Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number:	NCT02607306
Sponsor trial ID:	NN9068-4183
Official title of study:	A trial comparing the efficacy and safety of insulin degludec/ liraglutide, insulin degludec and liraglutide in Japanese subjects with type 2 diabetes mellitus
Document date:	01 June 2018

16.1.1 Protocol and protocol amendments

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Redacted protocol
Includes redaction of personal identifiable information only.

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Protocol

DUAL™ I Japan

Trial ID: NN9068-4183

A trial comparing the efficacy and safety of insulin degludec/liraglutide, insulin degludec and liraglutide in Japanese subjects with type 2 diabetes mellitus

Trial phase: 3a

Protocol originator

[redacted]

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
AP	alkaline phosphatase
AST	aspartate aminotransferase
BG	blood glucose
BMI	body mass index
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CLAE	clinical laboratory adverse event
CRF	case report form
CRO	clinical research organisation
CT	computerised axial tomography
CTR	clinical trial report
CV	coefficient of variation
DFU	direction for use
DUN	dispensing unit number
EAC	event adjudication committee
ECG	electrocardiogram
EDC	electronic data capture
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
ESC	European Society of Cardiology
ESH	European Society of Hypertension
EOT	end of treatment
FAS	full analysis set

FDA	U.S. Food and Drug Administration
FDAAA	Food and Drug Administration Amendment Act
FPG	fasting plasma glucose
FSFV	first subject first visit
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
ICMJE	International Committee of Medical Journal Editors
IDeg	Insulin degludec
IDegLira	Insulin degludec/liraglutide
IgE	immunoglobulin E
IMP	investigational medicinal product
IRB	institutional review board
ITT	Intention-to-treat
IWRS	interactive web response system
J-PI	Japanese package insert
LDL	low density lipoprotein
LLOQ	lower limit of quantification
LOCF	last observation carried forward
LSFV	last subject first visit
LSLV	last subject last visit
LSMeans	Least Square Means
MACE	major adverse cardiovascular event
MedDRA	Medical Dictionary for Regulatory Activities
MEN 2	multiple endocrine neoplasia syndrome type2

MESI	medical event of special interest
MHLW	Ministry of Health, Labour and Welfare
MI	myocardial infarction
MMRM	mixed model for repeated measurement
MRHD	maximum recommended tolerated dose
MRI	magnetic resonance imaging
MTC	medullary thyroid carcinoma
NDA	new drug application
NIMP	non-investigational medicinal product
NYHA	New York Heart Association
OAD	oral antidiabetic drug
OD	once daily
PG	plasma glucose
PK	pharmacokinetic(-s)
PMDA	Pharmaceuticals and Medical Devices Agency, Japan
PPG	postprandial glucose
SAE	serious adverse event
SAS	safety analysis set
s.c.	subcutaneous(ly)
SD	standard deviation
SDV	source data verification
SGLT2i	sodium glucose co-transporter 2 inhibitor
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
UNR	upper normal range
UTN	Universal Trial Number
VLDL	very low density lipoprotein

1 Summary

Objectives and endpoints

Primary objective

To confirm the efficacy of insulin degludec/liraglutide (IDegLira) in combination with one oral antidiabetic drug in controlling glycaemia in Japanese subjects with type 2 diabetes mellitus.

This is done by showing superiority of IDegLira vs. liraglutide and non-inferiority of IDegLira vs. insulin degludec (IDeg) on glycaemic control after 52 weeks of treatment.

Secondary objectives

To confirm superiority of IDegLira vs. IDeg after 52 weeks of treatment in terms of change from baseline in body weight, number of hypoglycaemic episodes and glycaemic control.

To compare general efficacy and safety of IDegLira, IDeg and liraglutide after 52 weeks of treatment.

Primary endpoint

Change from baseline in HbA_{1c} (glycosylated haemoglobin) after 52 weeks of treatment.

Key secondary endpoints

Confirmatory secondary endpoints

The following confirmatory secondary endpoints will be tested with the aim to confirm superiority of IDegLira vs. IDeg.

- Change from baseline in body weight (kg) after 52 weeks of treatment
- Number of treatment emergent severe or blood glucose (BG) confirmed hypoglycaemic episodes during 52 weeks of treatment
- Change from baseline in HbA_{1c} after 52 weeks of treatment

Supportive secondary endpoints

- Change from baseline in fasting plasma glucose (FPG) after 52 weeks of treatment

Trial design

This is a 52-week, multi-centre, randomised, parallel three arms, open label trial in Japanese subjects with type 2 diabetes inadequately controlled with one oral antidiabetic drug (OAD) belonging to the following 6 OAD classes: metformin, alpha-glucosidase inhibitor (α-GI), thiazolidinedione (TZD), sulphonylurea(SU), sodium-glucose co-transporter 2 inhibitors (SGLT2i) or glinide.

Subjects will receive either IDegLira, IDeg or liraglutide once daily (randomised 1:1:1) all in combination with the pre-trial OAD kept in unchanged dose.

The total trial duration will be approximately 55 weeks.

Trial population

The number of subjects to be randomised is 807 (269 per arm).

Key inclusion criteria

- Male or female Japanese subjects, age ≥20 years at the time of signing informed consent.
- Type 2 diabetes subjects (diagnosed clinically) ≥ 6 months prior to screening.
- HbA_{1c} 7.0-11.0 % (both inclusive) by central laboratory analysis, with the aim of a median of 8.3%. When approximately 50% of the randomised subjects have a HbA_{1c} above 8.3%, the remaining subjects randomised must have a HbA_{1c} below or equal to 8.3%; or when approximately 50% of the randomised subjects have a HbA_{1c} below or equal to 8.3%, the remaining subjects randomised must have a HbA_{1c} above 8.3%
- Body-mass index (BMI) ≥20 kg/m^2
- Subjects on stable therapy with one OAD (defined as unchanged medication and unchanged dose) for at least 60 days (metformin, α-GI, TZD, SU, SGLT2i or glinide) prior to screening according to current approved Japanese labelling.

Key exclusion criteria

- Previous treatment with insulin (except for short-term treatment in connection with intercurrent illness including gestational diabetes)
- Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria in a period of 60 days before screening.
- Anticipated initiation or change in concomitant medications in excess of 14 days known to affect weight or glucose metabolism.
- 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 III and IV

Assessments

Key efficacy assessments;

- HbA_{1c}
- Body weight
- FPG
- Insulin dose at the end of treatment

Key safety assessments;

- Hypoglycaemic episodes
- Adverse events

Trial products

- Insulin degludec/liraglutide, 100 units/mL + 3.6 mg/mL, 3 mL pre-filled PDS290 pen injector
- Insulin degludec (Tresiba®), 100 units/mL, 3 mL pre-filled PDS290 pen injector
- Liraglutide (Victoza®), 6.0 mg/mL, 3 mL pre-filled FlexPen® pen

2 Flow chart

Screening (SC) **Randomisation (R)** **Site visit (V)** **Telephone contact(T)**[1] **Follow-up visit (FU)**	SC	R	T	V	T	V	T	T	T	V	T	V	T	V	T	V	T	V	T	V	T	V	T	V	T	V	T	V	T	V	FU
Visit number	1	2	2B	3	3B	4	4B	5	5B	6	7 8 9	10	11 12 13	14	15 16 17	18	19 20 21	22	23 24 25 26 27	28	29 30 31 32 33	34	35 36 37 38 39	40	41 42 43 44 45	46	47 48 49	50	51 52 53	54	55
Time of visit (week)	-2	0[2]	0.5[3]	1	1.5[3]	2	2.5[3]	3	3.5[3]	4	5 6 7	8	9 10 11	12	13 14 15	16	17 18 19	20	21 22 23 24 25	26	27 28 29 30 31	32	33 34 35 36 37	38	39 40 41 42 43	44	45 46 47	48	49 50 51	52	53
Visit window (days)			±1	±1	±1	±1	±1	±1	±1	±1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3
SUBJECT RELATED INFORMATION/ASSESSMENTS																															
Informed consent	x																														
In/exclusion criteria	x	x																													
Randomisation		x																													
Withdrawal criteria			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Medical history/ Concomitant illness	x																														
Concomitant medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Demography	x																														
Diagnosis of diabetes	x																														
Diabetes history/ Diabetes complications	x																														
Family history of diabetes	x																														
NYHA classification	x																														
Tobacco use	x																														
EFFICACY																															
Body weight	x	x												x						x				x						x	
Waist circumference		x																		x										x	
Height	x																														
Blood pressure	x	x												x						x				x						x	

[1] A telephone contact may be converted to a site visit.
[2] Randomisation 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 Visit 1.
[3] Corresponding to previous visit date plus 3 days

Screening (SC) **Randomisation (R)** **Site visit (V)** **Telephone contact(T)**[1] **Follow-up visit (FU)**	SC	R	T	V	T	V	T	T	T	V	T	V	T	V	T	V	T	V	T	V	T	V	T	V	T	V	T	V	T	V	FU
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Visit window (days)			±1	±1	±1	±1	±1	±1	±1	±1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3
Lipids[4]		x												x						x				x						x	
Glucose metabolism																															
HbA1c	x	x								x		x		x		x		x		x		x		x		x		x		x	
Fasting plasma glucose[4]		x								x		x		x		x		x		x		x		x		x		x		x	
Fasting human insulin[4]		x												x						x				x						x	
Fasting pro-insulin[4]		x												x						x				x						x	
Fasting glucagon[4]		x												x						x				x						x	
Fasting C-peptide[4]		x												x						x				x						x	
Pre-breakfast SMBG[5]				x		x		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
9-point SMBG profile[6]		x																		x										x	
SAFETY																															
Adverse events		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	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	x	x	x	x	x	x	x	x	
Hypoglycaemic episodes		x		x		x		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ECG[7]	x																													x	
Eye examination[8]	x																													x	

[4] The subjects must attend visits fasting, having consumed only water for the last 8 hours prior to the visits. No diabetic medication is allowed during fasting. If a subject attends in a non-fasting condition, blood sampling should be re-scheduled, preferably within the visit window

[5] **For IDegLira and IDeg arm**: Daily pre-breakfast SMBG values should be recorded.
For liraglutide arm: Pre-breakfast SMBG values on 3 consecutive days prior to each visit/telephone contact should be recorded.

[6] 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 does not anticipate 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.

[7] ECG obtained within 14 days prior to Visit 2 as part of routine practice may replace the screening assessment and ECG obtained within 14 days prior to Visit 54 is acceptable, if results are available for evaluation at Visit 2 and Visit 54, respectively.

[8] Eye examination (fundoscopy/fundus photography) obtained within 90 days prior to Visit 2 as part of routine practise may replace the screening assessment if results are available for evaluation at Visit 2. Eye examination obtained within 28 days prior to Visit 54 is acceptable.

Screening (SC) **Randomisation (R)** **Site visit (V)** **Telephone contact(T)**[1] **Follow-up visit (FU)**	SC	R	T	V	T	V	T	T	T	V	T	V	T	V	T	V	T	V	T	V	T	V	T	V	T	V	T	V	T	V	FU
Visit number	1	2	2B	3	3B	4	4B	5	5B	6	7 8 9	10	11 12 13	14	15 16 17	18	19 20 21	22	23 24 25 26 27	28	29 30 31 32 33	34	35 36 37 38 39	40	41 42 43 44 45	46	47 48 49	50	51 52 53	54	55
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Physical examination	x																			x										x	
Pulse	x	x												x						x				x						x	
Antibodies[4]		x												x						x				x						x	x
Biochemistry	x									x				x		x				x				x						x	
Haematology	x													x						x				x						x	
Calcitonin	x													x						x				x						x	
Pregnancy test[9]	x	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	x	
OTHER ASSESSMENTS																															
PK sampling[10]						x						x				x				x						x				x	
TRIAL MATERIAL																															
IWRS session	x	x								x		x		x		x		x		x		x		x		x		x		x	
Dispensing visit		x								x		x		x		x		x		x		x		x		x					
Drug accountability		x								x		x		x		x		x		x		x		x		x		x		x	
Hand out and instruction in direction for use, DFU[11]		x								(x)		(x)		(x)		(x)		(x)		(x)		(x)		(x)		(x)		(x)			
REMINDERS																															
Hand out ID card	x																														
Hand out and instruct in BG-meter use	x																														
Attend visit fasting[4]		x								x		x		x		x		x		x		x		x		x		x		x	x

[9] For females of childbearing potential: A serum pregnancy test must be performed at Visit 1 and Visit 54. Urine pregnancy test should be performed at site if a menstrual period is missed, or if pregnancy is suspected, indicated by (x) in the flowchart.

[10] Exact date and time for pharmacokinetic (PK) sampling must be recorded by the investigator in the eCRF. The following dosing's (dose, injection site, date and time) prior to PK blood sampling must be recorded by the subject in the diary; dosing's from the three previous days and from the day of visit, if a dose is taken before blood sampling. For the IdegLira arm, two samples must be obtained from each visit and be handled separately to allow analysis of both components.

[11] DFU must be handed out to the subjects at Visit 2. At subsequent dispensing visits it is up to the investigator to assess if it is needed to hand out the DFU as indicated by (x) in the flow chart.

