

8.1.5 Randomisation

Randomisation should NOT take place more than 14 calendar days after screening (V1). 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.

At randomisation (V2), the subject will be supplied with trial product, receive training in trial product and pen handling, and given directions for use verbally and in writing. For further information on trial product please see section 9. The subject should take the first dose of trial product on the day of randomisation (V2) or the day after. The date and first dose of trial product should be recorded in the diary and the eCRF. In case a starting dose of more than 10 dose steps or units is selected, the reason for dose selection should be recorded. Pre-trial insulin and other OADs than metformin should be discontinued.

Randomisation of subjects and allocation of trial product will be done using the IWRS (see sections 10 and 11).

8.1.6 Visits and phone contacts during treatment period

If a site visit/phone contact for some reason is not performed at the scheduled time point, the investigator should ensure that the site visit/phone contact is performed as soon as possible and aim to schedule within the visit window. Date of visit and visit window is calculated in relation to the randomisation visit (V2).

8.1.7 End of treatment visit

At ET (V32), a completion session must be done in the IWRS and last date on trial product must be captured in the IWRS. Further, the final drug accountability must be performed via IWRS. Subjects can at the investigator's discretion be recommended a suitable marketed product at and after ET.

Anti-diabetic treatment initiated at or after ET (V32) and at the FU (P33) should not be recorded in the eCRF.

8.1.8 Follow-up phone contact

The FU phone contact (P33) should be scheduled at least 7-10 days after ET (V32). The end of trial form must be completed in the eCRF.

8.1.9 Unscheduled visits

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

- Additional laboratory samples are needed due to an AE requiring special forms in the eCRF (see section 8.5.1.2)
- A blood re-sampling (out of visit window) related to a specific visit is needed. Only if scheduled blood sample could not be analysed
- Confirmatory FPG test for withdrawal 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. Also, if only additional trial product dispensing or auxiliary supply is needed, no unscheduled visit form should be completed, but an additional dispensing session should be made in the IWRS.

8.2 Withdrawal from trial

If a subject withdraws consent, the investigator must aim to undertake procedures similar to those at ET (V32) as soon as possible. If the subject agrees, the FU contact (P33) must be performed at least 7 days after discontinuation 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 withdrawal session must be made in the IWRS. When all data has been monitored and all queries have been resolved the case book must be signed.

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

8.3 Subject related information/assessments

8.3.1 Demography

Demography will be recorded at screening and consists of:

- Date of birth
- Sex
- Race

8.3.2 Diabetes history and diabetes complications

Diabetes history and diabetes complications should be recorded in the eCRF at screening (V1). The following should be recorded in the diabetes history/diabetes complications form:

- Date of diagnosis of diabetes
- Diabetes complications (i.e. diabetic retinopathy/neuropathy/nephropathy and macro angiopathy (including peripheral vascular disease)

The following should be recorded in the family history form:

- Family history of diabetes

8.3.3 Concomitant illness and medical history

A **concomitant illness** is any illness that is present at the start of the trial (i.e. at V1) 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 and diabetes complications 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. Only relevant medical history related to the evaluation of this trial should be reported at the investigator's discretion.

The information collected for concomitant illness and medical history should include diagnosis, date of onset and date of resolution or continuation, as applicable. It should be recorded at screening (V1) in the eCRF at the medical history/concomitant illness form.

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

8.3.4 Concomitant medication

A **concomitant medication** is any medication, other than the trial product, which is taken during the trial. Anti-diabetic treatment (diabetes treatment history, i.e. pre-trial insulin and OADs) taken in the time between screening (V1) and randomisation (V2) will also be regarded as concomitant medication.

Details of any concomitant medication must be recorded at screening (V1) in the eCRF. Changes in concomitant medication must also be recorded at each visit as they occur until ET (V32).

The information collected for each concomitant medication includes trade name or generic name, dose (only for pre-trial insulin), 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.

Concomitant medication initiated at ET (V32) and at the FU (P33) should not be recorded in the eCRF.

8.3.4.1 Metformin

Metformin and its dosing information should be recorded at the concomitant specific drug metformin form in the eCRF.

The metformin treatment should be kept unchanged unless changed for safety reasons. In case of change in total daily dose, it must be reported at the concomitant specific drug metformin form in the eCRF. The information collected for metformin includes trade name or generic name, dose, start date and stop date or continuation.

8.3.5 Tobacco use

Details of tobacco use must be recorded at screening (V1). Smoking is defined as smoking at least one cigarette or equivalent daily.
Smoking status:

- Never smoked
- Previous smoker
- Current smoker

8.4 Efficacy assessments

8.4.1 Self-measured blood glucose (SMBG)

At screening (V1), subjects will be provided with a BG meter to be used for daily pre-breakfast SMBG measurements during the trial. The subjects will receive written instructions for use and demonstration on how to use the device including performance of regular calibrations according to the manufacturer´s instructions. As necessary, the instructions will be repeated 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.

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

Subjects should be instructed how to record the SMBGs in the diaries. The record of each pre-breakfast SMBG should include date and value. All data from the diary must be transcribed into the eCRF during or following the contact with site. If obtained via phone and a discrepancy is detected later on, the values in the eCRF should be corrected.

For SMBG values that meet the definition of a hypoglycaemic episode (see section 8.5.7), relevant information must be registered in the subject diary and a hypoglycaemic episode form must be completed in the eCRF.

8.4.1.1 9-point self-measured blood glucose (SMBG) profile

Subjects will be instructed to perform a 9-point SMBG profile three times during the trial and record it in the diary. The 9-point SMBG profiles should include date and value in addition to actual clock time of each measurement. As for daily SMBGs, the data from the diary must be transcribed into the eCRF. The measurements should take place preferably within the week prior to the site visit on days where the subject does not anticipate unusual strenuous exercise.

The points of SMBG measurements starts with a pre-breakfast SMBG on day 1 and ends with a pre-breakfast SMBG on the following day as listed in Table 8–1 below.

Table 8–1 9-point profile (SMBG)

Time point	Day 1	The following day
Pre-breakfast	√	√
90 min after start of breakfast	√	
Before lunch	√	
90 min after start of lunch	√	
Before dinner	√	
90 min after start of dinner	√	
At bedtime	√	
At 4 a.m.	√	

Trial product and metformin should be withheld until after the pre-breakfast SMBG measurements have been performed. Other prescribed concomitant medication can be taken as usual.

8.4.2 Body weight

Body weight should be measured (kilogram [kg], with one decimal) without shoes and only wearing light clothing and recorded in the eCRF. Preferably the same equipment should be used throughout the trial.

8.4.3 Waist circumference

The waist circumference is the minimal abdominal circumferences located midway between the lower rib margin and the iliac crest.

Waist circumference must be performed and recorded in the eCRF. The waist circumferences will be measured in cm using a non-stretchable measuring tape. It should be recorded to the nearest ½ cm preferably using the same measuring tape throughout the trial.

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

8.4.4 Blood pressure

Blood pressure (systolic and diastolic) should be measured after the subject has been resting for at least 5 minutes in a sitting position. It is recommended to use the same arm and preferably the same equipment throughout the trial.

At screening (V1) the blood pressure should be measured three times and all three values should be entered into the eCRF. The mean value will be calculated by the eCRF and must be in accordance with the relevant exclusion criteria (see section 6.2). For the subsequent visits, one measurement needs to be performed. If the investigator suspects white coat hypertension, re-assessment of the blood pressure (as described above) is allowed.

8.5 Safety assessments

8.5.1 Adverse events

All AEs must be collected and reported from the first trial-related activity, after the subject has signed the informed consent, to FU (P33). Information on AEs occurring between ET (V32) and FU (P33) must be collected and recorded in the eCRF. Procedures for reporting are outlined in section 12.2.

Mind that a clinically significant worsening of a concomitant illness (section 8.3.3) must also be reported as an AE.

8.5.1.1 Medication error

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

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

For definition of medication errors, see section 12.1.4.

8.5.1.2 Adverse events requiring additional data collection

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

The events of concern are:

- Fatal events
- Cardiovascular events
- Thyroid disease
- Neoplasm
- Renal failure
- Pancreatitis

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

Further details of AEs requiring additional data collection in the eCRF can be found in Appendix C.

Cardiovascular events

Acute coronary syndrome

All types of MI or hospitalisation for unstable angina. If an event of acute coronary syndrome is observed during the trial, this must be recorded as an AE and moreover 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
- Treatment given for the condition
- Revascularisation procedures

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

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. TIA, Stroke)
- Contributing condition
- Neurologic signs and symptoms
- History of neurologic disease
- Imaging supporting the condition
- Treatment given for the condition

Heart failure requiring hospitalisation

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, see Appendix B for definition
- Supportive imaging
- Supportive laboratory measurements
- Initiation or intensification of treatment for this condition

Thyroid disease

If an event of thyroid disease, including any thyroid neoplasms, is 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 peroxiodase antibodies
    - Thyroglobulin and thyroglobulin antibody
    - Thyroid stimulating hormone 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

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

Renal failure

If an event of renal failure is observed during the trial the following additional information should be reported if available:

- Signs and symptoms of renal failure
- Specific laboratory test supporting a diagnosis of renal failure
- Imaging performed supporting the diagnosis
- Kidney biopsy results
- Relevant risk factors associated with the event

Pancreatitis

If an event of pancreatitis is observed 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
    - ALT and AST
    - Bilirubin
    - Alkaline Phosphatase
- Imaging performed and consistency with pancreatic disease
- Complications to the event
- Relevant risk factors for pancreatic disease including:
    - History of gallstones
    - History of pancreatitis
    - Family history of pancreatitis
    - Trauma

8.5.2 Assessments in case of suspicion of acute pancreatitis

In case of acute, severe persistent abdominal pain leading to a suspicion of acute pancreatitis, the trial product should be interrupted until pancreatitis is ruled out. Appropriate examinations must be performed, including measurement of amylase and lipase. Subjects diagnosed with acute pancreatitis must be withdrawn from trial treatment. Diagnosis is usually based on at least 2 of the following 3 criteria:

- characteristic abdominal pain
- amylase and/or lipase > 3x upper normal range (UNR) or
- characteristic findings on ultrasound /computerised axial tomography/magnetic resonance imaging

If acute pancreatitis is ruled out, trial product should be re-initiated at the discretion of the investigator. The investigator should consider the last dose of trial product and moreover the recommendations outlined in Appendix A.

Appropriate treatment and careful monitoring of the subject should be initiated if pancreatitis is confirmed as per at least 2 of the criteria´s listed above.

