Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT02505334
Sponsor trial ID:	NN2211-4174
Official title of study:	A trial comparing the efficacy and safety of liraglutide 1.8 mg/day to liraglutide 0.9 mg/day in Japanese subjects with type 2 diabetes mellitus
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16.1.1 Protocol and protocol amendments

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Protocol

Trial ID: 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 type 2 diabetes mellitus

Redacted protocol
Includes redaction of personal identifiable information only.

Trial phase: 3b

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Protocol originator

[redacted], CMR Development Division, Novo Nordisk Pharma Ltd.

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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
CCDS	Company Core Data Sheet
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
DPP-4	dipeptidyl peptidase 4
DUN	dispensing unit number
EAC	Event adjudication committee
ECG	electrocardiogram
EDC	electronic data capture
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
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
HbA1c	glycosylated haemoglobin
hCG	human chorionic gonadotropin
HDL	high density lipoprotein
HOMA-IR	homeostasis model assessment as an index of insulin resistance
HOMA-B	homeotasis model assessment of beta-call function
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IMP	investigational medicinal product
IRB	institutional review board
ITT	Intention to treat
IV/WRS	interactive voice/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
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
MRI	magnetic resonance imaging
MTC	medullary thyroid carcinoma
NYHA	New York Heart Association
OAD	oral antidiabetic drug
PG	plasma glucose
PPG	postprandial glucose
SAE	serious adverse event
SAS	safety analysis set
s.c.	subcutaneous(ly)
SD	standard deviation
SDV	source data verification
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
UNR	upper normal range
UTN	Universal Trial Number
VLDL	very low density lipoprotein

1 Summary

Objective(s) and endpoint(s):

Primary objective

To confirm the superiority of liraglutide 1.8 mg/day vs. liraglutide 0.9 mg/day in controlling glycaemia after 26 weeks of treatment in Japanese subjects with type 2 diabetes mellitus inadequately controlled with liraglutide 0.9 mg/day

Primary endpoint

Change from baseline in HbA1c after 26 weeks of treatment

Secondary objectives

To compare the overall efficacy and safety parameters of liraglutide 1.8 mg/day and liraglutide 0.9 mg/day after 26 weeks of treatment

To evaluate the safety profile of liraglutide 1.8 mg/day over a period of 52 weeks and to monitor glycaemic control and other efficacy parameters over a period of 52 weeks

Key secondary endpoints

Key secondary efficacy endpoints

- Responder for HbA1c after 26 weeks of treatment (Yes/No):
    - HbA1c < 7.0% (53 mmol/mol)
    - HbA1c ≤ 6.5% (48 mmol/mol)
- Change from baseline in body weight after 26 weeks of treatment

Key secondary safety endpoints

- Number of treatment emergent adverse events during 26 weeks of treatment
- Number of treatment emergent adverse events during 52 weeks of treatment

Trial design:

This is a 26-week randomised, parallel, two-arm, open-label, multi-centre trial comparing the efficacy and safety of liraglutide 1.8 mg/day to liraglutide 0.9 mg/day in Japanese subjects with type 2 diabetes mellitus who are inadequately controlled on 1 oral anti-diabetic drug (OAD). Eligible subjects are presenting with an HbA1c level of 7.5-10.0 %. At Visit 2 the pre-trial OAD will be discontinued and liraglutide 0.9 mg/day will be initiated for a 12 week run-in period.

Subjects with an HbA1c ≥7.0% at the end of the run-in period will be randomised in a 1:1 manner; either continuing liraglutide 0.9 mg/day or dose escalation to liraglutide 1.8 mg/day. Only the liraglutide 1.8 mg/day treatment arm will be continued for a total of 52 weeks after randomisation for monitoring of long-term safety and glycaemic control over 52 weeks.

The total trial duration for the 1.8 mg/day treatment arm will be approximately 67 weeks, consisting of 2 weeks screening period, a 12 weeks run-in period, a 26-week main treatment period, a safety extension period of 26 weeks and a follow-up visit. The total trial duration for the 0.9 mg/daytreatment arm will be approximately 41 weeks, consisting of 2 weeks screening period, a 12 weeks run-in period, a 26-week treatment period, and a follow-up visit.