Screening (SC) **Randomisation (R)** **Site visit (V)** **Telephone contact(T)**[1] **Follow-up visit (FU)**	SC	R	T	V	T	V	T	T	T	V	T	V	T	V	T	V	T	V	T	V	T	V	T	V	T	V	T	V	T	V	FU
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Time of visit (week)	-2	0[2]	0.5[3]	1	1.5[3]	2	2.5[3]	3	3.5[3]	4	5 6 7	8	9 10 11	12	13 14 15	16	17 18 19	20	21 22 23 24 25	26	27 28 29 30 31	32	33 34 35 36 37	38	39 40 41 42 43	44	45 46 47	48	49 50 51	52	53
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Hand out and instruct in/collect diary	x	x		x		x				x		x		x		x		x		x		x		x		x		x		x	x
Confirmation of unchanged dose of OAD		x		x		x		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
For liraglutide arm: Confirmation of unchanged dose of liraglutide[12]											x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Make appointment for eye examination	x																											x			
End of trial[13] and sign off on case book																															x

[12] Subjects are to confirm unchanged dose of liraglutide once they have reached a dose of 1.8 mg.
[13] In case a subject is being withdrawn from the trial, the investigator must ensure that the procedures for the last treatment visit (Visit 54) and the follow up visit (Visit 55) are undertaken, if possible and that the end of trial form is completed.

3 Background information and rationale for the trial

The trial will be conducted in compliance with this protocol, ICH GCP[1] and applicable regulatory requirements, and in accordance with the Declaration of Helsinki[2].

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

3.1 Background information

Type 2 diabetes mellitus (T2DM) is a progressive disorder characterised by insulin resistance and impaired insulin secretion. 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 monotherapy or two oral anti-diabetic drugs (OADs) combined often fail to provide sustained glycaemic control. Treatment guidance from the Japanese Diabetes Society[5] suggests a stepwise approach comprising lifestyle changes followed by pharmacological intervention. Initial monotherapy is recommended, escalated with combination therapy with OADs, glucagon-like peptide 1 (GLP-1) receptor agonists

Insulin degludec

Insulin degludec (IDeg) is a long-acting basal insulin and the active ingredient used in Tresiba®, which has been approved for use in Japan and the European Union (EU), and several other countries.

For more details on IDeg see current Investigator's Brochure (IB) and any updates hereof[6] and locally approved Japanese labelling.[7]

Liraglutide

Liraglutide is an analogue native (human) glucagon-like peptide-1 (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 Investigator's Brochure[8] and the Japanese approved labelling for Victoza®.[9]

Insulin degludec/liraglutide (IDegLira)

IDegLira is a basal insulin and GLP-1 analogue combination solution for subcutaneous (s.c.) injection for treatment of T2DM with once daily (OD) use.[10] The combination bring complimentary

effects of the two compounds on fasting (insulin degludec and liraglutide) and postprandial (liraglutide) glycaemic control. The addition of liraglutide to insulin degludec 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 (MAA) in EU among others. 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 more information, see the IDegLira NN9068 IB current version or any updates hereof.[11]

Marketing authorisation has been granted in several countries, e.g. for countries in EU. IDegLira is marketed with the brand name Xultophy®.

IDegLira is not approved for use in Japan. The current trial, NN9068-4183 - DUAL™ I Japan, is part of the Japanese IDegLira development programme which includes trials; NN2211-4174, a trial comparing the efficacy and safety of liraglutide 1.8 mg/day to liraglutide 0.9 mg/day in Japanese subjects with T2DM, and NN9068-4184 - DUAL™ II Japan, a trial confirming efficacy and safety of IDegLira in subjects with T2DM previously treated with insulin.

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

3.2 Rationale for the trial

Given the progressive nature of T2DM, 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. The successful outcome of recent global trials combining basal insulin and GLP-1 receptor agonist treatment as separate injections led to the inclusion of this treatment combination in the most recent guidelines from the Japanese Diabetes Society, the American Diabetes Association (ADA) and in the

European Association for the Study of Diabetes (EASD) position statement on management of hyperglycaemia in T2DM.[12,5,13]

Both IDeg and liraglutide are on the market in Japan. Liraglutide is approved up to 0.9 mg/daily and the efficacy of Liraglutide 1.8 mg/daily is currently to be investigated in Japanese subjects (NN2211-4174). The present confirmatory trial (NN9068-4183 DUAL™ I Japan) in Japanese subjects with T2DM treated with OAD monotherapy aims to confirm efficacy and safety of once daily treatment with IDegLira, as compared to each of the components. Furthermore, safety and efficacy data of 1.8 mg liraglutide daily in combinations with OADs will be collected in this trial. As such the present trial (together with NN9068-4184) will be used for registration of IDegLira in Japan, (J-NDA), as agreed with the Japanese Pharmaceuticals and Medical Devices Agency (PMDA), and approval of 1.8 mg of liraglutide daily in Japan (together with NN2211-4174).

4 Objectives and endpoints

4.1 Objectives

Primary objective

To confirm the efficacy of IDegLira in combination with one oral antidiabetic drug in controlling glycaemia in Japanese subjects with type 2 diabetes mellitus.

This is done by showing superiority of IDegLira vs. liraglutide and non-inferiority of IDegLira vs. IDeg on glycaemic control after 52 weeks of treatment.

Secondary objectives

To confirm superiority of IDegLira vs. IDeg after 52 weeks of treatment in terms of change from baseline in body weight, number of hypoglycaemic episodes and glycaemic control.

To compare general efficacy and safety of IDegLira, IDeg and liraglutide after 52 weeks of treatment.

Pharmacokinetic objective

The objective for the population pharmacokinetic (PK) analysis is to compare the pharmacokinetics of IDegLira and its mono-components given separately at clinically relevant doses during 52 weeks of treatment. Furthermore, the effects of pre-specified covariates on plasma concentrations of IDegLira will be evaluated.

4.2 Endpoints

4.2.1 Primary endpoint

Change from baseline in HbA_{1c} (glycosylated haemoglobin) after 52 weeks of treatment.

4.2.2 Secondary endpoints

4.2.2.1 Confirmatory secondary endpoints

The following confirmatory secondary endpoints will be tested with the aim to confirm superiority of IDegLira vs. IDeg.

- Change from baseline in body weight (kg) after 52 weeks of treatment*
- Number of treatment emergent severe or blood glucose (BG) confirmed hypoglycaemic episodes during 52 weeks of treatment*
- Change from baseline in HbA_{1c} after 52 weeks of treatment*

4.2.2.2 Supportive secondary endpoints

Supportive secondary efficacy endpoints:

- Insulin dose after 52 weeks of treatment
- Responder after 52 weeks of treatment (yes/no):
  - $HbA_{1c} < 7.0\%$
  - $HbA_{1c} < 7.0\%$ and change in body weight from baseline below or equal to zero
  - $HbA_{1c} < 7.0\%$ without treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during the last 12 weeks of treatment.
  - $HbA_{1c} < 7.0\%$ and change in body weight from baseline below or equal to zero 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 change in body weight from baseline below or equal to zero
  - $HbA_{1c} \leq 6.5\%$ without treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during the last 12 weeks of treatment
  - $HbA_{1c} \leq 6.5\%$ and change in body weight from baseline below or equal to zero and without treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during the last 12 weeks of treatment
- Change from baseline after 52 weeks of treatment in:
  - Fasting plasma glucose (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 increments (from before meal to 90 min after for breakfast, lunch and dinner). The mean increment overall meals will be derived as the mean of all available meal increments.

- Fasting lipid profile (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 52 weeks of treatment
- Fasting C-peptide, fasting human insulin, fasting glucagon and proinsulin after 52 weeks of treatment

*Key secondary endpoint prospectively selected for disclosure on clinicaltrials.gov, clinicaltrials.jp and novonordisk-trials.com

Supportive secondary safety endpoints

- Number of treatment emergent adverse events (TEAEs) during 52 weeks of treatment
- Number of treatment emergent severe or blood glucose (BG) confirmed symptomatic hypoglycaemic episodes during 52 weeks of treatment.
- Number of treatment emergent nocturnal severe or BG confirmed symptomatic hypoglycaemic episodes during 52 weeks of treatment
- Number of treatment emergent hypoglycaemic episodes according to ADA definition during 52 weeks of treatment
- Anti-drug antibodies, i.e. anti-IDeg antibodies including both IDeg specific and antibodies cross reacting with human insulin and anti-liraglutide antibodies including cross reactivity to GLP-1 and neutralising effect.
- Change from baseline in clinical evaluation after 52 weeks of treatment:
  - Physical examination
  - Fundoscopy or fundusphotography
  - Electrocardiogram (ECG)
  - Pulse
- Change from baseline in laboratory assessments after 52 weeks of treatment:
  - Biochemistry (including amylase and lipase)
  - Haematology
  - Calcitonin

4.2.2.3 Supportive secondary pharmacokinetic endpoints

- Serum concentrations of insulin degludec and plasma concentrations of liraglutide to be evaluated in a population PK analysis.

5 Trial design

5.1 Type of trial

This is a 52-week, multi-centre, randomised, parallel three arms open label trial, in Japanese subjects with type 2 diabetes inadequately controlled with one oral antidiabetic drug (OAD) belonging to the following 6 OAD classes: metformin, alpha-glucosidase inhibitor (α-GI), thiazolidinedione (TZD), sulphonylurea(SU), sodium-glucose co-transporter 2 inhibitors (SGLT2i) or glinide - hereafter commonly referred to as OADs in this document. Inadequately controlled diabetes will be defined as HbA_{1c} level of 7.0-11.0 %, both inclusive.
A total of 807 subjects will be randomised into three treatment arms in a 1:1:1 manner, using a centralised allocation via interactive web response system (IWRS). Subjects will receive either IDegLira-, IDeg- or liraglutide once daily (OD), all in combination with pre-trial OAD kept in unchanged dose, see Figure 5-1 for trial design. Approximately 50% of the randomised subjects should have an HbA_{1c} above 8.3%. Further, it will be aimed for an even number of subjects with an $HbA_{1c} \leq 8.3\%$ and > 8.3% within each pre-trial OAD class. In formal agreement with PMDA, randomisation will be stratified based on pre-trial treatment aiming to obtain approximately 50 completers on SGLT2i- and 35 completers of each of the remaining 5 OAD classes, in each treatment arm.

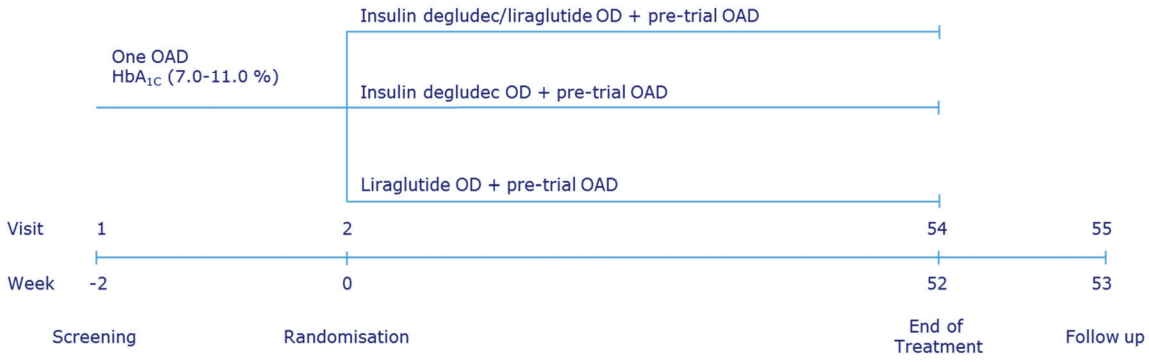


Figure 5–1 Trial design

The total trial duration will be approximately 55 weeks, consisting of 2 weeks screening period, a 52-week treatment period, and a follow-up visit (FU, i.e. Visit 55) 7 days after end of treatment (EOT, i.e. Visit 54). The purpose of the FU visit is to collect samples for antibody measurements and all adverse events (AEs) occurring in the week after end of treatment.

5.2 Rationale for trial design

The rationale for a treatment period of 52 weeks is to assess and compare efficacy and safety of the 3 treatments after longer-term exposure according to local requirement and agreement with PMDA.

The randomisation is stratified with regard to use of OAD at baseline, since this may influence the glycaemic control.

An open-label design has been chosen due to two different treatment regimens; fixed dose treatment of liraglutide arm and treat-to-target (TTT) for the IDeg and IDegLira arms.

Blinding of the trial by use of a double dummy design would mean an unacceptable number of injections, increase the complexity and thereby introduce an increased risk of non-compliance or withdrawal. The double-dummy design is therefore considered unacceptable for this trial.

The TTT approach is used in the IDeg and IDegLira trial arms (and thereby the high frequency of visits) has been chosen in order to ensure optimal titration of insulin degludec and insulin degludec/liraglutide based on pre-breakfast SMBG values and thereby to obtain improved HbA_{1c} results.

5.3 Treatment of subjects

IDegLira, IDeg and liraglutide will be given as an add on to the pre-trial OAD therapy, which should be continued in unchanged dose, except for safety issues, as judged by the investigator. The use of OAD should be in accordance with current approved Japanese labelling. Antidiabetic drugs other than IDegLira, IDeg and liraglutide and pre-trial OAD are not to be used during the treatment period. For IDegLira and IDeg the subjects will initiate on a starting dose (recommended starting dose is 10 dose steps for IDegLira and 10 units of IDeg, respectively) and twice weekly titration will ensure that subjects are treated to target. For liraglutide, subjects will initiate a 6 weeks planned dose escalation period which can be prolonged with a total maximum of 7 days and there after remain on a stable daily dose of 1.8 mg/day in a maintenance period, this dose can be reduced for a total maximum of 7 days, until end of treatment. Dose reduction or treatment pause of longer duration unrelated to the tolerability of liraglutide is acceptable. For further details on treatment see Appendix A and withdrawal criteria 10.