8.5.3 Eye Examination

Eye examination (fundoscopy/fundus photography) must be performed by the investigator or a local ophthalmologist or an optometrist according to local practice. Dilation is not a requirement. The result of the fundoscopy/fundus photography will be interpreted locally by the investigator. To document this, the investigator must sign and date the result page and the interpretation must follow the categories:

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

Fundoscopy/fundus photography performed within 90 days prior to randomisation (V2) is acceptable and does not need to be repeated, unless worsening of visual function since the last examination has been noted. The investigator must interpret, sign and date the result page. If fundoscopy or fundus photography is performed before a subject has signed the informed consent form, it must be documented in the medical record that reasons for performing the procedure was not related to this trial.

Eye examination performed within a period of 14 days before ET (V32) is acceptable if results are available at the ET visit.

8.5.4 Electrocardiogram (ECG)

A 12-lead ECG must be performed by the investigator or delegated staff and interpreted by the investigator. To document this, the investigator must sign and date the ECG print out and the interpretation must follow the categories:

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

ECG obtained as part of routine practise may replace the screening assessment, if results are available for evaluation at the randomisation visit and if obtained within 14 days prior to randomisation (V2). The ECG must be done at randomisation (V2) at the latest.

ECG obtained within 14 days before ET (V32) is acceptable, if results are available for evaluation at the ET visit.

8.5.5 Pulse

Pulse (beats per minute) should be measured after resting at least 5 minutes in a sitting position and recorded in the eCRF.

8.5.6 Physical Examination

A physical examination must be performed at the visits specified in the flowchart (section 2) and includes:

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

The interpretation must follow the categories:

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

Relevant findings present at or prior to screening should be recorded on the concomitant illness/medical history form in the eCRF in accordance with section 8.3.3. Findings not present at screening must be reported as AE according to section 12.2.

8.5.7 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) when they occur in conjunction with hypoglycaemic symptoms

should be recorded by the subject. These must be transcribed into the eCRF (hypoglycaemic episode form) throughout the trial from randomisation (V2) to FU (P33).

The record should include the following information:
- Date and time of hypoglycaemic episode
- The plasma glucose level before treating the episode (if available)
- Whether the episode was symptomatic
- Whether the subject was able to treat him/herself (if no, see below)
- Type, date, time and dose of last trial product and OAD administration prior to episode
- Date and time of last main meal prior to episode
- Whether the episode occurred in relation to physical activity
- Any sign of fever or other disease
- Whether the subject was asleep when the episode occurred
    - If yes, whether the symptoms of the episode woke up the subject

If the subject was not able to treat him/herself

The answer to the question: "Was 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[19].

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

- Who assisted in the treatment of the hypoglycaemic episode (i.e. family/friend/co-worker or similar, paramedic, doctor or other, please specify)
- Where the treatment was administered (i.e. at home/at friends/at work or similar, in an ambulance, emergency room/hospital or other, please specify)
- Type of treatment provided by other person (i.e. oral carbohydrates, glucagon, IV glucose or other, please specify)
- Were symptoms alleviated 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 trial product dose, other factors not listed, please specify or none)
- Did the subject experience seizure?
- Was the subject unconscious/comatose?
- Did the subject experience any of the following symptoms[20]
    - Autonomic: sweating, trembling, hunger or palpitations
    - Neuroglycopenic: confusion, drowsiness, speech difficulty, visual disturbances, odd behaviour, impaired balance or incoordination
    - General malaise: headache or malaise
- Did the subject experience other symptoms? Please specify
- Description of the episode, if applicable

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

A hypoglycaemic episode form must be filled in for each hypoglycaemic episode. If the hypoglycaemic episode fulfils the criteria for an SAE then an AE form and a safety information form (SIF) must also be filled in, see section 12.2.

Information on AEs and hypoglycaemic episodes occurring between ET (V32) and FU (P33) must be collected and recorded in the eCRF.

8.5.8 Suspicion of acute hypersensitivity to trial products

If trial product is discontinued as a consequence of suspicion of severe acute hypersensitivity (anaphylactic reaction) to the trial product, blood sampling for assessment of binding antibodies and IgE antibodies against the active components in the trial products, i.e. insulin degludec and liraglutide, should be conducted. Depending on treatment arm, samples will be analysed for anti-liraglutide antibodies, anti-insulin degludec antibodies including cross reacting antibodies to human insulin, anti-liraglutide IgE antibodies and anti-insulin degludec IgE antibodies.

Blood sampling should be performed at least 7 days after but no later than 4 weeks after the event. Treatment with insulin degludec (Tresiba®), insulin degludec/insulin aspart (Ryzodeg®) and any GLP-1 receptor agonists (e.g. Victoza® and Byetta®) is not permitted in this period.

8.6 Laboratory assessments

All laboratory samples will be analysed by a central laboratory contracted by Novo Nordisk. The central laboratory will provide all laboratory supplies for the sampling and transportation of all blood samples taken during the trial.

Description of assay methods and a description of the procedures for obtaining samples, handling, storage and shipment of the samples are specified in a trial-specific laboratory manual provided to the sites. Information regarding laboratory materials such as tubes and labels are also described.

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

The laboratory equipment may provide analyses not requested in the protocol but produced automatically in connection with the requested analyses according to specifications in the laboratory standard operating procedures. Such data will not be transferred to the trial database, but abnormal values will be reported to the investigator. The investigator must review the laboratory results for concomitant illnesses and AEs and report these according to section 12.2 and document it on the reports by date and signature.

8.6.1 Laboratory assessments for efficacy

Except from screening (V1), blood samples will be drawn in a fasting state (see section 8.1.2) according to flow chart (see section 2). They will be analysed to determine levels of the below efficacy laboratory parameters.

8.6.1.1 Glucose metabolism

- HbA_{1c}
- FPG

8.6.1.2 Lipids

- Cholesterol (total)
- LDL cholesterol
- VLDL cholesterol
- HDL cholesterol
- Triglycerides
- Free fatty acids

8.6.2 Laboratory assessments for safety

Except from screening (V1), blood samples will be drawn in a fasting state (see section 8.1.2). They will be analysed to determine levels of the below safety laboratory parameters.

8.6.2.1 Haematology

- Haemoglobin
- Haematocrit
- Thrombocytes
- Erythrocytes
- Leucocytes
- Differential count (eosinophils, neutrophils, basophils, monocytes and lymphocytes)

8.6.2.2 Biochemistry

- Creatinine
- eGFR value will be calculated using the serum creatinine result and the CKD-EPI formula by the central laboratory
- ALT
- AST
- Alkaline phosphatase
- Sodium
- Potassium
- Albumin
- Bilirubin (total)
- Urea
- Creatine kinase
- Calcium (total)
- Calcium, ionized (albumin corrected)
- Lipase
- Amylase

8.6.2.3 Hormones

- Calcitonin, if ≥ 10 ng/L, see Appendix D for monitoring of calcitonin.

8.6.2.4 Pregnancy test

- Human serum chorionic gonadotrophin (hCG)

Pregnancy testing must be performed on female subjects of childbearing potential. Female subjects of childbearing potential must be instructed to use adequate contraceptive methods throughout the trial and until 7-10 days after ET (V32).

Females of childbearing potential must have a serum pregnancy test (beta-human chorionic gonadotropin [beta-hCG]) performed at screening (V1) before entering the trial and at ET (V32).

Urine pregnancy tests will be performed at the site during the trial for females of childbearing potential if a menstrual period is missed or if pregnancy is suspected.

If subject reports missing menstrual period, the subject will have a urine-stick pregnancy test performed as soon as possible.

Pregnancy test will not be required for women of non-childbearing potential.

Female of non-childbearing potential is defined as:

- Female who has undergone a hysterectomy, bilateral oophorectomy or bilateral tubal ligation
- Postmenopausal defined as women above 50 years with no menses for 12 months and without an alternative medical cause
- Other medical reasons preventing childbearing potential

Non-childbearing potential reasons must be recorded at the medical history/concomitant illness form in the eCRF.

8.7 Other assessments

8.7.1 Height

Height should be measured without shoes in centimetres (cm) and recorded in the eCRF to nearest ½ cm. Height measured at screening (V1) will only be used for calculation of BMI.

8.7.2 Body Mass Index

BMI will be calculated at screening (V1) for assessment of eligibility (section 6.1).

The BMI will be calculated by the eCRF once body weight and height is entered at screening (V1).

It is calculated as follows:
BMI (kg/m^2) = body weight (kg)/(height [m] × height [m])

8.7.3 Patient reported outcomes

The following PRO questionnaires must be completed by the subject:

- DTR-QOL[21]
- EQ-5D-5L[22]

The investigator is only allowed to fill in the headings of the questionnaires and is not allowed to influence the subject in answering.

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.

8.7.4 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. However, after ET (V32), the diary data at the FU contact (P33) will be collected per phone. Consequently, source data from the FU contact (P33) will be the notes written by the investigator in the subject's medical record and based on an interview.

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

- Subject number
- Site contact details
- Time and date of next visit or phone contact
- Prescribed dose of trial product
- Prescribed metformin treatment
- Prescribed diabetes treatment at V32
- Doses and values from SMBG measurements from previous diary, if required to complete next dose adjustment
- Review signature and date

The subject must record the following information in the diary:

- Date and value of the daily pre-breakfast SMBG (see section 8.4.1)
- Date, actual clock time and value of the 9-point profile SMBG prior to V2, V18 and V32 (see section 8.4.1.1)

- Date and dose of trial product each day
    - Time for the first and the last trial product dose taken when randomised and at ET, respectively
- Hypoglycaemic episodes (see section 8.5.7)
- Medical issues
- Changes to concomitant medication (see section 8.3.4)
- Changes in total daily dose of metformin (see section 8.3.4.1)

If the subject is not able to complete the diary and need assistance from a third party to complete the diary, this must be stated in the subject's medical records.

Based on the values from the SMBG measurements, the investigator/subject will assess whether trial product dose needs adjustment according to the titration guideline (Appendix A).

The diary must be reviewed by the investigator to ensure that AEs, including medical issues and concomitant medication, are reported (see section 8.3.4, 8.5.1 and 12.2). In addition, the investigator must ensure that the SMBG measurements are reported as hypoglycaemic episodes if required (see section 8.5.7).

The investigator or delegated staff should transcribe the diary data to the eCRF as soon as possible, preferable within 24 hours after each site visit/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.

8.7.5 Training in the trial product and pen handling

The subjects must be trained in how to handle the trial product when handed out the first time at randomisation (V2) and one week after (V4) to ensure sufficient training. Moreover, directions for use (DFU) will be dispensed. Training must be repeated during the trial as needed.