Trial population:

Planned number of subjects to be included in the run-in period, starting liraglutide treatment: 1106

Planned number of subjects to be randomised: 470

Key inclusion criteria

- Male or female Japanese subjects ≥20 years of age at the time of informed consent.
- Type 2 diabetes subjects (diagnosed clinically) ≥ 6 months prior to screening.
- HbA1c 7.5-10.0 % [58 mmol/mol-86 mmol/mol] (both inclusive).
- Subjects on stable therapy with one OAD (stable therapy is defined as unchanged medication and unchanged dose) for ≥ 60 days before screening according to 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.
- Screening calcitonin ≥50 ng/l.
- History of pancreatitis (acute or chronic).
- Personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia type 2 (MEN 2).
- Subjects presently classified as being in New York Heart Association (NYHA) Class IV.
- Within the past 180 days any of the following: myocardial infarction, stroke or hospitalisation for unstable angina and/or transient ischemic attack.
- Diagnosis of malignant neoplasms within the last 5 years (except basal and squamous cell skin cancer, polyps and in-situ carcinomas).

- Any condition which, in the opinion of the investigator might jeopardise subject's safety or compliance with the protocol.

Assessments:

Key efficacy assessments

- HbA1c
- Body weight

Key safety assessment

- Adverse events

Trial product(s):

Liraglutide (Victoza®); 6.0 mg/mL, in a 3.0 mL pre-filled pen (FlexPen®), for subcutaneous (s.c.) injection.

2 Flow chart

Table 2-1 Flow chart

Trial Periods	Screening	Run-in						Randomisation	Main treatment							EOT 26[14]	FU[14]	Safety extension[15]					EOT 52[15]	FU[15]
Type of visit (V: visit, P: phone contact)	V	V	P	P	V	V	V	V	P	P	V	V	V	V	V	V	P	V	V	V	V	V	V	P
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Timing of visit (Weeks)	-14	-12	-11	-10	-8	-4	-1	0[13]	1[13]	2	4	8	12	16	21	26	1w after EOT	30	34	38	42	46	52	1w after EOT
Visit window (Days)		0	±1	±1	±3	±3	±1	±1	±1	±1	±3	±5	±5	±5	±5	±4	+3	±7	±7	±7	±7	±7	±4	+3
SUBJECT RELATED INFO/ASSESSMENTS																								
Informed consent	x																							
In/exclusion criteria	x	x[1]																						
Randomisation								x																
Randomisation criterion								x[2]																
Withdrawal criteria[8]			x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x	
Concomitant illness	x																							
Concomitant medication	x	x[12]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Demography	x																							
Medical history	x																							
NYHA classification	x																							
Smoking status	x																							
EFFICACY																								
Body weight	x							x					x			x				x			x	
Waist circumference	x							x					x			x				x			x	
Height	x																							
Blood pressure	x	x			x	x		x			x	x	x	x	x	x		x		x		x	x	
Glucose metabolism[9]																								
HbA1c	x	x					x	x			x	x	x	x	x	x				x			x	

Trial Periods	Screening	Run-in						Randomisation	Main treatment							EOT 26[14]	FU[14]	Safety extension[15]					EOT 52[15]	FU[15]
Type of visit (V: visit, P: phone contact)	V	V	P	P	V	V	V	V	P	P	V	V	V	V	V	V	P	V	V	V	V	V	V	P
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Timing of visit (Weeks)	-14	-12	-11	-10	-8	-4	-1	0[13]	1[13]	2	4	8	12	16	21	26	1w after EOT	30	34	38	42	46	52	1w after EOT
Visit window (Days)		0	±1	±1	±3	±3	±1	±1	±1	±1	±3	±5	±5	±5	±5	±4	+3	±7	±7	±7	±7	±7	±4	+3
Fasting plasma glucose		x						x			x	x	x	x	x	x		x		x		x	x	
Fasting glucagon		x						x					x			x							x	
Fasting insulin		x						x					x			x							x	
Fasting C-peptide		x						x					x			x							x	
Pro-insulin		x						x					x			x							x	
Lipids		x						x					x			x				x			x	
Self-measured blood glucose: 7-point profile[3]		x						x					x			x							x	
SAFETY																								
Adverse events		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	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
ECG	x[4]							x								x							x	
Eye examination	x[5]							x								x							x	
Physical examination	x							x								x							x	
Pulse	x	x			x	x		x			x	x	x	x	x	x		x		x		x	x	
Biochemistry	x							x					x			x				x			x	
Haematology	x							x					x			x				x			x	
Calcitonin	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	
Pregnancy test[6]	x	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	x		(x)	(x)	(x)	(x)	(x)	x	
TRIAL MATERIAL																								
Dispensing visit		x			x	x		x			x	x	x	x	x	x[10]		x	x	x	x	x		
Hand out directions for use		x			x	x		x			x	x	x	x	x	x[10]		x	x	x	x	x		