The investigational medicinal products (IMPs) used in this trial are described in section 9.

5.4 Treatment in the follow up period

After 52 weeks of trial product exposure, a 1-week interval between the end of treatment (Visit 54) and the follow-up (Visit 55) is necessary to allow for trial product washout. Subjects can at the investigator's discretion be switched to a suitable marketed product excluding long acting insulin analogues such as insulin degludec (Tresiba®), insulin detemir (Levemir®) and insulin glargine (Lantus®), or any GLP-1 receptor agonists as these may interfere with antibody measurements

performed at Visit 55. For instance intermediate acting human insulin like NPH may be used in the follow up period at the investigator's discretion limiting the risk of interference with antibody measurements performed at Visit 55.

5.5 Treatment after end of trial

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

5.6 Rationale for treatment

IDegLira will be investigated in this trial to demonstrate efficacy and safety, when administered to insulin-naïve subjects with T2DM, inadequately controlled on a stable dose of one OAD. This is in line with clinical practice to escalate treatment in this setting when glycaemic control is not achieved or sustained with the addition of another OAD, or initiation of GLP-1 receptor agonists, basal insulin or a combination of a basal insulin and a GLP-1 receptor agonists, such as IDegLira.

Pre-trial OAD treatment should be in accordance with current Japanese approved labelling. Subjects should be on 60 days of stable treatment defined as unchanged medication and unchanged dose. OAD treatment should remain unchanged during the trial, however in case of safety concerns the dose may be reduced at the discretion of the investigator.

IDeg and liraglutide have been included as comparators in order to comply with regulatory requirements to assess the risk benefit profile of the combination product as compared to the individual components.

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

6 Trial population

6.1 Number of subjects

Planned number of subjects to be screened (i.e. documented informed consent): 960

Number of subjects planned to be randomised: 807

Number of subjects expected to complete the trial: 675

The screening failure- and withdrawal rates are both assumed to be approximately 15%.

6.2 Inclusion criteria

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

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

2. Male or female Japanese subjects, age ≥20 years at the time of signing informed consent.

3. Type 2 diabetes subjects (diagnosed clinically) ≥ 6 months prior to screening.

4. HbA_{1c} 7.0-11.0 % (both inclusive) by central laboratory analysis, with the aim of a median of 8.3%. When approximately 50% of the randomised subjects have an HbA_{1c} above 8.3%, the remaining subjects randomised must have an HbA_{1c} below or equal to 8.3%; or when approximately 50% of the randomised subjects have an HbA_{1c} below or equal to 8.3%, the remaining subjects randomised must have an HbA_{1c} above 8.3%.

5. Body-mass index (BMI) ≥20 kg/m^2

6. Subjects on stable therapy with one OAD (defined as unchanged medication and unchanged dose) for at least 60 days (metformin, α-GI, TZD, SU, SGLT2i or glinide) prior to screening according to current approved Japanese labelling.

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.[14]
- 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 (7.0-11.0 %) is chosen to include subjects whose glycaemic control is not adequate on OAD treatment and treatment with insulin and/or liraglutide 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. The split by HbA_{1c} at 8.3% is included to ensure inclusion of subjects at both high and low levels of HbA_{1c} within the specified range as done in previous phase 3a trials with IDegLira, based on upon the knowledge of the mono-components.

- Criterion 5 is chosen in order to assure that subject's BMI will not change to the low BMI category, since weight loss has been observed in global trials with liraglutide 1.8 mg/day.
- Criterion 6 is applied to ensure that the subject's glycemic control is stabilised at randomisation. Sixty (60) days of unchanged pre-trial OAD treatment are required.

6.3 Exclusion criteria

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

1. Known or suspected hypersensitivity to trial product(s) or related products.
2. Previous participation in this trial. Participation is defined as signed informed consent.
3. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using adequate contraceptive methods (e.g., abstinence, diaphragm, condom [by the partner], intrauterine device, sponge, spermicide or oral contraceptives).
4. Receipt of any investigational medicinal product within 30 days before screening.
5. Previous treatment with insulin (except for short-term treatment in connection with inter current illness including gestational diabetes)
6. Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria in a period of 60 days before screening.
7. Anticipated initiation or change in concomitant medications in excess of 14 days known to affect weight or glucose metabolism.
8. Impaired liver function, defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥2.5 times upper limit of normal.
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 type 2 (MEN 2)
13. Subjects presently classified as being in New York Heart Association (NYHA) Class III and IV, see Appendix B for definitions.
14. Within the past 180 days any of the following: myocardial infarction, stroke or hospitalisation for unstable angina and/or transient ischemic attack prior to screening.
15. Inadequately treated blood pressure as defined as Class 2 hypertension or higher (Systolic≥160mmHg or diastolic ≥100 mmHg) in accordance with National High Blood Pressure Education Program, 7th Joint National Committee and European Societies of Hypertension/Cardiology (ESH/ESC) 2013 guidelines.
16. Proliferative retinopathy or maculopathy requiring acute treatment as verified by fundoscopy or fundus photography performed within 90 days prior to screening.
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. History of diabetic ketoacidosis
19. 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, 8-19 are chosen to ensure the safety of the subjects.
- Criterion 2 is chosen in order to exclude subjects who were judged as ineligible more than once, 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.

6.4 Withdrawal criteria

The subject may withdraw at will at any time. The subject's request to discontinue must always be respected.

The subject may be withdrawn from the trial at any time at the discretion of the investigator due to a safety concern. Subjects not tolerating the target dose of 1.8 mg liraglutide/day must be withdrawn from the trial due to safety concern, reporting the AE that led to the withdrawal.

The subject must be withdrawn from the trial 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 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 that are diagnosed with acute pancreatitis must be withdrawn from the trial (see 8.4.4).
8. Receipt of any investigational medicinal products after screening other than trial product.
9. If the pre-breakfast SMBG values taken on three consecutive days or if any of the FPG samples analysed by the central laboratory exceeds the limit of:
   - 15.0 mmol/L (270 mg/dl) from baseline to week 6
   - 13.3 mmol/L (240 mg/dl) from week 7 to week 12
   - 11.1 mmol/l (200 mg/dl) from week 13 to week 52

   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.
10. If subjects randomised to liraglutide do not tolerate the dose escalation or the target dose of 1.8 mg/day in the maintenance period as described in Appendix A, due to safety concern, they must be withdrawn. Dose reduction or treatment pause of longer duration than 7 days is acceptable, if unrelated to the tolerability of liraglutide.

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.
- Criterion 10 is applied to withdraw subjects who do not tolerate the maximum dose of 1.8 mg liraglutide/day, since the study objective is to investigate this maximum dose compared to IDegLira combination treatment.

6.5 Subject replacement

Withdrawn subjects will not be replaced.

6.6 Rationale for trial population

Japanese subjects with T2DM insulin naïve and inadequately controlled (HbA_{1c} within 7.0-11.0%) with one oral antidiabetic drug (OAD) are eligible for inclusion in the trial.

The rationale for the trial population, selected according to inclusion and exclusion criteria (see 6.2 and 6.3), is to ensure representation of subjects resembling the target T2DM population treated with OAD in need of increased glycaemic control with e.g. insulin and/or GLP1-analogue and to provide data on efficacy of IDegLira in combination with OAD treatment and safety of liraglutide 1.8 mg/day in combination with OAD treatment.

Only serious concomitant conditions (i.e. NYHA Class III and 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 (FSFV – LSFV): 44 weeks.

End of trial is defined as LSLV.

7.1 Recruitment

Recruitment will be done according to agreements with the individual investigational sites. The screening and distribution within the pre-specified OAD classes and defined HbA_{1c} distribution (see section 5.1 will be monitored closely during the entire recruitment period. 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 in order to estimate when to stop screening, see section 11 for randomisation procedure.

7.2 Trial registration

Information of the trial will be disclosed at clinicaltrials.gov, novonordisk-trials.com and the Clinical Trials Information/JapicCTI site (clinicaltrials.jp). According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure, it will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE)[15], the Food and Drug Administration Amendment Act (FDAAA)[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

8.1 Visit procedures

Timing of assessments and procedures are specified in the flow chart in section 2. This section 8 includes a description of the procedures and assessments.

The investigator must ensure that trial procedures and assessments are performed as described in the protocol. Any discrepancies are considered protocol deviations and the investigator must take appropriate actions to avoid recurrence.

The investigator must keep a subject screening log, a subject identification code list and a subject enrolment log. In addition, the investigator must keep a log of staff and a delegation of task(s) list at the site. The subject screening log and subject enrolment log may be combined in one list.

8.1.1 Informed consent

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

All subjects should be provided with a copy of their own signed and dated informed consent form.

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

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

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

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

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

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

8.1.2 Investigators assessments

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

8.1.3 Screening

Screening must take place within 14 days prior to randomisation. For procedures and assessments at screening visit please see flow chart, section 2.

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

Each subject will be assigned a unique 6-digit subject number which will remain the same throughout the trial. The first three digits in the subject number will consist of the site number and the last three digits of the subject number will indicate the individual number.

Subjects will continue on their current diabetes treatment until randomisation.

8.1.4 Screening failures

For screening failures the screening failure form in the case report form (eCRF) must be completed with the reason for not continuing in the trial. The reason(s) for failure should also be completed on the inclusion- and or exclusion form in the eCRF. Serious adverse events from screening failures must be transcribed by the investigator into the eCRF. Follow-up of serious adverse events (SAEs) must be carried out according to section 12.

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

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

8.1.5 Visits attended fasting

At the time points specified in the flowchart (section 2), subjects must attend the visits fasting. 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.

If the subject attends a fasting visit in a non-fasting state, subject should be asked to return to the site in a fasting state to have fasting assessments done preferably within the visit window for the relevant visit.

8.1.6 Randomisation visit

Randomisation (Visit 2) must take place within 14 days after the screening visit. 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.

The subjects must attend the randomisation visit fasting.

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

The subject should take the first dose of trial product on the day of Visit 2 after randomisation is done or the day after. The date of the first dose of trial product should be recorded in the diary and transcribed to the eCRF.

8.1.7 Visits

For visit numbers, timing of visits, phone contacts and visit windows during the trial period, please refer to the flow chart (section 2). Visits can be re-scheduled within the allowed visit window.

8.1.8 End of treatment visit

At the end of treatment visit (Visit 54), 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 switched to a suitable marketed product at Visit 54 according to section 5.4, to be taken in the follow up period.

8.1.9 Follow-up visit

The follow-up visit should be undertaken no earlier than 7 days after Visit 54. Subjects must attend this visit in a fasting state prior to the blood sampling for antibody analysis. Subjects on any type of insulin should not have administered this within 12 hours of the blood sampling, see section 8.4.5 for rationale.

At completion of this visit, subjects may be switched to another suitable marketed product at the discretion of the investigator.

The end-of-trial form (EOT form) must be completed in the eCRF.

8.1.10 Unscheduled visits

Unscheduled visits can be performed at any time at the discretion of the investigator. An unscheduled visit should be performed if, e.g. an AE occurs that needs further attention or blood samples needs to be re-taken (out of visit window).

An unscheduled visit form must be completed in the eCRF stating the reason for the visit.

If the subject attends the clinic only to obtain trial supplies, no unscheduled visit form should be completed but an additional dispensing call in the IWRS must be performed.

8.1.11 Re-scheduled visits

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

8.1.12 Withdrawals

If a subject is withdrawn from the trial, the investigator must aim to undertake procedures similar to those for Visit 54 as soon as possible and the procedures similar to those for the follow-up visit (Visit 55) not earlier than 7 days after Visit 54.

The end-of-trial form (EOT 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. The case book in the eCRF must be signed.

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

8.2 Subject related information

8.2.1 Concomitant illness and medical history

A **concomitant illness** is any illness that is present at the start of the trial i.e. at the first visit or found as a result of a screening procedure which also includes assessments performed between Visit 1 and Visit 2 and at Visit 2. T2DM should not be recorded as concomitant illness.

Any change to a concomitant illness should be recorded in the eCRF 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.

Information about the subject's medical history and history of diabetes should be recorded at the screening visit (Visit 1) in the eCRF at the medical history/concomitant illness form and diabetes history/diabetes complications form, respectively. Family history of diabetes should be reported at the family history form.

The following should be recorded in the diabetes history/diabetes complications form;

- Date of diagnosis of diabetes
- Diabetes complications

The following should be recorded in the family history form

- Family history of diabetes

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

8.2.2 Concomitant medication

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

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

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

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

Concomitant medication and anti-diabetic therapy initiated at end of treatment visit (Visit 54) and at the follow up visit (Visit 55) should not be recorded in the eCRF.

8.2.3 OAD medication

OADs are considered non-investigational medicinal products (NIMPs) and dosing information should be recorded at the Concomitant Specific Drug - OAD form in the eCRF.

All subjects should continue treatment with the pre-trial OAD and the dose should be kept unchanged, unless for safety reasons. If case of changes, it must be reported in the eCRF.

The information collected for OAD medication includes trade name or generic name, dose, start date and stop date or continuation.

8.2.4 Demography

Demography will be recorded in the IWRS system at screening visit (Visit 1) and consist of:

- Date of birth
- Sex

In addition, the following should be captured in the eCRF:

- Race (according to regulation in Japan)

8.2.5 Tobacco use

Details of tobacco use (smoking status) must be recorded in the eCRF at the screening visit (Visit 1). Smoking is defined as smoking at least one cigarette or equivalent daily. The collected information should include whether the subject is a current or previous smoker or never has smoked.