8.8 Subject compliance

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

The investigator should assess the 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 SMBG measurements.

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 used by any person not included in the trial. IDegLira and IDeg must not be used, if it does not appear clear and colourless.

9.1 Trial products

The following trial products will be provided by Novo Nordisk:

Table 9–1 Trial products

Trial product	Strength	Dosage form	Route of administration	Container/ delivery device
Insulin degludec/ liraglutide	100 units/mL + 3.6 mg/mL	Solution for injection	Subcutaneous	3 mL pre-filled PDS290 pen injector
Insulin degludec	100 units/mL			

IDegLira and IDeg are visually identical.

The trial products will be dispensed to each subject according to the treatment group they have been randomised to. The IWRS will allocate trial product (DUNs) to the subject at the randomisation visit and at each dispensing visit (see section 10).

9.2 Metformin

Metformin will not be supplied by Novo Nordisk.

9.3 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 screening and randomisation.

The investigator must document that direction for use (DFU) is given to the subject orally and in writing at the first dispensing visit (V2). At subsequent dispensing visits it is up to the investigator to assess if it is needed to hand out the DFU as indicated in the flow chart, see section 2).

9.4 Storage

Table 9–2 Storage conditions

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

*In-use time starts when the first dose is taken or product is taken out of the refrigerator at subject's residence

The investigator, the head of the study site or the trial product storage manager (if assigned by the head of the study site) 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). A temperature log must be kept to document storage within the right temperature interval and storage facilities should be checked frequently. Additional details regarding handling of temperature deviations can be found in the TMM.

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

9.5 Drug accountability and destruction

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

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

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

The trial products must be accounted for at pen level and either recorded as used/partly used, unused or lost. Returned pens must be sent for destruction, thus may not be re-allocated to new subjects.

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

9.6 Auxiliary supplies

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

- DFU for the PDS290 pen injector
- Needles (no longer than 8 mm) for the PDS290 pen injector
- BG meters and BG meter auxiliaries
- Glucose for treating a hypoglycaemia

Only needles provided by Novo Nordisk must be used for administration of trial product.

10 Interactive web response system

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

IWRS is used for:

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

IWRS user manuals will be provided to each trial site.

It is important that only DUNs allocated by the IWRS are dispensed to the subject. By doing this it will ensure that;

- The right trial product is dispensed to the right subject
- Needed stock is available at a site for the subjects
- Drug accountability can be made in the IWRS

If a subject requires additional trial product between dispensing visits, the site must perform an additional dispensing session in IWRS.

11 Randomisation procedure and breaking of blinded codes

11.1 Randomisation

Eligible screened subjects will be randomised via the IWRS into two treatment arms in a 1:1 manner.

11.2 Stratification

To ensure an even proportion of subjects on pre-trial basal or pre-mix/combination insulin in each treatment arm, the randomisation will be stratified as in the following with regards to these two different pre-trial insulin therapies combined with metformin with or without one other OAD:

- metformin + basal insulin
- metformin + basal insulin + one other OAD
- metformin + pre-mix/combination insulin
- metformin + pre-mix/combination insulin + one other OAD

11.3 Breaking of blinded codes

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

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

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

If the code has been broken, the subject must be withdrawn and a withdrawal session must be completed in IWRS.

12 Adverse events, technical complaints and pregnancies

12.1 Definitions

12.1.1 Adverse event

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

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

An AE includes:

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

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

- Pre-existing conditions, including those found as a result of screening or other trial procedures performed before exposure to trial product (pre-existing conditions should be reported as medical history or concomitant illness).
- Pre-planned procedures unless the condition for which the procedure was planned has worsened from the first trial-related activity after the subject has signed the informed consent.
- Non-serious hypoglycaemia is an AE, but is reported on a hypoglycaemic episode form instead of on an AE form, see section 8.5.7.

The following three definitions are used when assessing an AE:

- **Severity**
    - **Mild –** no or transient symptoms, no interference with the subject's daily activities.
    - **Moderate** – marked symptoms, moderate interference with the subject's daily activities.
    - **Severe** – considerable interference with the subject's daily activities; unacceptable.
- **Causality**
  Relationship between an AE and the relevant trial product*(s)*:
    - **Probable** - Good reason and sufficient documentation to assume a causal relationship.
    - **Possible** - A causal relationship is conceivable and cannot be dismissed.
    - **Unlikely** - The event is most likely related to aetiology other than the trial product.

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

12.1.2 Serious adverse event

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

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

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

[b] The term "hospitalisation" is used when a subject:

- Is admitted to a hospital or in-patient, irrespective of the duration of physical stay, or
- Stays at the hospital for treatment or observation for more than 24 hours

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

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

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

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

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

12.1.3 Non-serious adverse event

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

12.1.4 Medication errors

A medication error concerning trial products is defined as:

- Administration of wrong drug or use of wrong device.
- Use of wrong DUN is not considered a medication error.
- Wrong route of administration, such as intramuscular instead of subcutaneous
- Administration of an overdose with the intention to cause harm (e.g. suicide attempt), misuse or abuse of trial product.
- Accidental administration of a lower or higher dose than intended. That is a dose lower or higher than 20 % 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.

Medication errors must be reported on an AE form and a specific event form, see section 8.5.1.1.

12.1.5 Adverse events requiring additional data collection

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

Some events in this trial will be adjudicated by an independent external committee as described in section 12.7.2.

Table 12–1 lists AEs that require completion of specific event forms in the eCRFs and/or are subject to event adjudication.

Table 12–1 Adverse events requiring completion of specific event forms and/or are subject to event adjudication

Event	Specific event form	Event adjudication
Fatal event	No	Yes
Acute coronary syndrome (MI or hospitalisation for unstable angina)	Yes	Yes
Cerebrovascular event (stroke or TIA)	Yes	Yes
Heart failure (requiring hospitalisation)	Yes	Yes, 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
Thyroid disease (including thyroid neoplasm)	Yes	Yes, (only if thyroid neoplasm or resulting in thyroidectomy)
Neoplasm (excluding thyroid neoplasm)	Yes	Yes
Renal failure	Yes	No
Pancreatitis	Yes	Yes
Medication error (see section 12.1.4)	Yes	No

For details about specific event forms, see section 8.5.1.2 and Appendix C.

12.1.6 Technical complaints

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

Examples of technical complaints:

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

12.2 Reporting of adverse events

All events meeting the definition of an AE must be collected and reported. This includes events from the first trial-related activity after the subject has signed the informed consent until the end of the post-treatment follow-up period (P33), see flowchart in section 2. The events must be recorded in the applicable eCRF forms in a timely manner, see timelines below, Table 12–2 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.

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.

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

Timelines for initial reporting of AEs:
The investigator must complete the following forms in the eCRF within the specified timelines:

- **SAEs:** The AE form **within 24 hours** and the SIF **within 5 calendar days** of the investigator's first knowledge of the SAE. Both forms must be signed within 7 calendar days from the date the information was entered in the eCRF.
- **For SAEs requiring reporting on a specific event form**: In addition to the above the specific event form within **14 calendar days** from the investigator's first knowledge of the AE.
- **For non-serious AEs:** The AE form within **14 calendar days** of the investigators first knowledge of the AE.
- **For non-serious AEs requiring additional data collection:** The AE form and the specific event form within **14 calendar days** of the investigator's first knowledge of the event.
- **Events for Adjudication:** The adjudication form within **14 calendar days** of the investigator's first knowledge of the AE, see section 12.7.2.

Table 12–2 Summary of reporting timelines for adverse events

Event Type / Form	AE Form[1]	SIF[1]	Specific event form[1]	Adjudication form[1]
SAE	24 hours[2]	5 days[2]		
Non-serious AE	14 days			
Non-serious AE with additional data collection	14 days		14 days	14 days[3]
SAE with additional data collection	24 hours[2]	5 days[2]	14 days	14 days[3]

[1]All days are calendar days
[2]Forms must be signed within 7 days
[3]If qualifying for adjudication

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

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

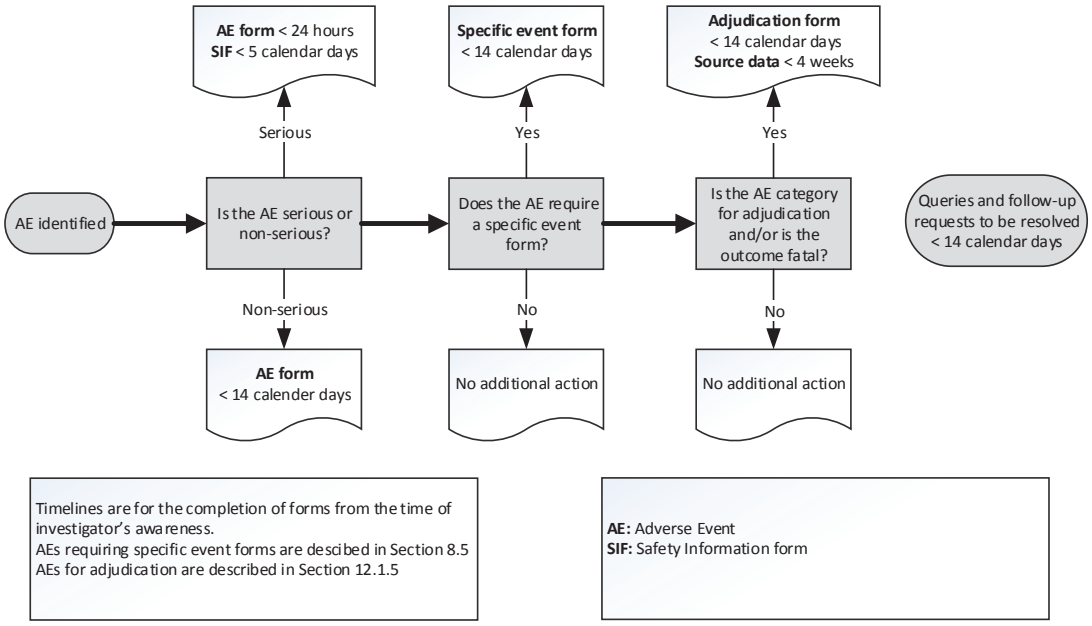


Figure 12–1 Reporting of adverse events

Novo Nordisk assessment of AE expectedness:
Novo Nordisk assessment of expectedness is performed according to the following reference documents:

- IDegLira; current version of the company core data sheet and any updates thereto.
- IDeg; current version of the company core data sheet and any updates thereto.