Trial Periods	Screening	Run-in						Randomisation	Main treatment							EOT 26[14]	FU[14]	Safety extension[15]					EOT 52[15]	FU[15]
Type of visit (V: visit, P: phone contact)	V	V	P	P	V	V	V	V	P	P	V	V	V	V	V	V	P	V	V	V	V	V	V	P
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Timing of visit (Weeks)	-14	-12	-11	-10	-8	-4	-1	0[13]	1[13]	2	4	8	12	16	21	26	1w after EOT	30	34	38	42	46	52	1w after EOT
Visit window (Days)		0	±1	±1	±3	±3	±1	±1	±1	±1	±3	±5	±5	±5	±5	±4	+3	±7	±7	±7	±7	±7	±4	+3
Dose escalation of trial product		x	x	x				x	x	x[7]														
Drug accountability		x			x	x		x			x	x	x	x	x	x		x	x	x	x	x	x	
IV/IWRS call	x	x			x	x		x			x	x	x	x	x	x		x	x	x	x	x	x	
REMINDERS																								
End of trial form								x								x							x	
Hand-out ID card	x																							
Attend visit fasting		x						x			x	x	x	x	x	x		x		x		x	x	
Training in trial product and pen handling		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x		
Hand out and instruct in diary[11]	x	x			x	x		x			x	x	x	x	x	x		x	x	x	x	x	x	
Hand out and instruct in BG meter use	x																							
End of treatment								x								x							x	
Sign off Casebook																	x							x

Flow chart explanatory descriptions

Footer	Description
1	All screening assessments must be completed prior to initiating run-in visit (V2) and all laboratory results at screening visit (V1) must be available and signed by investigator prior to V2
2	The HbA1c results at V7 must be available and signed by investigator prior to randomising the subject. Subjects will either be randomised and have the procedures done according to the flowchart, or be discontinued and have procedures for EOT performed.
3	7-point SMBG profile should be obtained on a normal day in the week prior to the scheduled visit (not anticipating unusual strenuous exercise).
4	The ECG should be obtained at V1 or between V1 and V2. The result must be available prior to performing any procedures related to V2.

5	Fundoscopy or fundus photography performed within 90 days prior to run-in visit (V2) is acceptable, and results should be available prior to V2.
6	For women of childbearing potential: A serum pregnancy test must be performed at V1, 16 and 23. Urine pregnancy test should be performed at site if a menstrual period is missed, or if pregnancy is suspected.
7	If subjects do not tolerate an increase in dose during dose escalation, the dose escalation period can be extended with 1 week at the discretion of the investigator.
8	Subjects meeting withdrawal criteria should attend EOT visit as soon after treatment discontinuation as possible.
9	Calculations will be performed on glucose metabolism parameters to assess beta-cell function and insulin resistance: HOMA-B and -IR, pro-insulin/insulin ratio.
10	This assessment only applies for subjects who will be randomised to 1.8 mg/day arm.
11	Diaries should be reviewed and data transcribed into the eCRF at every visit. At the phone visits the subject must confirm verbally the entries made and upon return to the site, the entries must be verified.
12	When initiating the run-in period pre-trial OAD must be terminated
13	For subjects not eligible for randomisation V8 will be an EOT and V9 will be conducted as follow-up visit 7-10 days after V8. For eligible subjects Visit 8 will be a randomisation visit and they will proceed to either 0.9mg or 1.8mg treatment arm and Visit 9 will be a normal phone contact.
14	EOT at week 26 and subsequent FU are only relevant for 0.9 mg/day treatment arm. 1.8 mg treatment arm will attend normal V16 at week 26 and won't need to attend V17 at week 27.
15	All assessments from V18 to V24 are only relevant for 1.8 mg/day treatment arm.

3 Background information and rationale for the trial

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

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

3.1 Background information

3.1.1 Type 2 diabetes

Type 2 diabetes mellitus (T2DM) is a progressive metabolic disease primarily characterised by abnormal glucose metabolism. The pathogenesis is not fully understood but seems to be heterogeneous, involving environmental, lifestyle, and genetic factors leading to chronic hyperglycaemia caused by peripheral tissue insulin resistance, impaired insulin secretion due to abnormal beta-cell function and abnormal glucose metabolism in the liver.[3]

Optimal glycaemic control is the treatment goal in subjects with T2DM, in order to prevent long-term complications associated with chronic hyperglycaemia.[4,5] Despite the availability of several OADs and insulin, a significant proportion of subjects with T2DM do not achieve the recommended blood glucose target levels.[6,7,8,9,10]

In addition to the need for new effective and safe glucose lowering agents, it is important to establish the benefits of the available marketed glucose lowering agents in order to optimise the individual treatment in the best possible way.