8.3 Assessments for efficacy

8.3.1 Blood samples for efficacy parameters

Blood samples will be drawn according to flow chart (see section 2) and analysed at the central- or special laboratories to determine levels of the following efficacy laboratory parameters:

Glucose metabolism

- HbA_{1c}
- Fasting plasma glucose (FPG)
- Fasting human insulin
- Fasting pro-insulin
- Fasting glucagon
- Fasting C-peptide

Pro-insulin/fasting human insulin ratio will be calculated on glucose metabolism parameters to assess beta-cell function and insulin resistance.

Lipids (fasting)

- Total cholesterol
- LDL-cholesterol
- VLDL-cholesterol
- HDL-cholesterol
- Triglycerides
- Free fatty acids

8.3.2 Self-measured blood glucose

At Visit 1, subjects will be provided with blood glucose (BG) meters to be used for all self-measured blood glucose (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 blood glucose 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. The term SMBG will be used consequently also for plasma values.

Subjects should be instructed in how to record the results of the SMBGs in the diaries. The record of each pre-breakfast SMBG should include date, and value and additionally the 9-point SMBG profiles must also include the actual clock time of each measurement. All data from the diary must be transcribed into the eCRF during or following the contact. If obtained via phone and a discrepancy is later detected, the values in the eCRF should be corrected.

For SMBG values that meet the definition of a hypoglycaemic episode (see section 8.4.9), relevant information must be registered in the subject diary and a hypoglycaemic episode form must be completed in the eCRF.

Subjects randomised to IDegLira and IDeg

Subjects randomised to IDegLira or IDeg should perform once daily SMBG measurement prior to breakfast and preferably after having only water since midnight. SMBG data from 3 consecutive days is used for titration, see Appendix A.

Subjects randomised to liraglutide

Subjects randomised to liraglutide should perform SMBG measurements prior to breakfast on 3 consecutive days prior to each visit/telephone contact. The SMBG data is used to assess subject’s glucose control.

8.3.3 9-point self-measured blood glucose profiles

Subjects will be instructed to perform a 9-point self-measured blood glucose (SMBG) profiles three times during the trial according to the flow chart in section 2. The measurements should take place on two consecutive days 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 are listed in Table 8.1 below. The subjects should always start with the pre-breakfast measurement and the SMBG values should be recorded in the diary including actual clock time and date for the measurements.

Trial product and OAD treatment should be withheld until after the pre-breakfast SMBG measurements have been performed.

Table 8–1 9-point profile (SMBG) (√)

Time point	Day 1	The following day
Before 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.	√	

8.3.4 Body measurements

Height

Height is measured without shoes in centimetres (cm) and recorded in the eCRF to nearest ½ cm. Height measured at Visit 1 will only be used for calculation of BMI.

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.

Body Mass Index

The body mass index (BMI) will be calculated at Visit 1 for assessment of eligibility (section 6.2) and at the other visits for efficacy assessment.

The BMI will be calculated by the eCRF once body weight at the visit specified in the flow chart (section 2 and height at Visit 1 are entered.

BMI will be calculated as follows:

BMI (kg/m^2) = Body weight (kg)/(Height [m] × Height [m])

Waist circumference

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

Three consecutive measurements of waist circumference must be performed and recorded in the eCRF. The waist circumferences will be measured in cm using a non-stretchable measuring tape provided by Novo Nordisk. It should be recorded to the nearest ½ cm preferably using the same measuring tape throughout the trial.

The subject should be measured in a standing position with an empty bladder and wearing light clothing with accessible waist. The subject should be standing with arms down their side and feet together. The tape should touch 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.

8.3.5 Blood pressure

Blood pressure (systolic and diastolic) must be measured at the visits specified in the flowchart in section 2.

The blood pressure must be measured after the subject has been resting for at least 5 minutes in a sitting position.

At Visit 1 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 6.3).

It is recommended to use the same arm, device and cuff as used at the first visit for the subsequent measurements. 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.

8.4 Assessments for safety

Any abnormal clinically significant finding that is present at the start of the trial, i.e. at the first visit or found as a result of a screening procedure which also includes assessments performed between

Visit 1 and Visit 2 and at Visit 2 should be recorded as a concomitant illness. Any new abnormal, clinically significant finding during the trial and any clinically significant worsening from baseline (up to Visit 2) must be reported as an AE (see section 12).

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

8.4.1 Adverse Events requiring special forms in the eCRF

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

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

In case any of these events fulfil the criteria for a SAE, report according to section 12.2.

Cardiovascular events

Cardiovascular events that are suspected as being related to below, requires special forms in the eCRF (see also Appendix C);

Acute coronary syndrome

All types of myocardial infarction 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 on a specific acute coronary syndrome form in the eCRF. The following information must be reported if available:

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

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 (AP)
- 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

Thyroid disease

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

- History of thyroid disease
- Signs and symptoms leading to investigations of thyroid disease
- Specific laboratory tests describing thyroid function including:
  - Thyroid stimulating hormone (TSH)
  - Total and free triiodothyronine (T3) and thyroxine (T4) and Free Thyroid Index
  - Calcitonin
  - Thyroid 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 to the event

8.4.2 Blood samples for safety parameters

Blood samples must be drawn according to flow chart (section 2) and will be analysed at the central- or specialised laboratory to determine levels of the following safety laboratory parameters:

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

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

- Hormones:
  - Calcitonin, if $\geq$ 10 ng/L, see Appendix D for monitoring of calcitonin
- Antibodies; see section 8.4.5

- Pregnancy test:
  - Human serum chorionic gonadotrophin (hCG), see section 8.4.3 below

8.4.3 Pregnancy test

Females of childbearing potential must have a serum pregnancy test (beta-human chorionic gonadotropin [beta-hCG]) performed according to the flow chart, section 2.

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

If at telephone contact, subject reports missing menstrual period, the subject will have to attend the site as soon as possible to have a urine-stick pregnancy test done.

Pregnancy test will not be required for women who have undergone a hysterectomy or tubal ligation, or for women above the age of 50 years, who have been without menses for at least 1 year. This must be documented in the subject's medical record and eCRF.

8.4.4 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 promptly be interrupted until pancreatitis is ruled out. Appropriate additional examinations must be performed, including local measurement of amylase and lipase. Subjects that are diagnosed with acute pancreatitis must be withdrawn from the trial. 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 [CT]/magnetic resonance imaging [MRI]

If acute pancreatitis is ruled out, trial product should be re-initiated. If, in subjects treated with liraglutide 1.8 mg/day, the discontinuation period is for three days or more, the trial product should be restarted with a dose of 0.3 mg/day, and dose escalation procedure described in Appendix A should be followed. In all other subjects the re-initiation should be at the discretion of the investigator. The investigator should consider both the last number of units or dose steps of last dose of IDeg or IDegLira and 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.

8.4.5 Antibody sampling

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

Samples from follow up visit (Visit 55) positive for anti-liraglutide antibodies will in addition be analysed for in vitro neutralising effect in a cell based assay.

Subjects should be fasting at blood sampling for antibody assessment and the sampling should be prior to administering the trial product in the treatment period and prior to other insulin products, if

administered, at the follow up visit (Visit 55). This will ensure that the drug concentrations are at their lowest at the time of sampling limiting the level of drug interference with the antibody analysis.

Antibody results will not be provided to the investigator during the trial conduct as these are not used for clinical evaluation. The results will be described in the clinical trial report (CTR) after end of trial.

Please see section 24.2 for information on storage/retention of antibody samples.

8.4.6 ECG (electrocardiogram)

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)

The ECG at screening must be done at the latest at Visit 2 and the results must be interpreted by the investigator prior to performing any procedures related to Visit 2.

ECG obtained within 14 days prior to Visit 2 as part of routine practise may replace the screening assessment, if results are available for evaluation at Visit 2.

ECG obtained within 14 days prior to Visit 54 is acceptable, if results are available for evaluation.

8.4.7 Eye Examination

Eye examination (fundoscopy/fundus photography) must be performed at the visits specified in the flowchart (see section 2) by the investigator or a local Ophthalmologist 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 Visit 2 is acceptable. If a funduscopy/fundus photography has been performed prior to the screening visit (Visit 1) the procedure does not need to be repeated, unless worsening of visual function since the last

examination has been noted. The investigator must still 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 the reason for performing the procedure was not related to the present trial.

Eye examination performed within a period of 28 days before Visit 54 is acceptable if results are available at Visit 54.

8.4.8 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 8.2.1. Findings not present at screening must be reported as AE according to section 12.

8.4.9 Hypoglycaemic episodes

Blood 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 Visit 2 to follow up visit.

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]

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

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

- 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

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

8.4.10 Pulse

Pulse (beats per minute) should be recorded in the eCRF at site visits according to section 2 after resting at least 5 minutes in a sitting position.

8.4.11 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 6 months 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.

8.5 Laboratory assessments

All laboratory samples will be analysed by a central- and specialised laboratories 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. The central laboratory may utilise subcontractors.

Description of assay methods and a detailed 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 by the central laboratory. Information regarding laboratory materials such as tubes and labels are also described.

Laboratory samples can be drawn another day than on the day of the actual visit as long as it is within the visit window stated in the flow chart (section 2).

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

Laboratory results (except PK and antibodies results) will be made available on an ongoing basis by the central laboratory. Laboratory reports must be reviewed, dated and signed by the investigator. It should be specified whether out of range results are clinically significant.

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

Antibody samples: The investigator will not be able to review the results of antibody measurements in relation to AEs as these are often analysed after LSLV.

8.6 Other assessments

8.6.1 Pharmacokinetics

Blood samples for PK will be drawn in all subjects at visits specified in the flow chart in section 2. Blood samples will be drawn once per subject per visit. Samples from the IDegLira and IDeg arms will be analysed for serum concentrations of insulin degludec and samples from the IDegLira and liraglutide arms will be assayed for plasma concentrations of liraglutide using validated ELISA assays. For subjects in the IDegLira arm, two samples must be obtained from each visit and be handled separately: a serum sample for insulin degludec assay and a plasma sample for liraglutide assay.

For a detailed description of the handling of the samples is referred to the laboratory manual.

The investigator must record the exact date and time for blood sampling in the eCRF.

Subjects must be instructed to write in their diary:

- Date, dose, injection site and exact clock time for injection from the previous three days of dosing and on the day of the visit, if a dose is taken before blood sampling

It is important to explain to the subjects the necessity of accurate diary recording as the investigator must transcribe all data into the eCRF subsequently and to ensure accurate PK evaluation.

The population PK analysis is outlined in section 17.5.

PK results will not be provided to the investigator as these are not used for clinical evaluation during the trial. The data will be included in a bio-analytical report that will be available before finalising the CTR and the data will be retained at Novo Nordisk.

PK samples will be destroyed no later than at the completion of the CTR.

Destruction of PK samples must only occur with permission from Novo Nordisk.

8.6.2 Subject diary

The subjects must be provided with the subject diaries at the specified visits (section 2). The investigator and/or delegate or site staff must instruct subjects to record the following in the diary:

- Date and dose of trial product (including first and last dose)
- Date and value of all SMBG measurements and also actual clock time of the 9-point SMBG measurements (see sections 8.3.2 and 8.3.3)
- PK sampling visits: date, dose, injection site and exact clock time for injection from the previous three days of dosing and on the day of the visit, if a dose is taken before blood sampling
- Hypoglycaemic episodes (see section 8.4.9)
- Medical problems (e.g. AEs)
- Changes in concomitant medication including OAD dose

The investigator and/or delegate or site staff are allowed to record the following in the diary:

- Prescribed doses of trial product
- Time and date of next visit and/or phone contact
- Subject ID and site contact details

The diary must be reviewed by the investigator to ensure that AEs, including overall change in health and concomitant medication, are reported see section 8.2.2 and 12. Review of the diaries must be documented either on the front page of the documents and/or in the subject's medical record. The investigator and/or delegate or site staff must transcribe data from the diary into the eCRF throughout the trial. If necessary, the investigator and/or delegate or site staff should convert the format of data used by the subject into the format used in the eCRF. The diaries dispensed to subjects at a previous visit should be collected at the following site visit.

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

8.6.3 Subject compliance

Throughout the trial, the investigator will remind the subjects to follow the trial procedures and requirements to ensure subject compliance. The investigator should assess the 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. Subject compliance will further be assessed by monitoring the drug accountability. The unused amount of trial product will be assessed against the dispensed amount and, in case of discrepancies, the subject must be asked. Further, the investigator will monitor the treatment compliance of the subjects during trial conduct by e.g. assessing the results of the laboratory samples on an ongoing basis.

9 Trial supplies

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

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

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

9.1 Trial products

The following investigational medicinal products (IMPs) will be provided by Novo Nordisk A/S, Denmark:

Table 9–1 Investigational medicinal 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 (s.c.)	3 mL pre-filled PDS290 pen injector
Insulin degludec (Tresiba®)	100 units/mL			
Liraglutide (Victoza®)	6.0 mg/mL			3 mL pre-filled FlexPen®

OADs are considered as non-investigational medicinal products (NIMPs) and hence will not be provided by Novo Nordisk.

9.2 Labelling

The trial products will be labelled in accordance with Annex 13[21], local regulations and trial requirements.

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

The investigator must document that direction for use (DFU) is given to the subject orally and in writing at the first dispensing visit (Visit 2). 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 in section 2.