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

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

Novo Nordisk products used as concomitant medication:
If an AE is considered to have a causal relationship with a Novo Nordisk marketed product used as concomitant medication in the trial, it is important that the suspected relationship is reported to

Novo Nordisk, e.g. in the alternative aetiology section on the SIF. Novo Nordisk may need to report this AE to relevant regulatory authorities.

12.3 Follow-up of adverse events

The investigator must record follow-up information by updating the forms in the eCRF. Follow-up information must be reported to Novo Nordisk according to the following:

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

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

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

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

12.4 Technical complaints and technical complaint samples

12.4.1 Reporting of technical complaints

All technical complaints on any of the following products:

- IDegLira, 100 units/mL + 3.6 mg/mL, 3 mL prefilled PDS290 pen injector
- IDeg (Tresiba®), 100 units/mL, 3 mL prefilled PDS290 pen injector
- Needles for prefilled pens

which occur from the time of first usage of the product until the time of the last usage of the product, must be collected and reported to Customer Complaint Center, Novo Nordisk. Contact details (fax, e-mail and address) are provided in Attachment I to the protocol.

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

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

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

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

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

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

12.4.2 Collection, storage and shipment of technical complaint samples

The investigator must collect the technical complaint sample and notify the monitor **within 5 calendar days** of obtaining the sample at trial site. The monitor must coordinate the shipment to Customer Complaint Center, Novo Nordisk (the address is provided in Attachment I) and ensure that the sample is sent as soon as possible. A copy of the technical complaint form must be included in the shipment of the sample. If several samples are returned in one shipment, the individual sample and the corresponding technical complaint form must be clearly separated.

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

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

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

12.5 Pregnancy

12.5.1 Pregnancy 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:

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

SAEs:

- AE form[a] **within 24 hours** of the investigator's first knowledge of the SAE.
- 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.

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

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

Treatment with glucose-lowering agents such as insulin and GLP-1 therapies carry the risk of hypoglycemia.

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

Hypoglycaemic episodes should be treated according to best practise at the discretion of the investigator. Attention should be given to the fact that the action profile of the insulin component in IDegLira and IDeg is 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 carbohydrate. Severe hypoglycaemia resulting in loss of consciousness must be treated according to best medical practice (e.g. 25mL of 50% dextrose solution given intravenously, or 0.5-1mg of glucagon given subcutaneously or intramuscularly).

From clinical trials and marketed use of liraglutide (Victoza®) overdoses up to 40 times the recommended maintenance dose of 1.8 mg (72 mg) outside Japan have been reported. Events

reported included severe nausea and severe vomiting. None of the reports included severe hypoglycaemia. All patients recovered without complications.

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

For more information, see the current IB version of IDegLira[11], IDeg[8] and liraglutide[9] or any updates hereof.

12.7 Committees related to safety

12.7.1 Novo Nordisk safety committee

Novo Nordisk will constitute an internal IDegLira safety committee to perform ongoing safety surveillance. The IDegLira safety committee will be informed about the results of continuous on-going safety surveillance activities for IDegLira and may recommend unblinding of any data for further analysis. 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 event adjudication committee (EAC) is established to perform qualitative or quantitative validation of selected AEs according to pre-defined diagnostic criteria. The validation is based on review of pre-defined clinical data related to the specific AE.

The events are reviewed by the EAC in a blinded manner.

The AEs for adjudication are listed in Table 12–1. A full list of AEs for adjudication and rationales for adjudicating these can be found in Appendix C.

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 investigator must provide medical documentation as soon as possible, when they receive the request from Novo Nordisk.

The EAC can evaluate an event not initially reported as an AE for adjudication to be adjudicated. If so then the investigator must provide medical documentation as soon as possible, when they receive the request from Novo Nordisk or the Event Adjudication vendor.

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 within 4 weeks according to instructions in the event adjudication site manual.

The assessment made by the EAC will be included in the clinical trial report as well as the assessments made by the investigator. However, the adjudication made by the event adjudication committee, given its independent analysis of each event, will be attributed with greater importance of the two.

13 Case report forms

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

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

The following will be provided as paper CRFs:

- Pregnancy forms

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

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

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

indicate this by writing "NA" (not applicable) in the appropriate answer field. Further guidance can be obtained from the instructions in the CRF.

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

13.1 Corrections to case report forms

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

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

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

13.2 Case report form flow

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

The SMBG measurements and corresponding trial drug doses for titration purpose should be entered within **24 hours** after the site visit/phone contact throughout the trial.

At the end of trial the investigator should ensure that all remaining data have been entered into the eCRF no later than **3 days** after LPLV at the site 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.

13.2.1 Paper case report form flow

The pregnancy forms are paper based CRFs. Also, the technical complaint form, SIF and AE form will be provided in paper but are only to be used if for any reason the eCRF is unavailable. If corrections are needed, see section 13.1.

14 Monitoring procedures

During the course of the trial, the monitor will visit the trial site to ensure that the protocol is adhered to, that all issues have been recorded, to perform source data verification and to monitor drug accountability. The first monitoring visit will be performed as soon as possible after FPFV at the trial site and no later than 4 weeks after. The monitoring visit intervals will depend on the outcome of the remote monitoring of the eCRFs, the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP, but will not exceed 12 weeks until LPLV at the trial site.

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

All data must be verifiable in source documentation other than the eCRF, except age and BMI which are calculated by the eCRF.

For all data recorded the source document must be defined in a source document agreement at each trial site. There must only be one source defined at any time for any data element.

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

The diary is considered source document for the SMBG values, trial product dosing information and hypoglycaemic episodes.

Source data generated by the trial site can be corrected by another person than the person entering the source data; any correction must be explained, signed and dated by the person making the correction.

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

The monitor will ensure that the eCRFs are completed on an ongoing basis.

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

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

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

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

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 will be summarised using the FAS and safety endpoints will be summarised using the safety analysis set (SAS).

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

Unless otherwise specified, all continuous measurements will be summarised descriptively at each visit by treatment using observed data. After 26 weeks of treatment, descriptive statistics will be

presented based both on observed and last observation carried forward (LOCF) imputed data. Endpoints that are analysed untransformed and endpoints that are not formally analysed are summarised by the arithmetic mean, standard deviation (SD), median, and minimum and maximum value. Endpoints that are analysed log-transformed are supplemented with the geometric mean and coefficient of variation (CV).

For measurements over time, mean values will be plotted to explore the trajectory over time. LOCF imputed data will be used as the basis for plotting data, if not otherwise specified. For endpoints that are analysed log-transformed, the geometric mean values will be plotted.

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

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

Handling of missing data

The expected percentage of missing data is around 15%. In accordance with industry guidance[24] endpoints will be assessed at frequent visits. If an assessment has been made both at screening (V1) and randomisation (V2), and if not otherwise specified, the value from the randomisation visit will be used as the baseline value. If the value measured at the randomisation visit is missing and the assessment also has been made at screening, then the screening value will be used as the baseline value.

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

17.1 Sample size calculation

The primary objective of this trial is to confirm the superiority of insulin IDegLira versus IDeg in controlling glycaemia in Japanese subjects with T2DM. The primary endpoint is the change from baseline in HbA1c after 26 weeks.

Formally, let D be the mean difference (IDegLira - IDeg) in change from baseline in HbA_{1c} . Superiority will thus be considered confirmed if the upper bound of the two-sided 95% confidence interval for D is strictly below 0.0%. Equivalently, if the p-value for the two-sided test of

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

is less than 5% and D < 0, where D is the mean treatment difference. This is equivalent to using a one-sided test of size 2.5%, which means that the type 1 error rate is controlled at 2.5%.

The sample size is determined using a t-statistic under the assumptions of a two-sided test of size 5%, a mean treatment difference of 0.45% for the completers, a retained effect of 0.2% for the 15% withdrawals and a standard deviation of 1.0%. Superiority will be investigated on the FAS. The above assumptions are based on experience from the phase 3a development programmes for IDegLira and IDeg. From these assumptions and based on a 1:1 randomisation the sample size is set to 105 subjects per treatment arm; in total 210 subjects will be randomized. This will ensure a nominal power of at least 84.5% (see Table 17–1).

Table 17–1 Power for various rates of withdrawal and efficacy retention (adjusted treatment difference)

	Withdrawal rate			
Eff.ret.(%)	**5%**	**10%**	**15%**	**20%**
0.00	86.9% (0.428)	83.2% (0.405)	78.8% (0.383)	73.8% (0.360)
0.10	87.7% (0.433)	84.9% (0.415)	81.8% (0.398)	78.2% (0.380)
0.15	88.0% (0.435)	85.7% (0.420)	83.2% (0.405)	80.3% (0.390)
0.20	88.4% (0.438)	86.5% (0.425)	84.5% (0.413)	82.2% (0.400)

Considering 0% efficacy retention as the most conservative approach for the anticipated 15% of subjects discontinuing randomised treatment, for the multiple imputation sensitivity analysis, the expected treatment difference is reduced to 0.38% for the superiority test. A total of 105 subjects per treatment arm will then yield a superiority power of at least 78.8%.

17.2 Definition of analysis sets

The following analysis sets are defined in accordance with the ICH-E9 guidance[25]:

- **Full Analysis Set (FAS)**: includes all randomised subjects. In exceptional cases, subjects may be eliminated from the full analysis set. In such cases the elimination will be justified and documented. The statistical evaluation of the FAS will follow the intention-to-treat principle and subjects will contribute to the evaluation "as randomised"
- **Safety Analysis Set (SAS)**: includes all subjects receiving at least one dose of the investigational product or comparator. Subjects in the safety set will contribute to the evaluation "as treated"
- **Completer Analysis Set (CAS)**: includes all randomised subjects who have completed the trial. Subjects in the CAS will contribute to the evaluation "as randomised"

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

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

17.3 Primary endpoint

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

The change from baseline in HbA_{1c} after 26 weeks of treatment will be analysed using an ANCOVA model with treatment, pre-trial anti-diabetic treatment (metformin + basal insulin, metformin + one other OAD + basal insulin, metformin + pre-mix/combination insulin, metformin + one other OAD + pre-mix/combination insulin) as fixed factors and baseline HbA_{1c} as covariate. Missing values after 26 weeks of treatment will be imputed applying LOCF using HbA_{1c} values at and after baseline.

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

17.3.1 Sensitivity analysis

Sensitivity analysis will be performed on FAS using the mixed model for repeated measurement (MMRM) to evaluate the robustness of using LOCF. All HbA_{1c} values available post baseline at scheduled measurement times will be analysed in a linear mixed normal model using an unstructured residual covariance matrix for HbA_{1c} measurements within the same subject. The model will include treatment, visit and pre-trial anti-diabetic treatment as fixed factors and baseline HbA_{1c} as covariate. Interactions between visit and all factors and between visit and baseline HbA_{1c} are also included in the model.