3.1.2 Glucagon-like peptide-1

Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted from the L-cells in the small intestine. An incretin hormone is a gut-derived peptide with important physiological function in augmenting post-prandial insulin secretion in response to ingestion of a meal. GLP-1 has a glucose-dependent stimulatory effect on insulin- and inhibitory effect on glucagon secretion from the pancreatic islets (i.e., when plasma glucose levels are above normal).[11,12,13] Both these effects are considered of importance for the glucose lowering effect of GLP-1.[12] Physiologically GLP-1 has a pronounced inhibitory effect on gastric emptying.[14] This effect seems to diminish upon chronic exposure to GLP-1.[15,16] GLP-1 reduces appetite in lean and normal weight individuals, as well as in obese individuals,[17,18,19] and has been shown to reduce body weight in people with T2DM and obese subjects without diabetes.[20] The underlying mechanism mediating the weight-reducing effects of GLP-1 is most likely a combination of reduced appetite/increased satiety with a subsequent reduction in food intake. Patients with diabetes have a decreased incretin effect.[21,22,23,24] However,

the insulinotropic action of GLP-1 and thus the ability to lower blood glucose is preserved in subjects with T2DM when administered at supra-physiological levels.[25]

The mechanism of actions makes GLP-1 an attractive pharmacological tool for treatment of T2DM[26,27,28] and a potential candidate for weight management.[29]

The very short elimination half-life ($t_{½}$) of endogenous GLP-1 ($t_{½}$ < 1.5 minutes after intravenous [i.v.] administration) due to rapid degradation by ubiquitous dipeptidyl peptidase 4 (DPP-4)[30] makes native GLP-1 an unattractive treatment option. Clinical trials have revealed that 24-hour infusion of native GLP-1 would be necessary to achieve satisfactory glycaemic control.[31] Therefore, to benefit from the potentials of GLP-1 in treatment of diabetes it has been necessary to develop GLP-1 receptor agonists with longer half-life.

3.1.3 Liraglutide

Liraglutide is a once-daily human GLP-1 analogue, obtained by derivatising GLP-1 with a fatty acid, providing a compound with kinetic properties suitable for once-daily injection.[32] The mechanism of protraction is believed to be self-association in the pharmaceutical solution, binding to albumin and metabolic stability against DPP-4. This leads to delayed absorption from the s.c. injection site and decreased clearance. *In vitro* studies have shown that liraglutide is a full and potent agonist on the cloned human GLP-1 receptor.[33,34] Animal studies have shown blood glucose lowering, stimulation of insulin secretion, decrease in plasma glucagon levels, inhibition of gastric emptying, inhibition of appetite, decreased body weight and an improved beta cell function.[34]

Liraglutide has been approved under the trade name Victoza® in more than 85 countries for the treatment of adults with T2DM, with a maximum maintenance dose of liraglutide of 1.8 mg/day. In Japan, Victoza® was approved by Ministry of Health, Labour and Welfare (MHLW) in 2010 with the indication as monotherapy and combination therapy with SU in subjects with T2DM. Thereafter, in Aug 2014, the indication of Victoza® has been broadened to treat T2DM without limitations [see Japanese Package Insert (J-PI) current version[35] and its update] based on further trials. The currently approved maximum dose for liraglutide in Japan is 0.9 mg/day.

The safe and efficacious use of liraglutide has been established through the clinical development of liraglutide (the phase 3 global clinical programme) in which more than 4000 subjects were exposed to liraglutide. In Japanese population, four phase 3 trials in Japanese subjects including NN2211-1700 (monotherapy), NN2211-1701 (add-on to SU) and NN2211-3924 (add-on to either glinide, metformin, α–GI or TZD) and NN2211-3925 (add-on to insulin) were conducted. These trials demonstrated the efficacy and safety of liraglutide 0.9 mg/day within these treatment scenarios. In addition, safety data for exposure to liraglutide at doses higher than 0.9 mg/day in Japanese subjects have been obtained from a phase 1 trial (NN2211-1694). In that trial, multiple escalating doses of liraglutide up to the dose levels of 15, 20 and 25 µg/kg were administered to healthy Japanese

subjects. When considering the higher dose levels of 20 and 25 µg/kg (each of which was tested in 6 subjects), the mean absolute doses were 1.25 mg and 1.63 mg, respectively. There were no adverse events (AEs) reported in these subjects, and no adverse effects on laboratory parameters or physical examination were noted.