9.3 Storage

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

Table 9–2 Storage conditions for investigational medicinal products

Trial product	Storage conditions (not-in-use)	In-use conditions	In-use time*
Insulin degludec/ liraglutide	Store in refrigerator (2ºC-8ºC) Do not freeze Protect from light	Store below 30°C Do not freeze Protect from light	Use within 3 weeks
Insulin degludec	Store in refrigerator (2ºC-8ºC) Do not freeze Protect from light	Do not store above 30°C Protect from light	Use within 8 weeks
Liraglutide	Store in refrigerator (2ºC-8ºC) Do not freeze Protect from light	Store at room temperature (not above 30°C) Do not freeze Protect from light	Use within 30 days

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

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.

Trial product that has been stored improperly must not be dispensed to any subject and must be stored separately from other trial products but within allowed temperature range before it has been evaluated and approved for further use by Novo Nordisk. The investigator must take appropriate action to ensure correct storage.

9.4 Drug accountability and destruction

Drug accountability is the responsibility of the investigator, the head of the study site or the trial product storage manager if assigned by the head of the study site.

Subjects must be instructed to return all used, partly used and unused trial products including empty packaging material at each dispensing visit.

Returned trial product (used/partly used or unused including empty packaging material) can be stored at room temperature and must be stored separately from non-allocated trial product.

Drug accountability is performed by using the IWRS. Only dispensed DUNs returned by the subject (used/partly used or unused) are accounted for.

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

9.5 Auxiliary supplies

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

- Directions for Use (DFU) for pen devices

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

- Needles for pen devices
- Blood glucose meters (BG meters) and BG meter auxiliaries
- Glucose for treating a hypoglycaemia

10 Interactive web response system

A trial-specific interactive web response system (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 user manuals will be provided to each trial site.

IWRS is used for:

- Screening
- Screening failure
- Randomisation
- Medication arrival
- Dispensing (including additional dispensing)
- Withdrawal
- Completion
- Drug accountability
- Data change

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

11.1 Randomisation

The IWRS, a centralised randomisation /allocation system, must be used for randomisation. Only eligible subjects are allowed to be randomised. The subjects will be randomised into three treatment arms in a 1:1:1 manner and the randomisation will be stratified based on pre-trial OAD.

It will be strived for a trial population with a median HbA_{1c} level of 8.3%. When the number of subjects with an HbA_{1c} below or equal to 8.3% reach approximately 50% of the required number of subjects to be randomised, it will only be possible to randomise subjects with an HbA_{1c} above 8.3%, or vice versa.

The HbA_{1c} distribution of subjects (including the OAD stratification) will be followed closely and investigators will be notified before screening is closed. Eligible subjects for randomisation will be randomised if closing occurs while they are in the screening period.

11.1.1 Stratification

To ensure a fixed proportion of subjects on each of the 6 OAD classes (metformin, α-GI, TZD, SUs, SGLT2i or glinide), in each of the treatment arms, the randomisation will be stratified with regards to pre-trial OAD treatment (see section 5.1 for number of completers within each strata). Further, it will be aimed for an even number of subjects with an $HbA_{1c} \leq 8.3\%$ and $> 8.3\%$ within each pre-trial OAD class. The stratification will be controlled by Novo Nordisk trial management in close collaboration with the sites participating in the trial.

12 Adverse events, and technical complaints and pregnancies

12.1 Definitions

Adverse event

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

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a product, whether or not considered related to the product. AEs should be reported from the first trial-related activity after the subject has signed the informed consent until the end of the post treatment follow-up period (Visit 55).

An AE includes:

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

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

- Pre-existing conditions, including those found as a result of screening procedures (pre-existing conditions should be reported as medical history or concomitant illness).
- Pre-planned procedures unless the condition for which the procedure was planned has worsened from the first trial related activity after the subject has signed the informed consent.
- Non-serious hypoglycaemia is an AE, but is reported on a hypoglycaemic episode form instead of on an AE form, see section 8.4.9.

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.

Serious adverse event

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

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

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

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

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

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

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

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

Non-serious adverse event

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

Medical event of special interest

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

Medication errors concerning trial products:

- Administration of wrong drug or use of wrong device.
- Note: Use of wrong DUN is not considered a medication error unless it results in administration of wrong drug.
- Wrong route of administration, such as intramuscular instead of subcutaneous.
- Administration of an overdose with the intention to cause harm (e.g. suicide attempt).
- Accidental administration of a lower or higher dose than intended. That is a dose lower or higher than 20 % of the intended dose; however the administered dose must deviate from the intended dose to an extent where clinical consequences for the trial subject were likely to happen as judged by the investigator, although they did not necessarily occur.

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

Adverse events with additional data collection

AEs with additional data collection are AEs defined as critical for the evaluation of product safety.

For these AEs the investigator must fill in additional forms in the eCRF. The AEs that require additional forms in the eCRF are:

1. Acute coronary syndrome (MI or hospitalisation for unstable angina)
2. Cerebrovascular event (stroke or TIA)
3. Heart failure requiring hospital admission
4. Neoplasms
5. Pancreatitis
6. Thyroid disease
7. Renal failure

For detailed information on AEs with additional data collection, see section 8.4.1.

Along with **fatal events**, the above mentioned events with additional data collection will be adjudicated by an external independent event adjudication committee (EAC) as described in section 12.7.2. For further information regarding definitions, rationales, and events that will be adjudicated, see Appendix C.

Technical complaint

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

Examples of technical complaints:

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

12.2 Reporting of adverse events

All events meeting the definition of an AE must be collected and reported. This includes events from the first trial-related activity after the subject has signed the informed consent until the end of the post-treatment follow-up period (Visit 55). Please be aware that hypoglycaemic episodes should not be reported before any trial drug is given e.g. hypoglycaemic episodes should be reported from Visit 2.The AEs must be recorded in the applicable CRF forms in a timely manner, see timelines below and Figure 12–1.

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

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

IDegLira, IDeg, liraglutide: Current version of the product specific company core data sheets (CCDSs) or any updates thereto.

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

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

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

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

The AE form for a non-serious AE not fulfilling the MESI criteria should be signed when the event is resolved or at the end of the trial.

Timelines for initial reporting of AEs:

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

- **SAEs**: The AE form **within 24 hours** and the safety information form **within 5 calendar** days of the investigator's first knowledge of the SAE. For SAEs with additional data collection; in addition also the specific event form **within 14 calendar** days of the investigator's first knowledge of the AE. Both forms must be signed within **7 calendar days** from the date the information was entered in the eCRF.
- **SAEs fulfilling the MESI criteria:** In addition to above, the MESI form **within 14 calendar days** of the investigator's first knowledge of the AE.
- **Non-serious AE fulfilling the MESI criteria:** The AE form, and safety information form and MESI form **within 14 calendar days** of the investigator's first knowledge of the event.
- **Non-serious AEs with additional data collection:** The AE form and the specific event form within **14 calendar days** of the investigator's first knowledge of the event
- **Events for adjudication**: Event Adjudication Document Collection Form must be populated within **14 calendar days**. The investigator should provide the medical documentation within **4 weeks** of event identification

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

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

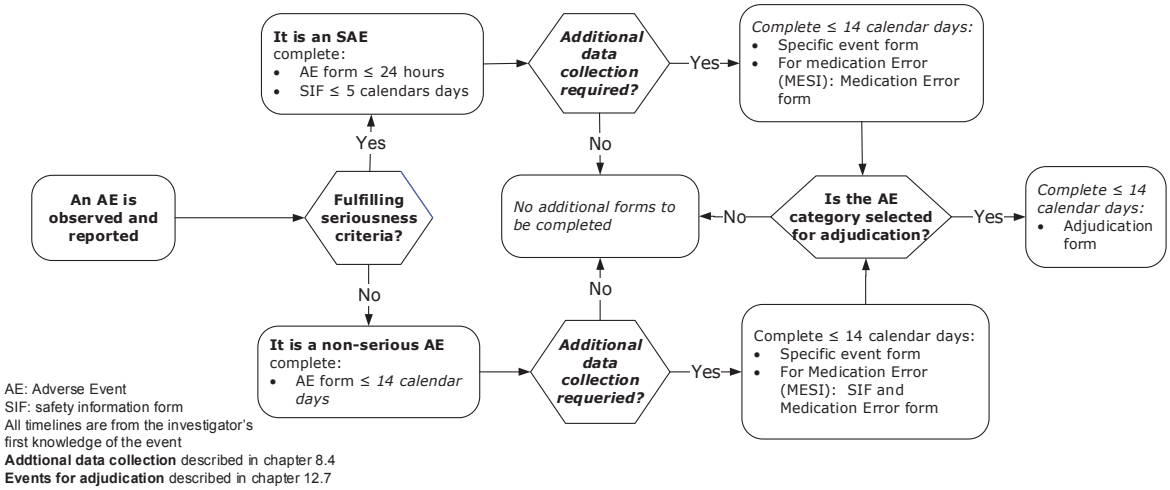


Figure 12–1 Initial reporting of AEs

Reporting of trial product-related SUSARs by Novo Nordisk:

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

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

12.3 Follow-up of adverse events

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

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

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

information. This is also the case for previously non-serious AEs which subsequently become SAEs.

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

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

12.4 Technical complaints and technical complaint samples

12.4.1 Reporting of technical complaints

All technical complaints on any of the following products:

- Insulin degludec/liraglutide, 100 units/mL + 3.6 mg/mL, 3 mL pre-filled PDS290 pen injector
- Insulin degludec (Tresiba®), 100 units/mL, 3 mL pre-filled PDS290 pen injector
- Liraglutide (Victoza®), 6.0 mg/mL, 3 mL pre-filled FlexPen® pen
- 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, SAEs, and/or MESI.

Technical complaints must be reported on a separate technical complaint form. A technical complaint form for each batch or lot number or for each DUN must be completed.

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

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

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

12.4.2 Collection, storage and shipment of technical complaint samples

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

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

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

Storage of the technical complaint sample must be done in accordance with the conditions prescribed for the product. The shipment of the technical complaint sample should be done in accordance with the same conditions as for storage (see section 9).

12.5 Pregnancies 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 until 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:

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.

Reporting of AE information

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

Forms and timelines for reporting AEs:

- Non-serious AEs:
  - Paper AE form* **within 14 calendar days** of the investigator's first knowledge of the initial or follow-up information to the non-serious AE.
- SAEs:
  - Paper AE form* **within 24 hours** of the investigator's first knowledge of the SAE.
  - Paper safety information form **within 5 calendar days** of the investigator's first knowledge of the SAE.
  - **SAE follow-up information** to the AE form and/or safety information form **within 24 hours** of the investigator's first knowledge of the follow-up information.

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

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

12.6 Precautions and/or overdose

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 blood glucose 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 s.c. 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 and liraglutide, the subject may in some cases experience loss of fluids/dehydration, due to vomiting, nausea or diarrhoea. It is important to avoid dehydration by drinking plenty of fluids.

For further information see the NN9068, NN1250 and NN2211 IB's or any update hereof. [11 ,6,8]

12.7 Committees related to safety

12.7.1 Novo Nordisk safety committee

Novo Nordisk has an established internal IDegLira safety committee overseeing ongoing safety surveillance. The IDegLira safety committee will be informed about the results of continuous on-going safety surveillance activities for IDegLira.

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 following AEs will be adjudicated in this trial:

- Fatal events
- Acute coronary syndrome (MI or hospitalisation for unstable angina)
- Cerebrovascular event (stroke or TIA)
- Heart failure requiring hospital admission
- Neoplasms including thyroid neoplasm (all kinds of abnormal growth)
- Pancreatitis
- Thyroid disease requiring thyroidectomy

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

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

The EAC will review translated copies in English of medical documentation received in the adjudication packages (for example X-ray, ECGs, ultrasound images, discharge summaries, pathology reports, and death certificates). The 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 and all relevant predefined documents provided according to instructions in the event adjudication site manual.

13 Case report forms

Novo Nordisk will provide a system for the electronic case report forms (eCRF). This system and support services to the system will be provided by an external supplier.

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

The following will be provided as paper CRFs;

- Pregnancy forms

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

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

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

13.1 Corrections to case report forms

Corrections to the CRF 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 LSLV 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 FSFV 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.

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

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

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

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

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 from the laboratory performing the analysis. Data from special laboratories will be transferred to Novo Nordisk via the central laboratory. 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 trial sites together.

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

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

Unless otherwise specified, all continuous measurements will be summarised descriptively at each visit by treatment using observed data. After 52 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 and pre-trial OAD treatment (metformin, α-GI, TZD, SU's, SGLT2i or glinide) 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[22] endpoints will be assessed at frequent visits and also on subjects who withdraw prematurely. Also, the combined information on frequent outcomes and information on reason for drop-out is assumed to account for the missing data anticipated.

If an assessment has been made both at screening (Visit 1) and randomisation (Visit 2), and if not otherwise specified, the value from the randomisation visit will be used as the baseline value. If the

value measured at the randomisation visit is missing and the assessment also has been made at screening, then the screening value will be used as the baseline value.

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

17.1 Sample size calculation

The primary objective of this trial is to confirm the efficacy of IDegLira in combination with one oral antidiabetic drug in controlling glycaemia in Japanese subjects with type 2 diabetes mellitus. This is done by comparing the difference in change from baseline in HbA_{1c} after 52 weeks of treatment to a non-inferiority margin of 0.3% for IDegLira vs. IDeg and to a superiority margin of 0.0% for IDegLira vs. liraglutide. The non-inferiority margin of 0.3% was chosen in accordance with the Food and Drug Administration (FDA) guidance.[22] The primary objective will be fulfilled only if both non-inferiority of IDegLira vs. IDeg and superiority of IDegLira vs. liraglutide are confirmed.