Further, a pattern mixture model approach, mimicking an intention-to-treat scenario will be applied. The imputation in the IDegLira arm will be based on IDeg values. It will be done as follows:

- In the first step intermittent missing values are imputed using a Markov Chain Monte Carlo method, in order to obtain a monotone missing data pattern. This imputation is done for each treatment group separately and 1000 copies of the dataset will be generated.
- In the second step, for each of the 1000 copies of the dataset, an analysis of variance model with treatment and pre-trial anti-diabetic treatment as fixed factors, and baseline HbA_{1c} as covariates is fitted to the change in HbA_{1c} from baseline to 4 weeks (V10) for the comparator group only. The estimated parameters, and their variances, from this model are used to impute missing values at 4 weeks for subjects in comparator and IDegLira treatment groups, based on pre-trial anti-diabetic treatment and HbA_{1c} at baseline.
- In the third step, for each of the 1000 copies of the dataset, missing HbA_{1c} values at 8 weeks (V14) are imputed in the same way as for 4 weeks. Now the imputations are based on an analysis of variance model with the same factors and the HbA_{1c} values at baseline and 4 weeks as covariates, fitted to the comparator group.
- This stepwise procedure is then repeated sequentially over the available planned visits, adding one visit in each step until the last planned visit at 26 weeks (V32)
- For each of the complete data sets, the change from baseline to 26 weeks is analysed using an analysis of variance model with treatment and pre-trial anti-diabetic treatment as fixed factors and baseline HbA_{1c} value as a covariate.

The estimates and standard deviations for the 1000 data sets are pooled to one estimate and associated standard deviation using Rubin's rule[26]. From these pooled estimates the confidence interval for the treatment differences and the associated p-value are calculated.

The results of sensitivity analyses will be compared to the result of the standard ANCOVA method using LOCF for imputation of missing data. Any marked difference between the MMRM, the pattern mixture approach and ANCOVA LOCF approach regarding the estimated treatment difference will be commented upon in the clinical trial report.

17.4 Secondary endpoints

17.4.1 Supportive secondary endpoints

17.4.1.1 Efficacy endpoints

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

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

- $HbA_{1c} < 7.0\%$
- $HbA_{1c} \leq 6.5\%$

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

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

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

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

Fasting plasma glucose (FPG)
Change from baseline in FPG after 26 weeks of treatment will be analysed using the standard ANCOVA model.

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

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

Self-measured blood glucose (SMBG) 9-point profile
The following six endpoints from the 9-point profile will be defined:

- 9-point profile (individual SMBG values) [One endpoint]
- Mean of the 9-point profile, defined as the area under the profile (calculated using the trapezoidal method) divided by the measurement time [One endpoint]
- 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 [Four endpoints]

A linear mixed effect model will be fitted to the 9-point SMBG profile data. The model will include treatment, pre-trial anti-diabetic treatment, time, the interaction between treatment and time and the interaction between pre-trial anti-diabetic treatment and time as fixed factors and subject as random effect. From the model mean profile by treatment and relevant treatment differences will be estimated and explored.

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

Lipids
Total cholesterol, low density lipoprotein cholesterol (LDL cholesterol), high density lipoprotein cholesterol (HDL cholesterol), very low density lipoprotein cholesterol (VLDL cholesterol), triglycerides, and free fatty acids after 26 weeks of treatment will be analysed separately by using the standard ANCOVA model. In these statistical analyses the endpoint will be log-transformed and so will the 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 first day of exposure to randomised treatment and no later than 7 days after the last day of randomised treatment. If the event has onset date before the first day of exposure on randomised treatment and increases in severity during the treatment period and until 7 days after the last drug date, then this event should also be considered as a TEAE. Here the first day of IMP administration is defined as the first day of exposure to randomised treatment.

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 one event (N), the percentage of subjects with at least one event (%), the number of events (E) and the event rate per 100 years of exposure (R).

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

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

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

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

Classification of Hypoglycaemia

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

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

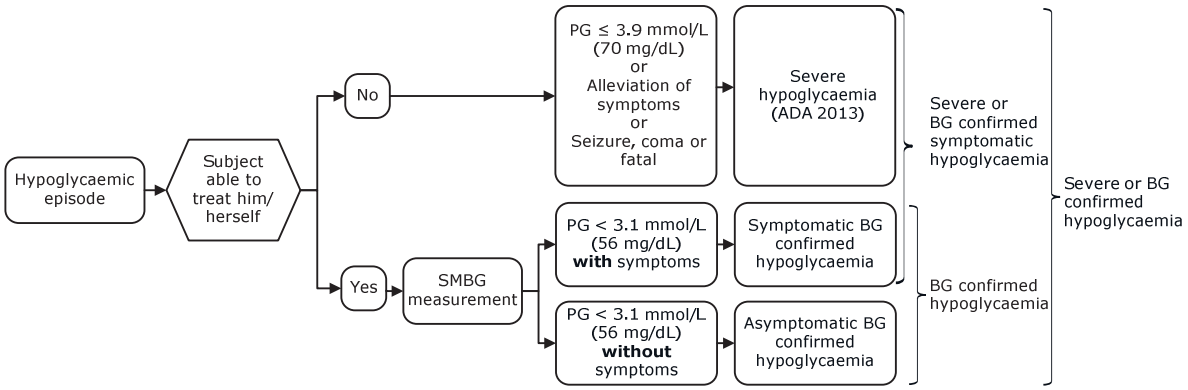
Hypoglycaemic episodes are classified according to the Novo Nordisk classification of hypoglycaemia (see Figure 17–1) and the ADA classification of hypoglycaemia (see Figure 17–2).

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)[27]. Therefore, Novo Nordisk has included hypoglycaemia with plasma glucose levels below this cut-off point in the definition of BG confirmed hypoglycaemia.

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

- Severe or BG confirmed symptomatic hypoglycaemia: An episode that is severe according to the ADA classification[19] or BG confirmed by a plasma glucose value < 3.1 mmol/L (56 mg/dL) **with** symptoms consistent with hypoglycaemia.
- Severe or BG confirmed hypoglycaemia: An episode that is severe according to the ADA classification[19] or BG confirmed by a plasma glucose value < 3.1 mmol/L (56 mg/dL) **with** or **without** symptoms consistent with hypoglycaemia.



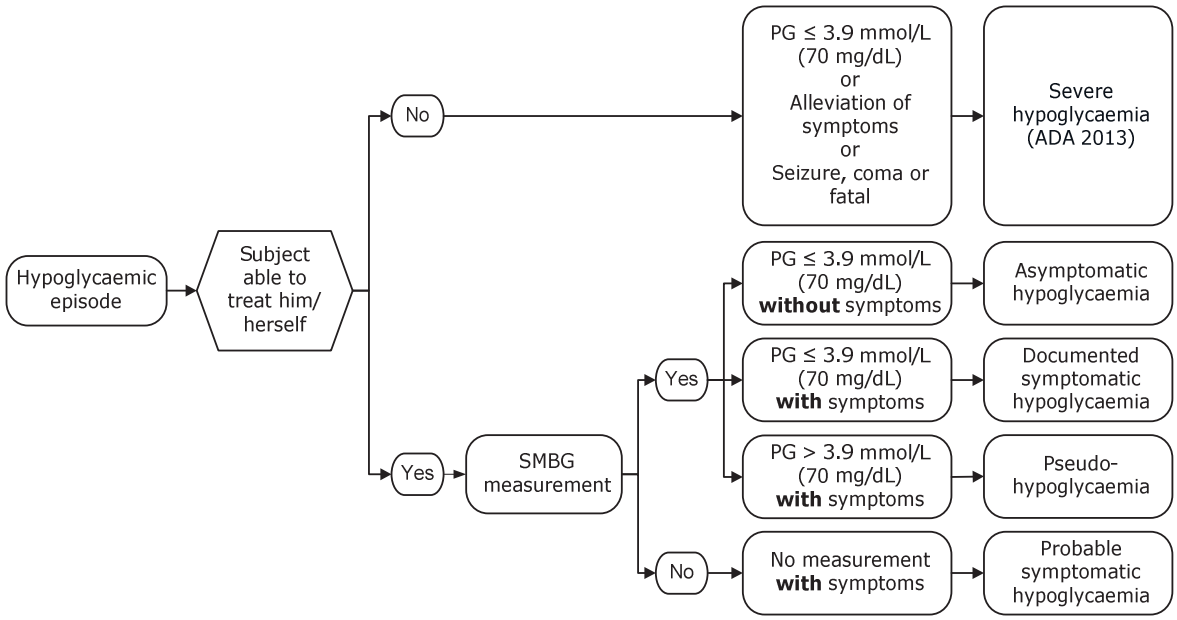
Note: Glucose measurements are performed with capillary blood calibrated to plasma equivalent glucose values

Figure 17–1 Novo Nordisk classification of hypoglycaemia

ADA classification[19] 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

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

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

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

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

- summaries for each visit
- shift table from baseline to after 26 weeks of treatment

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

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

Laboratory assessments
All laboratory parameters will be summarised descriptively.

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

- Shift tables from baseline to after 26 weeks of treatment
- Proportion of subjects with measurements outside reference range by treatment and week

Laboratory values will be presented graphically as box plots by treatment and week. For each laboratory parameter, individual values outside the reference ranges (abnormal values) will be listed.

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

Calcitonin will be displayed in terms of the number of subjects (N), the percentage of subjects (%) and the incidence rate per 100 years of exposure (R).

The following criteria are defined for tabulations:

Persistent (all post baseline measurements)

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

Incidental (at least one post baseline measurements)

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

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

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

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

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

17.5 Patient reported outcomes

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

- DTR-QOL questionnaire
- EQ-5D-5L questionnaire

The questionnaires will be summarised descriptively by visit and treatment.

For the DTR-QOL questionnaire change from baseline in the following scores will be analysed separately using the standard ANCOVA:

- Domain QOL scores
    - Burden on social activities and daily activities
    - Anxiety and dissatisfaction with treatment
    - Hypoglycemia
    - Satisfaction with treatment
- Total QOL score

For the EQ-5D-5L questionnaire change from baseline in QOL and VAS scores will analysed separately using the standard ANCOVA.

Quality Adjusted Life Years will be evaluated in a separate report by the Novo Nordisk Health Economics and Outcomes Research department.

18 Ethics

18.1 Benefit-risk assessment of the trial

The trial will be conducted in compliance with ICH GCP [1] and applicable regulatory requirements, and in accordance with the Declaration of Helsinki [2]. All subjects will be included after an evaluation in regards to inclusion/exclusion criteria defined in order to ensure that subjects are eligible for participating in the trial. Randomised subjects will be treated with IDegLira or IDeg in combination with metformin. Such regimen is anticipated to be equal to or better than basal insulin or pre-mix/combination insulin combined with metformin with or without one other OAD as received by subjects before entering the trial. A potential benefit of participating in the trial is that the investigator will obtain an additional knowledge of the subjects' disease and will therefore be able to provide recommendations for the best treatment to be used following trial participation.

Both trial products are marketed in several countries. 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 products 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 products and gradual dose adjustment. Furthermore, subjects will be fully informed about possible AEs and inconveniences and will be instructed to contact the investigator in case of any concerns regarding the trial participation.

Withdrawal criteria have been defined to ensure that subjects are considered for discontinuation if the level of glycaemic control exceeds unacceptable limits during trial participation.

IDeg and liraglutide have shown to be effective in lowering BG levels[28-32].

It can therefore be expected that the majority of subjects with insufficiently controlled BG, randomised to treatment with fixed combination of IDegLira, will experience an improved glucose control during the trial as also shown in clinical trials conducted outside Japan[10]. In addition, these subjects may benefit from the effect of treatment on weight previously demonstrated for liraglutide[28-32].

The most common side effect of all available insulin products is hypoglycaemic episodes. IDeg is a basal insulin preparation with a long acting effect. So, recovery from a hypoglycaemic episode may be delayed as for other long acting insulin's.

There have been a few 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 rare events of acute pancreatitis, Novo Nordisk will analyse blood samples for amylase and lipase during the trial to monitor the subjects' safety.

In both genders of rats and mice, liraglutide causes dose-dependent and treatment-duration dependent thyroid C-cell tumours at clinically relevant exposures. It is unknown whether liraglutide causes thyroid C-cell tumours, including MTC, in humans, as human relevance could not be ruled out by clinical or non-clinical studies. Liraglutide is contraindicated in subjects with a personal or family history of MTC and in subjects with MEN 2. Based on the findings in rodents, monitoring with serum calcitonin or thyroid ultrasound was performed during clinical trials, but this may have increased the number of unnecessary thyroid surgeries. It is unknown whether monitoring of serum calcitonin or thyroid ultrasound will mitigate human risk of thyroid C-cell tumours. Subjects with thyroid disease will be closely monitored and in case of elevated calcitonin a recommendation for follow-up is included in Appendix D.

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 Food and Drug Administration 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.

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

Areas of special interest with regards to safety of trial product are described in detail in the current IB version of IDeglira[11], liraglutide[9] and IDeg[8] and in the current version of the Japanese approved labelling for Vicoza® and Tresiba®.

When treatment with trial product ends, the subject and investigator will decide on the best available treatment. Novo Nordisk will not offer investigational drugs after the end of trial treatment.

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 that the subject has ample time to come to a decision whether or not to participate in the trial and before obtaining a voluntary, signed and personally dated informed consent from the subject.

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.

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 an abnormality is found in the foetus or new-born infant.

18.3 Data handling

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

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

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

18.4 Information to subjects during trial

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

All written information to subjects must be sent to IRB 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 or a regulatory authority may decide to stop the trial, part of the trial or a trial site at any time, but agreement on procedures to be followed must be obtained.

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

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

19 Protocol compliance

19.1 Protocol deviations

Deviations from the protocol should be avoided.

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

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

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

19.2 Prevention of missing data

The importance of subject retention will be addressed by Novo Nordisk in the training and communication with the trial sites. Moreover, the subjects will be carefully informed about the trial procedures by the investigator before signing informed consent, so that they know the implications of participating in the trial (see 8.1.3).

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

20 Audits and inspections

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

21 Critical documents

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

- Regulatory approval and/or acknowledgement of notification as required
- Approval/favourable opinion from IRBs 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 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 IB
- 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)

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

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

22 Responsibilities

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

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

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

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

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

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

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

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

23 Reports and publications

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

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

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

One investigator will be appointed by Novo Nordisk to review and sign the clinical trial report (signatory investigator).

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[14].

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[33] (sometimes referred to as the Vancouver Criteria).

Publication(s) will be prepared for submission to scientific congresses and peer-reviewed journals in collaboration between Novo Nordisk and investigator(s) appointed by Novo Nordisk. These investigator(s) must meet the International Committee of Medical Journal Editors authorship criteria to be named authors on publications.

23.1.2 Site-specific publication by investigator

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

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

23.2 Investigator access to data and review of results

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

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

24 Retention of clinical trial documentation

24.1 Retention of clinical trial documentation

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

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

The investigator must be able to access his/her trial documents without involving Novo Nordisk in any way. Site-specific CRFs and other subject data (in an electronic readable format or as paper copies or prints) will be provided to the investigator before access is revoked to the systems 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 at least 20 years after discontinuation of the marketing authorisation, termination of the trial or cancellation of the research project whichever is longest.

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

25 Institutional Review Boards and regulatory authorities

25.1 Institutional Review Boards

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

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

The investigator must ensure submission of the clinical trial report synopsis to the IRB according to local regulatory requirements.

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. The records must be filed in the investigator trial master file and copies must be sent to Novo Nordisk.

25.2 Regulatory Authorities

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

26 Indemnity statement

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

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

27 References

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Appendix A

Insulin Titration Guideline

Trial ID: NN9068-4184

DUAL™ II Japan

A double-blinded trial comparing the efficacy and safety of insulin degludec/liraglutide and insulin degludec both in combination with metformin in Japanese subjects with type 2 diabetes mellitus inadequately controlled with basal or pre-mix/combination insulin therapy and oral anti-diabetic drugs

Trial Phase: 3a

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1 Introduction

The goal of insulin therapy is to achieve near normoglycaemia, i.e. to reach a pre-defined HbA_{1c} level with a low rate of hypoglycaemic episodes and as little weight gain as possible. Several trials have shown that this is difficult to achieve, unless plasma glucose values are intensively monitored and the insulin dose(s) frequently adjusted (1-4).

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

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

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

2 Treatment regimens

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

- IDegLira once daily
- IDeg once daily

First dosing should take place on the day of randomisation (V2) or on the day following randomisation.

Maximum dose for IDegLira is 50 dose steps.

Maximum dose for IDeg is 50 units.

There are no minimum doses for IDegLira or IDeg.

2.1 Injection area

Both IDegLira and IDeg should be injected subcutaneously into the thigh, upper arm (deltoid region) or the abdomen.

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

2.2 Time of injection

Dosing time can be anytime of the day, but should be approximately on the same time each dosing day throughout the trial.

3 Initiation and titration

3.1 Initiation of IDegLira

The recommended start dose of IDegLira is 10 dose steps (10 units of IDeg and 0.36 mg liraglutide) daily, with the option of choosing up to 16 dose steps (16 units IDeg/0.6 mg liraglutide) at the investigator's discretion.

3.2 Initiation of IDeg

The recommended start dose of IDeg is 10 units, with the option of choosing up to 16 units at the investigator's discretion.

3.3 Titration of IDegLira and IDeg

IDegLira and IDeg will be titrated twice weekly according to a predefined titration algorithm aiming to reach a FPG target of 4.0-5.0 mmol/L (72-90 mg/dL).

The doses of IDegLira or IDeg should be adjusted twice weekly by the subject on fixed days (Tuesdays and Fridays), according to a predefined titration algorithm described in Table 1. The investigator will support titration at all contacts.

Table 1 Twice weekly titration on fixed days (Tue/Fri)

	Sun	Mon	Tue	Wed	Thu	Fri	Sat
SMBG	X[1]	X[1]	X[1]	X[2]	X[2]	X[2]	X[2]
Dose titration			Titration[1]			Titration[2]	
Dose (D)	D[2]	D[2]	D[1]	D[1]	D[1]	D[2]	D[2]

[1] The dose for Tuesday, Wednesday and Thursday will be determined based on the mean pre-breakfast SMBG values, obtained on the last Sunday, Monday and Tuesday.

[2] The dose for Friday, Saturday, Sunday and Monday will be determined based on the mean pre-breakfast SMBG values, obtained on the last Wednesday, Thursday and Friday.

[3] SMBG measurements on Saturdays are not used for titration

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

Table 2 Twice weekly adjusted titration

Mean pre-breakfast SMBG values		Dose adjustment
mmol/L	mg/dL	Dose steps/units
< 4.0	< 72	-2
4.0-5.0	72-90	0
> 5.0	> 90	+2

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

3.4 Deviations from the algorithm

It is recommended that the algorithm is followed. However, it is also important that the decision to adjust the trial drug doses are based on all relevant information as described in section 3.3. A reason for deviating from the algorithm should be entered into the eCRF.

4 Data collection

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

- Pre-breakfast SMBG values measured since last visit/phone contact
- Doses of IDegLira or IDeg taken before and after titration
- Reasons for deviation from the titration algorithms, if applicable
- Hypoglycaemic episodes

5 Review procedure

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

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

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

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

6 References

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Appendix B

New York Heart Association Criteria for Functional Capacity

Trial ID: NN9068-4184

DUAL™ II Japan

A double-blinded trial comparing the efficacy and safety of insulin degludec/liraglutide and insulin degludec both in combination with metformin in Japanese subjects with type 2 diabetes mellitus inadequately controlled with basal or pre-mix/combination insulin therapy and oral anti-diabetic drugs

Trial Phase: 3a

1 Criteria for Functional Capacity [1]

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

2 Reference

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

Appendix C

Events with additional data collection and events requiring adjudication

Trial ID: NN9068-4184

DUAL™ II Japan

A double-blinded trial comparing the efficacy and safety of insulin degludec/liraglutide and insulin degludec both in combination with metformin in Japanese subjects with type 2 diabetes mellitus inadequately controlled with basal or pre-mix/combination insulin therapy and oral anti-diabetic drugs

Trial phase: 3a

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 must be reported including all-cause mortality: • Cardiovascular death • Non-cardiovascular death • Undetermined cause of death	An U.S Food and Drug Administration (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: • MI • Hospitalisation for unstable angina	All types of 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 TIA)	**Stroke** (ischaemic, haemorrhagic or undetermined) is defined as an acute episode of neurological dysfunction, caused by focal or global brain, spinal cord, or retinal vascular injury. **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 requiring admission.	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
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
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

Events with additional data collection and/or events requiring adjudication	Definitions	Rationale	Event Adjudication Committee
Renal failure	• All events of renal failure should be reported, including events fulfilling one of the following three diagnostic criteria, fulfilling the diagnosis of acute renal failure: • Increase in serum creatinine ≥ 0.3 mg/dL within 48 hours • Increase in serum creatinine to ≥ 1.5 times baseline within 7 days • Urine volume < 0.5 mL/kg/h for 6 hours	The liraglutide component in IDegLira has been associated with dehydration/volume depletion. Severe dehydration/volume depletion per se can be associated with development of renal impairment and acute renal failure. Therefore renal impairment and acute renal failure are followed closely.	No adjudication
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 and/or 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

2 References

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

Appendix D

Monitoring of calcitonin

Trial ID: NN9068-4184

DUAL™ II Japan

A double-blinded trial comparing the efficacy and safety of insulin degludec/liraglutide and insulin degludec both in combination with metformin in Japanese subjects with type 2 diabetes mellitus inadequately controlled with basal or pre-mix/combination insulin therapy and oral anti-diabetic drugs

Trial phase: 3a

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 where liraglutide is included as in this trial where it is a component of the trial product, 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 exclusion criteria of this trial. 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.