Formally, let D be the mean difference (IDegLira minus IDeg and IDegLira minus liraglutide respectively) in change from baseline in HbA_{1c}. Non-inferiority and superiority will thus be considered confirmed if the upper bound of the two-sided 95% confidence interval for D is below 0.3% and 0.0% respectively. 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 null-hypotheses (H_0) are given as

- Non-inferiority: H_0 $D \geq 0.30\%$ against H_A $D < 0.30\%$
- Superiority: H_0 $D \geq 0.0\%$ against H_A $D < 0.0\%$

For sample size calculations for non-inferiority a mean difference in treatment of -0.1% and a standard deviation of 1.0% are assumed. For superiority an assumed mean difference in treatment of -0.3% and a standard deviation of 1.0% are applied in sample size calculations.

For evaluation of non-inferiority per protocol (PP) population is used for the sample size calculations, while the full analysis set (FAS) is used for evaluation of superiority. It is assumed that 15% of the randomised subjects will be excluded from the PP analysis set. The above assumptions

are based on experience from the phase 3a development programmes for IDegLira and IDeg. The sample size is determined using a t-statistic under the assumption of a one-sided test of size 2.5% for both the superiority and non-inferiority testing. Based on these assumptions a sample size of 807 patients results in a non-inferiority power of 98.9% and a superiority power of 93.5% i.e. the combined power for meeting the primary objective is 98.9% * 93.5% = 92.5%.

Considering 0% efficacy retention as the most conservative approach for the anticipated 15% of subjects discontinuing randomised treatment reduces the expected treatment difference to -0.26% for the superiority test and to -0.085% for the non-inferiority test. A total of 269 subjects per treatment arm will then yield a superiority power of at least 83.9%, a non-inferiority power of at least 98.4% and a combined power of at least 98.4%*83.9% = 82.6%.

17.2 Definition of analysis sets

The following analysis sets are defined in accordance with the ICH-E9 guidance[23]

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

  Subjects will contribute to the evaluation "as treated".
- **Safety Analysis Set (SAS)**: includes all subjects receiving at least one dose of the investigational product or comparator. Subjects in the safety set will contribute to the evaluation "as treated"
- **Completer Analysis Set (CAS)**: includes all randomised subjects who have completed the trial. Subjects in the completer analysis set will contribute to the evaluation "as randomised"

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

Before data are released for statistical analysis, a review of all data will take place to identify protocol deviations that could potentially affect the results. Any decision to exclude any subject or observation from the statistical analysis is the joint responsibility of the members of the 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 52 weeks of treatment.

The change from baseline in HbA_{1c} after 52 weeks of treatment will be analysed using the standard analysis of covariance (ANCOVA) model with treatment and pre-trial OAD treatment (metformin, α-GI, TZD, SU's, SGLT2i or glinide) as fixed factors and baseline HbA_{1c} as covariate. Missing values after 52 weeks of treatment will be imputed applying LOCF using HbA_{1c} values at and after baseline.

Non-inferiority of IDegLira vs. IDeg will be considered as confirmed if the 95% confidence interval for the mean treatment difference lies entirely below 0.3%; equivalent to a one-sided test with significance level of 2.5%. Non-inferiority will be investigated on the FAS. Sensitivity analysis will be performed on the PP analysis set.

Superiority of IDegLira vs. liraglutide 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. The primary objective will be fulfilled only if both non-inferiority of IDegLira vs. IDeg and superiority of IDegLira vs. liraglutide are confirmed.

17.3.1 Sensitivity analysis

The primary analysis will be repeated on the PP analysis set and the completer analysis set (CAS) as sensitivity analysis. Furthermore, 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 OAD 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 ITT scenario will be applied. The imputation will follow the hypothesis being tested. i.e., when deriving the IDegLira vs. IDeg contrast the imputation in the IDegLira arm will be based on IDeg values, whereas for the IDegLira vs. Liraglutide contrast the imputation in the IDegLira arm will be based on Liraglutide values. In each of the analysis the third arm will be kept in the model. Furthermore, 0.3 will be added to the imputed values in the IDegLira arm for the non-inferiority comparison against IDeg to mimic a scenario where subjects discontinued from IDegLira treatment are assumed to be switched to a treatment inferior to IDeg. In other words: two imputation datasets will be made for IDegLira and

only one for each of the comparator arms. Which imputed IDegLira dataset to include in the model depends on the treatment contrast to be estimated. The imputations will be done as follows:

- In the first step intermittent missing values are imputed using a Markov Chain Monte Carlo (MCMC) method, in order to obtain a monotone missing data pattern. This imputation is done for each treatment 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 OAD treatment as fixed factors, and baseline HbA_{1c} as covariates is fitted to the change in HbA_{1c} from baseline to 4 weeks (Visit 6) 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 OAD 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 (Visit 10) 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 52 weeks (Visit 54)

- For each subject discontinued from treatment in the IDegLira treatment group, a value of 0.3% (the non-inferiority limit) is added to the change in HbA_{1c} at 52 weeks for the comparison against IDeg.

- For each of the complete data sets, the change from baseline to 52 weeks is analysed using an analysis of variance model with treatment and pre-trial OAD 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.[24] 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 CTR.

17.4 Secondary endpoints

17.4.1 Confirmatory secondary endpoints

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

- Change from baseline in body weight (kg) after 52 weeks of treatment.
- Number of treatment emergent severe or blood glucose (BG) confirmed hypoglycaemic episodes during 52 weeks of treatment.
- Change from baseline in HbA_{1c} after 52 weeks of treatment

In order to control the overall type I error on a 5% level with regards to the confirmatory secondary endpoints, a hierarchical testing procedure will be used. The tests for superiority of the confirmatory secondary endpoints will be based on the FAS and will only be carried out if non-inferiority of IDegLira vs. IDeg and superiority of IDegLira vs. liraglutide with regards to the primary endpoint are confirmed.

If and only if superiority is confirmed with respect to change from baseline in body weight after 52 weeks of treatment the number of treatment emergent severe or BG confirmed hypoglycaemic episodes during 52 weeks of treatment will be tested for superiority. If and only if superiority is confirmed with respect to the number of treatment emergent severe or BG confirmed hypoglycaemic episodes during 52 weeks of treatment the change from baseline in HbA_{1c} after 52 weeks of treatment will be tested for superiority.

None of the sensitivity analysis are part of the hierarchical testing procedure.

The change from baseline in body weight after 52 weeks of treatment will be analysed using the standard ANCOVA model with treatment and pre-trial OAD treatment as fixed factors and baseline body weight as covariate. Missing values after 52 weeks of treatment will be imputed applying LOCF using body weight values at and after baseline.

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

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

is less than 2.5%, where D is the treatment difference. Conclusion of superiority will be based on FAS.

As sensitivity analyses for body weight the analysis will be repeated on the PP analysis set and the CAS as sensitivity analysis. Furthermore, sensitivity analysis will be performed on FAS using the MMRM to evaluate the robustness of using LOCF. All body weight values available post baseline at scheduled measurement times will be analysed in a linear mixed normal model using an

unstructured residual covariance matrix for body weight measurements within the same subject. The model will include treatment, visit and pre-trial OAD treatment as fixed factors and baseline body weight as covariate. Interactions between visit and all factors and between visit and baseline body weight are also included in the model. Finally, a pattern mixture model approach similar to that described for HbA_{1c} but without the added non-inferiority penalty, will be applied.

Number of treatment emergent severe or BG confirmed hypoglycaemic episodes during 52 weeks of treatment will be analysed using a negative binominal regression model with a log-link function and the logarithm of the time period in which a hypoglycaemic episode is considered treatment emergent as offset. The model will include treatment and previous OAD treatment as fixed factors.

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

H_0 RR$\geq$1.0 against H_A RR<1.0,

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

A sensitivity analysis will carried out to evaluate the impact of subject withdrawing from the trial. A pattern mixture approach using a copy difference from control method will be applied.[25]

- In the first step samples from the posterior distribution of model parameters using a Bayes negative binomial log-link model with the same covariates as in the original hypo analysis and log of the treatment emergent exposure time as an offset will be extracted. 1000 samples are to be made. Number of burn-in iterations will be set to nbi=1000, number of iterations after burn-in, nmc=1000, and thinning set to thin=10. This leaves 1000 different sets of imputed parameter estimates to be used

- For each imputation the expected number of events is calculated for the period before and after withdrawal. The period after withdrawal (*missing the exposure*) is derived as the max of either 27 weeks or max over all the exposure times for withdrawn subjects within a trial minus that subjects the exposure. For the copy reference approach a subject expected event rate both before and after withdrawal is assumed to be the same as the reference group.

- The total number of hypos for each subject is then derived as number of observed hypos plus a random sample from a negative binomial distribution with the first parameter being (the inverse of the dispersion parameter + expected number of hypos before withdrawal) divided by (the inverse of the dispersion parameter + expected number of hypos before withdrawal + expected number of hypos after withdrawal), and the second parameter being the inverse of the dispersion parameter + number of observed hypos)

- For each imputation, the imputed numbers are then analysed using a negative binomial model with log link and the same covariates as in the original hypo analysis and the log of the total subjects treatment emergent exposure (observed treatment emergent exposure plus missing exposure for withdrawn subjects) as offset.

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

- Subjects with missing treatment emergent exposure time will not contribute to the analysis

The imputation will follow the hypothesis being tested. i.e., first step getting samples from the posterior distribution is unchanged. The derivation of period after withdrawal is also unchanged, i.e., max is taken over all subjects in all 3 treatment arms. When deriving the IDegLira vs. IDeg contrast this will be based on a dataset with all 3 treatment arms, where event rate before and after withdrawal is assumed to be the same as in the IDeg group. An imputation of events in the missing period is only done for the IDegLira and IDeg arm, but all 3 arms will enter the model. Similarly for the IDegLira vs liraglutide contrast, the event rate before and after withdrawal is assumed to be the same as in the liraglutide arm. In other words: two imputation datasets will be made based on different reference groups. Which imputed IDegLira dataset to be included in the model will depend on the treatment contrast to be estimated.

The change from baseline in HbA_{1c} after 52 weeks of treatment will be analysed using the standard ANCOVA model with treatment and pre-trial OAD treatment as fixed factors and baseline HbA_{1c} as covariate. Missing values after 52 weeks of treatment will be imputed applying LOCF using HbA_{1c} values at and after baseline.

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

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

is less than 2.5%, where D is the treatment difference. Conclusion of superiority will be based on FAS. As sensitivity analyses for the superiority of HbA_{1c} the same sensitivity analyses will be applied as for the primary endpoint as described in section 17.3.1, only without adding non-inferiority margin of 0.3% for subjects discontinuing IDegLira.

17.4.2 Supportive secondary endpoints

17.4.2.1 Efficacy endpoints

In the following the statistical models will be fitted to all data simultaneously (all treatment groups) and from this model the treatment differences for IDegLira vs. IDeg and IDegLira vs. liraglutide will be estimated.

Insulin dose after 52 weeks of treatment

The actual daily dose after 52 weeks of treatment will be analysed using the standard ANCOVA model including treatment and pre-trial OAD treatment as fixed factors and baseline HbA_{1c} value and baseline insulin dose as covariates.

Responder after 52 weeks of treatment

Two dichotomous endpoints (responder/non-responder) will be defined based on whether a subject has met a specific target level after 52 weeks of treatment:

- $HbA_{1c} < 7.0\%$[26]
- $HbA_{1c} \leq 6.5\%$[26, 27]

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

HbA_{1c} responder endpoints and change in body weight from baseline below or equal to zero

Responder for HbA_{1c} without weight gain after 52 weeks of treatment will be defined as HbA_{1c} $< 7.0\%$ or $\leq 6.5\%$ at end 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 OAD treatment as 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 52 weeks of treatment will be defined as $HbA_{1c} < 7.0\%$ or $\leq 6.5\%$ at end of treatment 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 OAD treatment as fixed factors and baseline HbA_{1c} values as a covariate.

HbA_{1c} responder endpoints without hypoglycaemic episodes change in body weight from baseline below or equal to zero

Responder for HbA_{1c} without hypoglycaemic episodes and weight gain after 52 weeks of treatment will be defined as $HbA_{1c} < 7.0\%$ or $\leq 6.5\%$ at end of treatment, 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 OAD treatment as fixed factors and baseline HbA_{1c} and body weight values as covariates.

Fasting plasma glucose (FPG)

Change from baseline in FPG after 52 weeks of treatment will be analysed using the standard ANCOVA model.

Waist circumference

Change from baseline in waist circumference after 52 weeks of treatment will be analysed using the standard ANCOVA model.

Blood pressure (systolic and diastolic)

Change from baseline in blood pressure after 52 weeks of treatment will be analysed using the standard ANCOVA model.

Self-measured blood glucose (SMBG) 9-point profile

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

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

A linear mixed effect model will be fitted to the 9-point SMBG profile data. The model will include treatment, pre-trial OAD treatment, time, the interaction between treatment and time and the interaction between pre-trial OAD 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 explore

Change from baseline after 52 weeks of treatment in mean of the 9-point profile and post-prandial increment endpoints will be analysed separately using the standard ANCOVA model.

Fasting lipid profile

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 52 weeks of treatment will be analysed separately were using

the standard ANCOVA model. In these statistical analyses the endpoint will be log-transformed and so will the baseline covariate.

Fasting C-peptide, fasting human insulin, fasting glucagon and proinsulin

These endpoints after 52 weeks of treatment will be analysed separately using the standard ANCOVA model. In these statistical analyses the endpoint will be log-transformed and so will the baseline covariate.