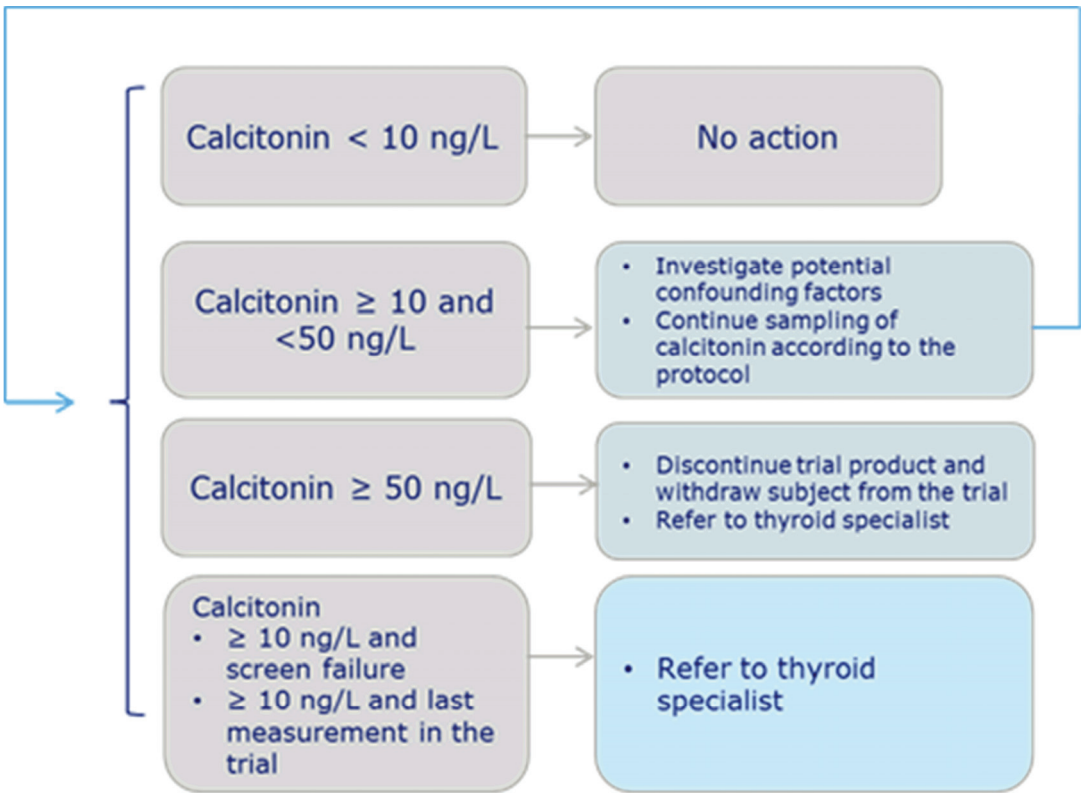

Figure 1 Flow of calcitonin monitoring

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 withdrawn from the trial. All medications suspected to relate to this condition should 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 (medullary thyroid cancer) resulting in a positive predictive value of 100 %.

Diagnostic evaluation should include:

- thyroid ultrasound
- 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 (multiple endocrine neoplasia type 2) 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 subject must be withdrawn from the trial. All medications suspected to relate to this condition should be discontinued.

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 calcitonin > 10 ng/L to screen for C-cell disease, but they do not provide sufficient information on patients with basal calcitonin >10 and <20 ng/L to allow conclusions[2, 3].

3 References

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Protocol Amendment

No 1
to Protocol, final version 2.0
dated 02 May 2016

DUAL™ II Japan
Trial ID:NN9068-4184

A double-blinded trial comparing the efficacy and safety of insulin degludec/liraglutide and insulin degludec both in combination with metformin in Japanese subjects with type 2 diabetes mellitus inadequately controlled with basal or pre-mix/combination insulin therapy and oral anti-diabetic drugs

Trial phase: 3a

Applicable to Japan

Amendment originator:

[redacted], PhD

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1 Introduction including rationale for the protocol amendment

An inquiry to protocol section 5.3.1 have been received from PMDA concerning that the recommended start dose of IDegLira is 10 dose steps (10 units IDeg/0.36 mg liraglutide), with the option of choosing up to 16 dose steps (16 units IDeg/0.6 mg liraglutide), at the investigator's discretion, but the 16 dose steps correspond a starting dose of 0.6 mg liraglutide which is not an approved starting dose of Victoza in Japan. Accordinly, PMDA request additional text in section 5.3.1 to cover that consideration of patient safety is at the investigators discretion when starting at 16 dose steps corresponding to 0.6 mg liraglutide.

PMDA inquiry was as follows:
There is an explanation about the starting dose of IDegLira in protocol section 5.3.1, 'The recommended start dose of IDegLira is 10 dose steps (10 units IDeg/0.36 mg liraglutide), with the option of choosing up to 16 dose steps (16 units IDeg/0.6 mg liraglutide) at the investigator's discretion. The 0.36 mg of liraglutide contained in the recommended starting dose almost corresponds to the approved starting dose (0.3 mg) of Victoza® in Japan.'

PMDA request for added text was as follows:
With regard to the starting dose of 16 dose steps, please consider adding the explanation in the protocol such as '*The 0.6 mg of liraglutide contained in the starting 16 dose steps is different from the approved starting dose of Victoza® in Japan, however in consideration of each subject's safety status including the possibility of hypoglycaemia or hyperglycaemia up to 16 dose steps can be chosen at the investigator's discretion'*.:.

We have applied according to PMDA request in this amendment No 1 to protocol version 2.0

In this protocol amendment:

- Any new text is written *in italics.*

2 Changes

The following changes in section 5.3.1 have been made:

2.1 Section 5.3.1– PMDA request for added text is implemented

2.1.1 Change:

The recommended start dose of IDegLira is 10 dose steps (10 units IDeg/0.36 mg liraglutide), with the option of choosing up to 16 dose steps (16 units IDeg/0.6 mg liraglutide) at the investigator's discretion. The 0.36 mg of liraglutide contained in the recommended starting dose almost corresponds to the approved starting dose (0.3 mg) of Victoza® in Japan. *The 0.6 mg of liraglutide contained in the starting 16 dose steps is different from the approved starting dose of Victoza® in Japan, however in consideration of each subject's safety status, including the possibility of hypoglycaemia or hyperglycaemia, up to 16 dose steps can be chosen at the investigator's discretion*. IDegLira will be titrated twice weekly according to a predefined titration algorithm to a maximum of 50 dose steps (50 units insulin degludec/1.8 mg liraglutide) aiming to reach a FPG target between 4.0 mmol/L (72 mg/dL) and 5.0 mmol/L (90 mg/dL).

2.1.2 Rationale:

The starting dose of liraglutide could potentially be 0.6 mg (at the discretion of the investigator) which is not an approved starting dose of Victoza in Japan. So PMDA request it further stated that consideration in relation to subject safety is at the discretion of the investigator when choosing up to 16 dose steps (16 units IDeg/0.6 mg liraglutide) as the starting dose.

Protocol Amendment

No 2
to Protocol, final version 3.0
dated 08 Sep 2016

Trial ID: NN9068-4184

A double-blinded trial comparing the efficacy and safety of insulin degludec/liraglutide and insulin degludec both in combination with metformin in Japanese subjects with type 2 diabetes mellitus inadequately controlled with basal or pre-mix/combination insulin therapy and oral anti-diabetic drugs

Trial phase: 3a

Applicable to Japan

Amendment originator:

[redacted], PharmD

TrialOps 2, Insulin & Devices

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1 Introduction including rationale for the protocol amendment

1.1 Eligibility criteria update

The trial population is insulin-treated type 2 diabetes mellitus subjects. Originally these were required to have a 90-day stable treatment of anti-diabetic drugs; insulin (pre-mix/combination insulin or basal insulin) and oral anti-diabetic drugs (OADs) (metformin, sulphonylureas [SU], glinides, α-glucocidase inhibitors [α-GI], sodium-glucose co-transporter-2 inhibitors [SGLT2i], or thiazolidinediones [TZD]) prior to screening. Moreover, the pre-trial insulin fluctuation should not be greater than 10% over the 90-day stable pre-trial insulin treatment. Additionally the subjects were required to be naïve to glucacon-like peptide-1 (GLP-1) receptor agonist treatment, and not have been treated with dipetidyl peptidase-4 (DPP-4) inhibitors for 90 days prior to screening. These treatment criteria were set in place to avoid bias and minimize the risk of carry-over effect while preserving the overall aim of the trial.

These criteria have, however, been considered to be over restrictive in Japanese clinical practice and due to seriously low recruitment rate, it has been decided to reduce the required period on stable treatment to 60 days. The same reduction from 90 to 60 days has been imposed on the period where DPP-4 inhibitors are not allowed. Correspondingly, it has been decided to include subjects previously treated with, but not currently on GLP-1 receptor agonists for at least 60 days. Furthermore, to maintain the integrity of the trial additional requirements are set in place if GLP-1 receptor agonists have been discontinued previously (i.e. 60 days or more before screening). Additionally, to more closely mirror the target population in Japanese clinical practice, the pre-trial insulin fluctuation rate has been allowed to be up to 20%. All changes are set in place because of seriously low recruitment rates discovered during the trial, which are deemed to be due to over restrictive criteria in Japanese clinical practice.