17.4.2.2 Safety endpoints

Adverse events

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

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

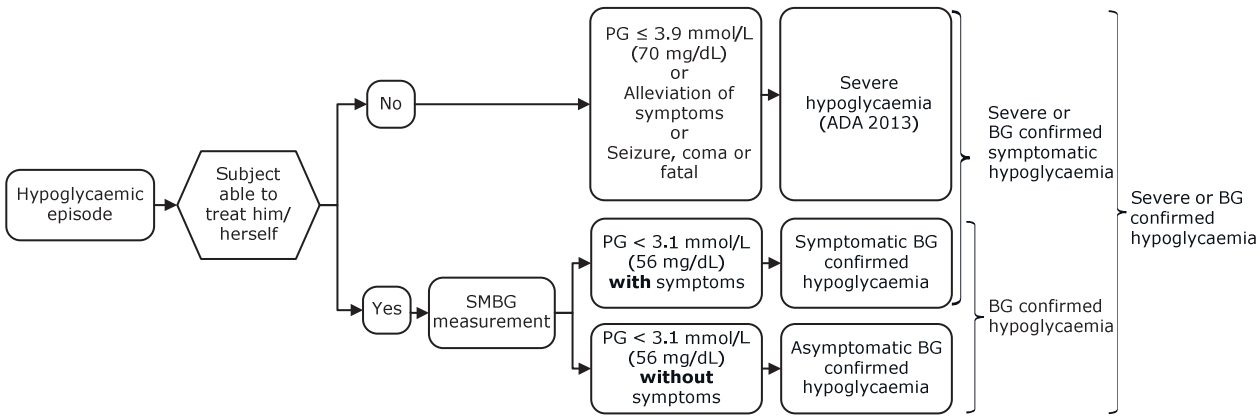
Hypoglycaemic episodes are classified according to the Novo Nordisk classification of hypoglycaemia (see Figure 17.1) and the ADA classification of hypoglycaemia (see Figure 17.2).

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

Novo Nordisk 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[26] 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[26] or BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) **with** or **without** symptoms consistent with hypoglycaemia.

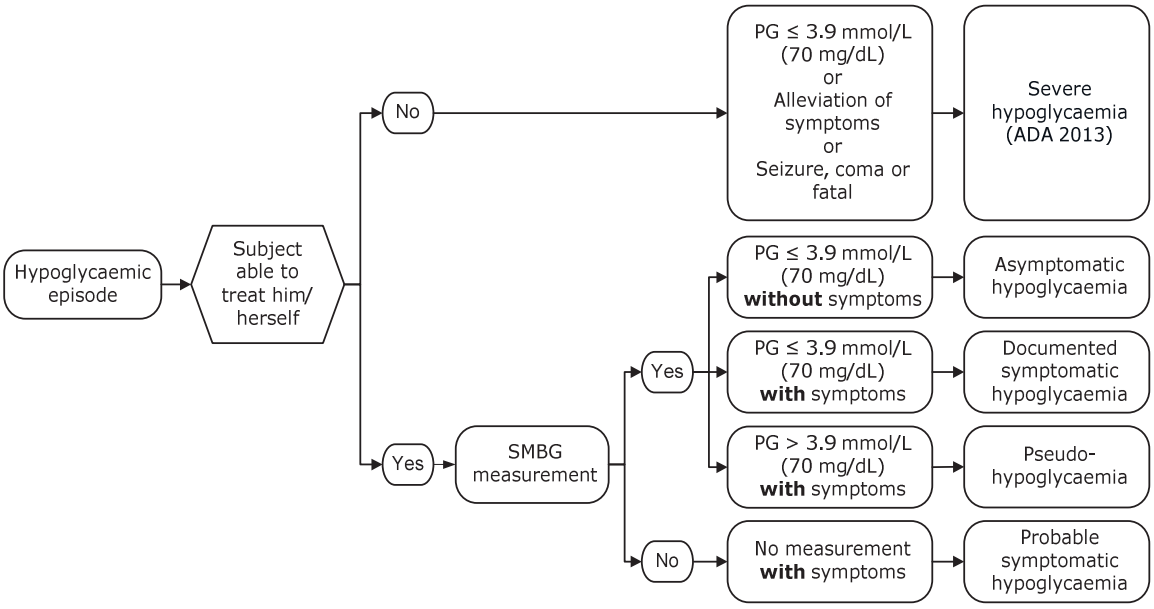


Note: Glucose measurements are performed with capillary blood calibrated to plasma equivalent glucose values

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 severe or BG confirmed symptomatic hypoglycaemic episodes and nocturnal severe or BG confirmed symptomatic hypoglycaemic episodes will be analysed separately using the same model as used for the treatment emergent severe or BG confirmed hypoglycaemic episodes.

Clinical evaluations (physical examination, eye examination and ECG)

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

- summaries for each visit
- shift table from baseline to after 52 weeks of treatment

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

Pulse

Change from baseline in pulse after 52 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 52 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 EOT measurement - LOCF) and within treatment group by week. Plots will be done by each gender, separately.

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

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

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

Anti-drug antibodies

Anti-IDeg antibodies, anti-human insulin antibodies, anti-liraglutide antibodies, anti-liraglutide antibodies cross reacting with native GLP-1 and in vitro neutralising effect of anti-liraglutide antibodies will be summarised and tabulated. The correlation between change from baseline after 52

weeks of treatment in anti-IDeg and anti-insulin antibodies respectively, to insulin dose after 52 weeks of treatment, HbA1c after 52 weeks of treatment and change from baseline after 52 weeks of treatment in HbA_{1c} will be illustrated using scatter plots.

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

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

17.5 Pharmacokinetic modelling

Population pharmacokinetic analysis

The objective for the population pharmacokinetic (PK) analysis is to compare the pharmacokinetics of IDegLira and its mono-components given separately at clinically relevant doses during 52 weeks of treatment. Furthermore, the effects of pre-specified covariates on plasma concentrations of IDegLira will be evaluated.

The population PK analysis will be performed by the Quantitative Clinical Pharmacology Department at Novo Nordisk A/S. A more technical and detailed elaboration of the population PK analysis will be given in the modelling analysis plan (MAP) which will be finalised before DBL.

The pre-specified analysis will explore the effects of covariates on the insulin degludec and liraglutide exposure. The structural models and covariate relationships will be predefined in detail in the MAP. In brief, previously developed population PK models for insulin degludec and liraglutide will be used. For both PK models, the absorption rate constant (Ka) will be fixed and the apparent clearance (CL/F) and the apparent volume of distribution (Vd/F) will be estimated.

The covariates of interest will be incorporated into the PK models using criteria which will be specified in the MAP.

Exposure-response analysis

The exposure-response relationship will be investigated for selected response variables, such as HbA_{1c}.

The population PK and exposure-response analyses will be reported in a separate modelling report, which will not be a part of the clinical trial report.

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 a thorough evaluation in regards to inclusion/exclusion criteria defined in order to ensure that subjects are eligible for trial treatment. Randomised subjects will be treated with IDegLira, IDeg or liraglutide and pre-trial OAD, a regimen anticipated being equal to or better than the OAD treatment they received prior to 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 the trial participation.

All three trial products are used in the clinic 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 product may be associated with AEs, but relevant precautions have been implemented in the design and planned conduct of the trial in order to minimise the risks and inconveniences of participating in the trial. These precautions include thorough information regarding the correct administration of the trial product and gradual dose adjustment. Furthermore, subjects 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.[29, 30, 31, 32, 33]

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. [29, 30, 31, 32, 33]

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

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 MEN2. 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 with serum calcitonin or thyroid ultrasound will mitigate human risk of thyroid C-cell tumours. Based on the above, monitoring of serum calcitonin will be performed during the trial according to the flow chart, section 2. 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 (MRHD) of 1.8 mg/day. The US Victoza® Prescribing Information includes the Pregnancy Category C (US FDA Pharmaceutical Pregnancy Categories: "Animal reproduction studies have shown an adverse effect on the foetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks"). Due to this pregnant women and women with the intention to become pregnant, are excluded from the trial

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

Areas of special interest with regards to safety of trial product are described in detail in the current versions of the IB´s of the trial products [6,8,11], and in the Japanese approved labelling for IDeg and liraglutide, respectively.

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

18.2 Data handling

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

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

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

18.3 Information to subject during trial

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

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

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

19 Protocol compliance

Deviations from the protocol should be avoided.

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

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

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

20 Audits and inspections

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

21 Critical documents

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

- Regulatory approval and/or acknowledgement of notification as required
- Approval/favourable opinion from IRBs 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-investigators (current, dated and signed - must include documented GCP training or a certificate)
- Signed receipt of Investigator's Brochure
- 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, each investigator agrees to comply fully with ICH GCP[1], applicable regulatory requirements and the Declaration of Helsinki.[2]

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

22 Responsibilities

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

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

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

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

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

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

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

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

The investigator and other site personnel must have sufficient English skills according to their assigned tasks.

23 Reports and publications

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

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

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

One investigator will be appointed by Novo Nordisk to review and sign the clinical trial report (signatory investigator) on behalf of all participating investigators. The signatory investigator will

be appointed based upon the criteria defined by the International Committee of Medical Journal Editors for research publications.[34]

23.1 Communication of results

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

The results of this trial will be subject to public disclosure on external web sites according to international and national regulations, as reflected in the Novo Nordisk Code of Conduct for Clinical Trial Disclosure.[35]

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[18] (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 ICMJE authorship criteria to be named authors on publications.

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

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

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

23.2 Investigator access to data and review of results

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

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

24 Retention of clinical trial documentation and human biospecimens

24.1 Retention of clinical trial documentation

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

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

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

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

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

24.2 Retention of antibody samples

Antibody samples will be analysed and then stored by the special laboratory analysing the samples until final feedback from the Japanese regulatory authorities, but no longer than 15 years from end of trial. Only Novo Nordisk will have access to these samples. Further characterisation of antibody response may be requested by the regulatory authorities.

None of the data will be identified by name. Antibody samples will be identified only by a subject number, a visit number and a trial identification number. In the event that the collected antibody samples will be used in the future, the investigator will become directly informed by Novo Nordisk about the results if the findings are deemed clinically relevant. In such case, a written summary of the findings, including listings of subject specific values, will be provided once a firm conclusion from the results has been drawn by Novo Nordisk.

The antibody samples will be destroyed in a way not revealing the identity of the subjects.

25 Institutional Review Boards and regulatory authorities

Institutional Review Boards (IRBs)

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

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.

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.

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Appendix A

Insulin titration-and liraglutide dose escalation guidelines

Trial ID: NN9068-4183
DUAL™ I Japan

A trial comparing the efficacy and safety of insulin degludec/liraglutide, insulin degludec and liraglutide in Japanese subjects with type 2 diabetes mellitus

Protocol originator

[redacted]

Table of Contents

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List of in-text tables

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1 Introduction

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

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 PG levels.

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

To optimise and maintain glycaemic control, the Investigator should, throughout the trial be at least in weekly contact with the subjects to assist the subjects in adjusting insulin degludec/liraglutide (IDegLira) or insulin degludec (IDeg) doses and to ensure the subject's welfare.

Liraglutide treatment information is further described in this document. Please notice that the glycaemic control of liraglutide will not be monitored.

2 Treatment regimens

At randomisation the subjects will be randomised 1:1:1 into three parallel arms:

- IDegLira once daily
- IDeg once daily
- Liraglutide once daily

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

Maximum dose of IDegLira is 50 dose steps (50U insulin degludec/1.8 mg liraglutide).
There is no maximum dose of IDeg.
Liraglutide dose is 1.8 mg (fixed dose).

All subjects will continue with the pre-trial OAD at pre-trial dose.

2.1 Injection area

IDegLira, IDeg and liraglutide should be injected subcutaneously once daily in the thigh, the upper arm (deltoid area) or abdomen. The chosen injection region should remain unchanged throughout the trial, although rotation within a given area is recommended.

2.2 Injection time

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

Liraglutide should be injected once daily in the morning or the evening, and approximately be at the same time of the day throughout the trial.

3 Initiation and titration of IDegLira and IDeg

3.1 Initiation of IDegLira

The recommended start dose of IDegLira is 10 dose steps (10U of insulin degludec and 0.36 mg liraglutide) daily.

3.2 Initiation of IDeg

The recommended start dose of IDeg is 10U of insulin degludec.

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 fasting plasma glucose (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), see table 3.1 for illustration, according to a predefined titration algorithm described in table 3.2. The investigator will support titration at all contacts.

Table 3-1 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[3]
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 3-2.

Table 3-2 Adjustment of IDeg and IDegLira doses

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

If one SMBG value is missing, the adjustment should be performed by the mean of the two available SMBG values. If two SMBG values are missing the adjustment should be made on the one SMBG value.

3.4 Deviation 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 Initiation and dose escalation of liraglutide

The maintenance dose of liraglutide in this trial is 1.8 mg/day, this dose will be reached after a dose escalation period of 6 weeks. Trial product will be provided in a prefilled device.

4.1 Escalation period

Liraglutide will be initiated with 0.3 mg/day and subsequent weekly dose escalation by 0.3 mg weekly to a maximum dose of 1.8 mg/day during the first 6 weeks, see Table 4-1.

Table 4-1 Liraglutide dose escalation

	1st week	2nd week	3rd week	4th week	5th week	6th week
Liraglutide	0.3 mg/day (50 µL=5 clicks)	0.6 mg/day (100 µL=10 clicks)	0.9 mg/day (150 µL=15 clicks)	1.2 mg/day (200 µL=20 clicks)	1.5 mg/day (250 µL=25 clicks)	1.8 mg/day (300 µL=30 clicks)

4.1.1 Extension of dose escalation period

If subjects do not tolerate an increase in dose during dose escalation, e.g. due to safety reasons, the total dose escalation period can be extended with 1 week at the discretion of the investigator. The Investigator must emphasise to subjects the necessity of reaching the target dose of 1.8 mg.

4.2 Maintenance period

The dose of liraglutide should remain unchanged in the maintenance period (i.e. after the escalation period) at 1.8 mg/day.

If subjects do not tolerate the target dose they must be withdrawn from the trial due to safety concerns, reporting the AE that led to the withdrawal.

4.2.1 Dose reduction in maintenance period

After the end of dose escalation, dose reduction in the 1.8 mg/day treatment arm to 1.5 mg or 1.2 mg is allowed at the discretion of the investigator due to safety reasons. This should not extend more than 7 days in total from end of dose escalation to end of treatment. Dose reduction or treatment pause of longer duration unrelated to the tolerability of liraglutide is acceptable. Dose reduction lower than 1.2 mg/day is not allowed except temporarily for safety reasons, at the discretion of the investigator (as for instance while ruling out a suspected pancreatitis). The Investigator must emphasise to subjects the necessity of maintaining the target dose of 1.8 mg.

5 Data collection for IDegLira and IDeg

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

- Per protocol pre-breakfast SMBG values measured since last visit/telephone contact as described in section 3.3
- Doses of IDegLira or IDeg taken before and after titration
- Reasons for deviation from the titration algorithms, if applicable
- Hypoglycaemic episodes

6 Review procedure of titration data for IDegLira and IDeg

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 5 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 SMBG values and HbA_{1c}. This will be done in an unbiased and whenever possible in a blinded manner.

7 References

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

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

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

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

Appendix B

New York Heart Association Criteria for Functional Capacity

Trial ID: NN9068-4183
DUAL™ I Japan

A trial comparing the efficacy and safety of insulin degludec/liraglutide, insulin degludec and liraglutide in Japanese subjects with type 2 diabetes mellitus

Trial Phase: 3a

Protocol originator

[redacted]

Insulin & Diabetes Outcomes, Clinical Operations

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

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

Trial ID: NN9068-4183

DUAL™ I Japan

A trial comparing the efficacy and safety of insulin degludec/liraglutide, insulin degludec and liraglutide in Japanese subjects with type 2 diabetes mellitus

Protocol originator

[redacted]

Insulin and Diabetes Outcomes, Clinical Operations

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 FDA guidance document [1] requests that Sponsors demonstrate the cardiovascular safety profile of any new therapy for type 2 diabetes in order to ensure, that the new therapy does not increase the cardiovascular risk to an unacceptable extent.	All events will be adjudicated
Acute coronary syndrome; myocardial infarction (MI) or hospitalisation for unstable angina	All types of myocardial infarction (MI) must be reported: • Spontaneous MI (including re-infarction and MI associated with stent thrombosis) • Percutaneous coronary intervention (PCI) related MI • Coronary artery bypass graft surgery (CABG) related MI • Silent MI All events with symptoms of unstable angina requiring hospitalization must be reported.	An FDA guidance document[1] requests that Sponsors demonstrate the cardiovascular safety profile of any new therapy for type 2 diabetes in order to ensure, that the new therapy does not increase the cardiovascular risk to an unacceptable extent.	All events will be adjudicated
Cerebrovascular event; stroke or transient ischemic attack	**Stroke** (ischemic, haemorrhagic or undetermined) is defined as an acute episode of neurological dysfunction, caused by focal or global brain, spinal cord, or retinal vascular injury. **Transient Ischemic Attack** (TIA) is defined as a transient (<24 hours) episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction.	An FDA guidance document[1] requests that Sponsors demonstrate the cardiovascular safety profile of any new therapy for type 2 diabetes in order to ensure, that the new therapy does not increase the cardiovascular risk to an unacceptable extent.	All events will be adjudicated
Heart failure requiring hospital admission	Clinical manifestations of a new episode or worsening of existing heart failure.	An FDA guidance document[1] requests that Sponsors demonstrate the cardiovascular safety profile of any new therapy for type 2 diabetes in	All cases of heart failure requiring hospitalisation, defined as an admission to an

Events with additional data collection and/or events requiring adjudication	Definitions	Rationale	Event Adjudication Committee
		order to ensure, that the new therapy does not increase the cardiovascular risk to an unacceptable extent.	inpatient unit or a visit to an emergency department that results in at least a 24 hour stay, will be adjudicated
Pancreatitis	Two of the following three diagnostic criteria fulfilling the diagnosis of acute pancreatitis: • Severe acute upper abdominal pain • Elevated blood levels of pancreatic enzymes (lipase, amylase) > 3xUNR • Characteristic imaging finding (ultrasound, computerised axial tomography (CT), magnetic resonance imaging (MRI)) Chronic pancreatitis will be defined by characteristic imaging finding (ultrasound, CT, MRI) with abnormal pancreatic function tests or characteristic histological findings.	Treatment with GLP-1 receptor agonists has been associated with acute pancreatitis. Novo Nordisk therefore monitors these events closely.	All events 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 per thyroid events and should not be reported as a Neoplasm MESI)	Neoplasm is an event we follow closely for GLP-1 analogues due to non-clinical findings in rats and mice treated with GLP-1 agonists.	All neoplasm events, irrespective of malignancy stage, will be adjudicated
Thyroid disease	All disorders of thyroid gland (incl. thyroid neoplasms) must be reported. Please refer to the protocol for further details on the assessments.	Thyroid C-cells carcinogenicity has been reported in rats and mice treated with GLP-1 receptor agonists in non-clinical studies	Only thyroid disorders requiring thyroidectomy and thyroid neoplasms will be adjudicated
Renal failure	All events of renal failure should be reported, including events fulfilling one of	Liraglutide (a component of IDegLira) and SGLT2i have	No adjudication

Events with additional data collection and/or events requiring adjudication	Definitions	Rationale	Event Adjudication Committee
	the following three diagnostic criteria 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 < 0.5mL/kg/h for 6 hours	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.	

2 Medical Events of Special Interest (MESI)

MESIs	Definitions	Rationale	Event Adjudication Committee
Medication errors concerning trial products	a. Administration of wrong drug or use of wrong device b. Wrong route of administration, such as intramuscular instead of subcutaneous c. Administration of a high dose with the intention to cause harm, e.g. suicide attempt d. Administration of an accidental overdose i.e. a dose which may lead to significant health consequences, as judged by the investigator, irrespective of whether the SAE criteria are fulfilled or not.	Standard MESI in all Novo Nordisk clinical trials. Medication errors are captured to collect information which may be used to improve the design, name or packaging of the product and/or information which may have an impact on product labelling (for example information about substantial overdoses).	No adjudication

3 Reference

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

Appendix D

Monitoring of Calcitonin

Trial ID: NN9068-4183

DUAL™ I Japan

A trial comparing the efficacy and safety of insulin degludec/liraglutide, insulin degludec and liraglutide in Japanese subjects with type 2 diabetes mellitus

Trial phase: 3a

Protocol originator

[redacted]

Insulin & Diabetes Outcomes, Clinical Operations

1 Background

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

While there is general agreement on the clinical interpretation of substantially elevated calcitonin levels (>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 at screening cannot be randomised according to protocol section 6.3 and further if the calcitonin value is measured to be ≥ 50 ng/L during the treatment period, the subjects must be withdrawn according to section 6.4 in the protocol.
In case a subject has a calcitonin value ≥ 10 ng/L the algorithm outlined in Figure 1 and described below should be followed. The algorithm applies for all calcitonin values including screening values.

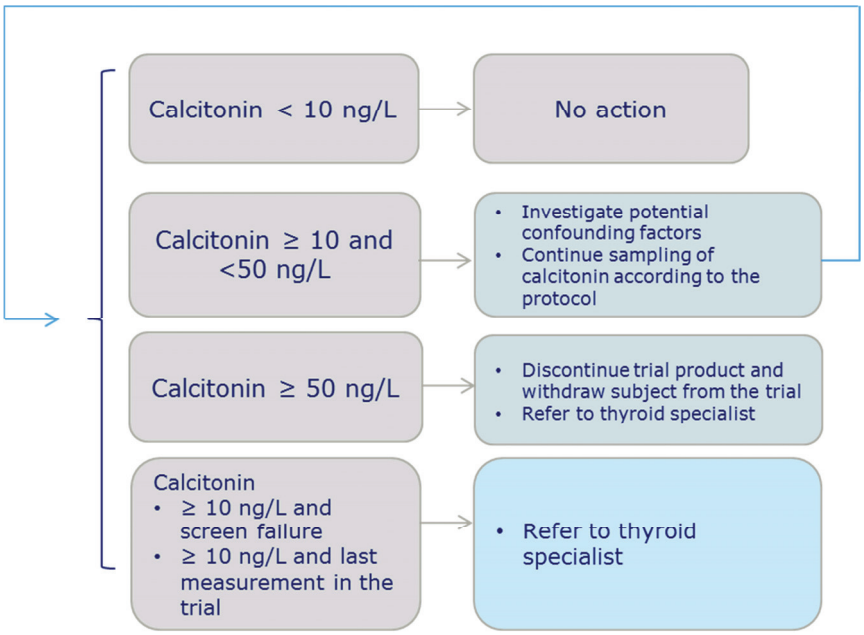

Figure 1 Flow of calcitonin monitoring

2.1 Calcitonin ≥ 100 ng/L

Action: The subject (even if a screen failure) must immediately be referred to a thyroid specialist for further evaluation and the subject must be withdrawn from the trial. All medications suspected to relate to this condition should be discontinued.
Background: These values were found in 9 (0.15%) of a population of 5817 patients with thyroid nodular disease[1]. All of these patients were diagnosed with MTC resulting in a positive predictive value of 100%.

Diagnostic evaluation should include:

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

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

2.2 Calcitonin ≥ 50 and < 100 ng/L

Action: The subject (even if a screen failure) should be referred to a thyroid specialist for further evaluation and the 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 CT > 10 ng/L to screen for C-cell disease, but they do not provide sufficient information on patients with basal CT >10 and <20 ng/L to allow conclusions[2 3].

3 References

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

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

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

Global and country key Novo Nordisk staff

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

Content: Global key staff and Country key staff

Protocol Amendment

No 1
to Protocol, final version 2.0
dated 15 July 2015

DUAL™ I Japan
Trial ID:NN9068-4183

A trial comparing the efficacy and safety of insulin degludec/liraglutide, insulin degludec and liraglutide in Japanese subjects with type 2 diabetes mellitus

Trial phase: 3a

Applicable to Japan

Amendment originator:

[redacted]

ClinOps2, Insulin & Diabetes Outcomes

Table of Contents

Page

1 Introduction including rationale for the protocol amendment

It has been identified, that the protocol exclusion criterion 16 was not consistent with the text in other sections of the protocol which is why, it's deemed necessary to correct this error. While amending the above inconsistency, two minor corrections were made in order to improve clarity and quality of the protocol.

In this protocol amendment:

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

2 Changes

The following changes listed in section 2.1-2.3 have been made:

2.1 Section 6.3 – Exclusion Criteria 16 corrected for consistency throughout protocol

2.1.1 Change:

16. Proliferative retinopathy or maculopathy requiring acute treatment as verified by fundoscopy or fundus photography performed within 90 days prior to *randomisation* ~~screening~~.

2.1.2 Rationale:

The exclusion criterion was not phrased as intended by mistake. Importantly it should be allowed to perform the eye examination at the screening (Visit 1) or in the period between Visit 1 and Visit 2 (randomisation), as long as results are available prior to randomising a subject into the trial. This is in accordance with the protocol Section 2: Flow Chart; foot note 8 & Section 8.4.7 stating the following:

Section 2: Flow chart footnote 8:

”Eye examination (fundoscopy/fundus photography) obtained within 90 days prior to Visit 2 as part of routine practise may replace the screening assessment if results are available for evaluation at Visit 2.”

Section 8.4.7 Eye Examination

”**Fundoscopy/fundus photography performed within 90 days prior to Visit 2 is acceptable.** If a funduscopy/fundus photography has been performed prior to the screening visit (Visit 1) the procedure does not need to be repeated, unless worsening of visual function since the last examination has been noted.”

2.2 Section 6.4 – Withdrawal Criteria 5 modified to align with excl. criterion 7

2.2.1 Change:

5. Initiation of any systemic treatment with products which in the investigator's opinion could interfere with *subjects weight, or* glucose or lipid metabolism (e.g. systemic corticosteroids)

2.2.2 Rationale

The reason for adding this is in order to align with and exclusion criterion 7, stating the following:

“7. Anticipated initiation or change in concomitant medications in excess of 14 days known to **affect weight** or glucose metabolism.”

2.3 Section 8.2.2 – Concomitant Medication – definition changed.

2.3.1 Change:

A **concomitant medication** is any medication, other than the trial products and OADs, which is taken during the trial~~, including screening and follow-up periods~~.

2.3.2 Rationale:

The reason for deleting the 'including screening' is, that text is redundant, since in the paragraph below the following is stated:

"Details of any concomitant medication must be recorded at Visit 1."

Further, 'and the follow up periods' will be deleted in order to avoid confusion, since in fact it is not intended to record any concomitant medication in the follow-up period, please refer to the last paragraph of section 8.2.2 stating as follows:

"Concomitant medication and anti-diabetic therapy initiated at end of treatment visit (Visit 54) and at the follow up visit (Visit 55) should not be recorded in the eCRF."