1.1.1 Medical rationale for why the suggested changes do not challenge the integrity of the trial

The pre-screen period on stable treatment is changed from 90 to 60 days (inclusion criterion #5, exclusion criteria [EC] #6 and #7), in line with the Japanese DUAL I trial. Furthermore, the allowed fluctuation for pre-trial insulin dose is changed from 10 % to 20 %, still ensuring a stable pre-trial insulin treatment, but allowing for somewhat greater fluctuations (inclusion criterion #5). Both of these changes will make the identification of the subjects less cumbersome, while it is not judged to affect risk of carry-over effect in the beginning of the trial. Therefore the subjects will still be in a stable condition at start of investigational treatment. Furthermore, safety of subjects is not likely to be affected by this change.

The less strict approach to GLP-1 receptor agonists (EC #6) is set in place to better reflect Japanese clinical practice where GLP-1 receptor agonists are often used in shorter periods. Due to the overall

aim of the trial, which is to examine the additional effect of liraglutide in insulin degludec/liraglutide (IDegLira) as compared to insulin degludec (IDeg), it is judged unethical to include subjects in whom previous GLP-1 receptor agonists therapy were discontinued due to safety concerns and/or tolerability issues. If we include patients who discontinued due to lack of efficacy we will jeopardize the overall aim of the trial. Initial versions of trial synopsis, trial outline, and protocol secured the overall aim by excluding previous treatment with GLP-1 receptor agonists or DPP-4 inhibitors completely – and moving forward with a more relaxed set of inclusion criteria the protocol must be very clear on how we ensure not to include subjects previously failing or showing intolerance towards GLP-1 receptor agonists. To minimize carry-over effect of incretin-based treatments neither GLP-1 receptor agonists nor DPP-4 inhibitors should have been used in the previous 60 days.

1.2 Recruitment extension

Given the massive challenges to identify the trial population, the recruitment period is extended with 8 weeks (i.e. in total 24 weeks) in order to allow sufficient time for recruitment.

In this protocol amendment:

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

2 Changes

1 Summary

1.4 Key inclusion criteria

- Male or female Japanese subjects, age ≥ 20 years at the time of signing informed consent T2DM subjects (diagnosed clinically) ≥ 6 months prior to screening
- HbA1c 7.5-11.0% [58 mmol/mol-97 mmol/mol] (both inclusive) by central laboratory analysis
- Subjects on stable daily insulin doses for at least *60* ~~90~~ days prior to screening administered once or twice daily, either as basal insulin (e.g. IDeg, insulin glargine, insulin detemir, NPH insulin) or pre-mix/combination insulin (e.g. biphasic insulin aspart, insulin degludec/insulin aspart). Total daily insulin dose in the previous *60* ~~90~~ days should be within 20-50 units, both inclusive, and on the day of screening, but fluctuations of ± *20*~~10~~% within the *60* ~~90~~ days prior to screening are acceptable. The specified insulin treatment should be administered in combination
    - with a stable daily dose of metformin within current approved Japanese label for at least *60* ~~90~~ days prior to screening,

- additionally, the anti-diabetic treatment can be with or without a stable daily dose of one of the following other OADs: SU, glinides, α-GI, SGLT2i or TZD within current approved Japanese label for at least *60* ~~90~~ days prior to screening

- Body Mass Index (BMI) ≥ 23 kg/m^2

1.5 Key exclusion criteria

- Receipt of any investigational medicinal product (IMP) within 30 days before screening
- Use of any anti-diabetic drug in a period of *60* ~~90~~ days before screening (except pre-mix/combination or basal insulin, metformin, SU, glinides, α-GI, SGLT2i, or TZD) or anticipated change in concomitant medication, which in the investigators opinion could interfere with glucose metabolism (e.g. systemic corticosteroids or bolus insulin)
- *Treatment with glucagon-like peptide-1 (GLP-1) receptor agonist during the last 60 days prior to screening and furthermore, the discontinuation of GLP-1 receptor agonist at any point in time must not have been due to safety concerns, tolerability issues or lack of efficacy, as judged by the investigator* ~~Previous treatment with glucagon-like peptide-1 (GLP-1) receptor agonists~~
- Treatment with dipetidyl peptidase-4 (DPP-4) inhibitors during the last *60* ~~90~~ days prior to screening
- Impaired liver function, defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 2.5 times upper limit of normal
- Renal impairment estimated Glomerular Filtration Rate (eGFR) < 60mL/min/1.73m^2 as per Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)
- Screening calcitonin ≥ 50 ng/L
- History of pancreatitis (acute or chronic)
- Personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia type 2 (MEN 2)
- Subjects presently classified as being in New York Heart Association (NYHA) Class IV

5 Trial design

5.5 Rationale for treatment

Pre-trial insulin and OAD treatment should be in accordance with current Japanese approved labelling. Subjects should be on at least *60* ~~90~~ days of stable treatment (insulin and OADs) defined as unchanged medication and unchanged dose. To reduce the risk of hypoglycaemia all other OADs apart from metformin will be discontinued at randomisation. After randomisation metformin treatment should remain unchanged during the trial, however in case of safety concerns the dose may be reduced at the discretion of the investigator. To avoid impact on trial objectives, no other

treatments affecting weight, glucose or lipid should be used, and certain drugs should not be used before the trial (see exclusion criteria no. 5, 6 and 7).

6 Trial population

6.1 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 Japanese subjects ≥ 20 years of age at the time of signed informed consent.
3. Type 2 diabetes mellitus subjects (diagnosed clinically) ≥ 6 months prior to screening.
4. HbA1c 7.5-11.0% [58 mmol/mol-97 mmol/mol] (both inclusive) by central laboratory analysis.
5. Subjects on stable daily insulin doses for at least *60* ~~90~~ days prior to screening administered once or twice daily according to current Japanese label, either as basal insulin (e.g. IDeg, insulin glargine, insulin detemir, NPH insulin), or pre-mix/combination insulin (e.g. biphasic insulin aspart, insulin degludec/insulin aspart). Total daily insulin dose in the previous *60* ~~90~~ days should be within 20-50 units, both inclusive, and on the day of screening, but fluctuations of ± *20*~~10~~% within the *60* ~~90~~ days prior to screening are acceptable. The specified insulin treatment should be administered in combination
    - with a stable daily dose of metformin within current approved Japanese label for at least *60* ~~90~~ days prior to screening,
    - additionally, the anti-diabetic treatment can be with or without a stable daily dose of one of the following other oral anti-diabetic drugs: sulphonylureas (SU), glinides, α-glucocidase inhibitors (α-GI), sodium-glucose co-transporter-2 inhibitors (SGLT2i) or thiazolidinediones (TZD) within current approved Japanese label for at least *60* ~~90~~ days prior to screening.
6. Body Mass Index (BMI) ≥ 23 kg/m^2.

Rational for inclusion criteria:

- Criterion 1 is applied through an ethical consideration, in accordance with the GCP [1]
- Criterion 2 is applied to exclude minors through an ethical consideration. Subjects aged 65 year or older are included in accordance with the ICH guideline: Studies in support of special populations: Geriatrics[12]
- Criteria 3 and 4 are chosen according to the objective of the trial. Being diagnosed for 6 months or more is required in order to ensure correct diagnosis and metabolic stabilisation. HbA1c range (7.5-11.0 %) is chosen to include subjects whose glycaemic control is not adequate on pre-trial treatment and intensification is considered possible. The upper limit of HbA1c is

chosen in order to exclude subjects with unacceptable glycaemic control who need a more intensive therapy.

- Criterion 5 is applied to ensure that the subject's glycaemic control is stabilised at randomisation. *60* ~~90~~ days of unchanged pre-trial treatment are required.
- Criterion 6 is chosen in order to ensure a population allowing for exploring the full dose range of IDegLira, and to minimize the individual impact of any weight loss that may be associated with IDegLira treatment.

6.2 Exclusion criteria

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

1. Known or suspected hypersensitivity to trial product(s) or related products.
2. Previous participation in this trial. Participation is defined as signed informed consent.
3. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using adequate contraceptive methods (e.g., abstinence, diaphragm, condom [by the partner], intrauterine device, sponge, spermicide or oral contraceptives).
4. Receipt of any investigational medicinal product (IMP) within 30 days before screening.
5. Use of any anti-diabetic drug in a period of *60* ~~90~~ days before screening (except pre-mix/combination insulin or basal insulin, metformin, sulphonylureas (SU), glinides, α-glucocidase inhibitors (α-GI), sodium-glucose co-transporter-2 inhibitors (SGLT2i), or thiazolidinediones (TZD) or anticipated change in concomitant medication, which in the investigators opinion could interfere with glucose metabolism (e.g. systemic corticosteroids or bolus insulin).
6. *Treatment with glucagon-like peptide-1 (GLP-1) receptor agonist during the last 60 days prior to screening and furthermore, the discontinuation of GLP-1 receptor agonist at any point in time must not have been due to safety concerns, tolerability issues or lack of efficacy, as judged by the investigator.* ~~Previous treatment with glucagon-like peptide-1 (GLP-1) receptor agonist.~~
7. Treatment with dipetidyl peptidase-4 (DPP-4) inhibitors during the last *60* ~~90~~ days prior to screening.
8. Impaired liver function, defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 2.5 times upper limit of normal (UNL).
9. Renal impairment estimated glomerular filtration rate (eGFR) <60ml/min/1.73m^2 as per Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI).
10. Screening calcitonin ≥ 50 ng/L.
11. History of pancreatitis (acute or chronic).
12. Personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN 2).
13. Subjects presently classified as being in New York Heart Association (NYHA) Class IV.
14. Within the past 180 days have had any of the following: myocardial infarction (MI), stroke or hospitalisation for unstable angina and/or transient ischemic attack (TIA) prior to screening.

15. Inadequately treated blood pressure as defined as Class 2 hypertension or higher (Systolic ≥ 160 mmHg or diastolic ≥ 100 mmHg) in accordance with National High Blood Pressure Education Program, 7th Joint National Committee and European Societies of Hypertension/Cardiology 2013 guidelines[13].
16. Proliferative retinopathy or maculopathy requiring acute treatment as verified by fundoscopy or fundus photography performed within 90 days prior to randomisation.
17. Diagnosis of malignant neoplasms within the last 5 years (except basal and squamous cell skin cancer, polyps and in-situ carcinomas) prior to screening.
18. Any condition that in the opinion of the investigator might jeopardise subject's safety or compliance with the protocol.

7 Milestones

Planned duration of recruitment period (first patient first visit (FPFV) – last patient first visit (LPFV): *24*~~16~~ weeks.
End of trial is defined as last patient last visit (LPLV).

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