Liraglutide is generally well tolerated, and the AEs most frequently reported are from the gastrointestinal system (e.g., diarrhoea, nausea and vomiting, constipation, abdominal pain) and central and peripheral nervous system (e.g., dizziness and headache). These events were mostly mild-to-moderate in severity and typically resolved after the first 4–8 weeks.

Cases of acute pancreatitis (including necrotising pancreatitis) presenting with persistent severe abdominal pain have been reported with liraglutide and other incretin based therapy in clinical trials and from marketed use.[34,36,37] In the majority of cases there were confounding factors potentially contributing to the diagnosis of pancreatitis. Continued safety surveillance obtained post-marketing has not altered the favourable risk-benefit ratio of liraglutide in this regard. The risk appears to be relatively small and adequately reflected in the labelling of Victoza®.

In two-year rodent carcinogenicity studies treatment with liraglutide was associated with thyroid C-cell tumours as described below. Based on the extensive exposure to Victoza® in the post-marketing setting there is currently no indication of a causal relationship between treatment with Victoza® and the development of any cancer.

Liraglutide caused dose-dependent and treatment-duration-dependent thyroid C-cell tumours at clinically relevant exposures in both genders of rats and mice. It is unknown whether liraglutide causes thyroid C-cell tumours, including medullary thyroid carcinoma in humans, as human relevance has not been ruled out by clinical and non-clinical studies. Due to the findings in rodents, monitoring of serum calcitonin was performed during clinical trials. It is unknown whether monitoring of serum calcitonin will mitigate human risk of thyroid C-cell tumours.

For further information of liraglutide, please refer to investigator's brochure[34], Victoza® J-PI current version[35] and their update.

For an assessment of benefits and risks of the trial, see section 18.

3.2 Rationale for the trial

The HbA1c lowering effect of liraglutide 0.9 mg/day in Japanese subjects with T2DM is well examined. The four completed phase 3 trials with liraglutide in Japanese subjects have tested 0.9 mg/day liraglutide as monotherapy as well as in combination with OAD treatment or insulin. These trials demonstrated the efficacy and safety of liraglutide 0.9 mg/day within these treatment scenarios. Although a substantial proportion of subjects completing the trials (37% - 65%) met the HbA1c target of <7.0%, the fact that a proportion of subjects did not reach the target indicates that

there are Japanese subjects that may benefit from higher doses of liraglutide. Across trials, the subjects who did not reach the HbA1c target of <7.0% were characterised by mean end-of-trial fasting plasma glucose (FPG) levels above the Japan Diabetes Society target of good glycaemic control (< 130 mg/dL [< 7.2 mmol/L])[38] and above the American Diabetes Association (ADA) target of 80–130 mg/dL (4.4–7.2 mmol/L)[39].

The present trial will evaluate if Japanese subjects with T2DM who are not adequately controlled on liraglutide 0.9 mg/day may benefit from the dose of 1.8 mg/day approved outside of Japan. Treatment compliance generally decreases with increasing complexity of the treatment regimen[40], which supports a dose increase of liraglutide if clinically indicated rather than additional anti-diabetic medication.

4 Objectives and endpoints

4.1 Objectives

4.1.1 Primary objective

To confirm the superiority of liraglutide 1.8 mg/day vs. liraglutide 0.9 mg/day in controlling glycaemia after 26 weeks of treatment in Japanese subjects with type 2 diabetes mellitus inadequately controlled with liraglutide 0.9 mg/day

4.1.2 Secondary objectives

- To compare the overall efficacy and safety parameters of liraglutide 1.8 mg/day and liraglutide 0.9 mg/day after 26 weeks of treatment.

- To evaluate the safety profile of liraglutide 1.8 mg/day over a period of 52 weeks and to monitor glycaemic control and other efficacy parameters over a period of 52 weeks

4.2 Endpoints

4.2.1 Primary endpoint

Change from baseline in HbA1c after 26 weeks of treatment

4.2.2 Secondary endpoints

4.2.2.1 Secondary efficacy endpoints

- Responder for HbA1c after 26 weeks of treatment (Yes/No):
    - HbA1c < 7.0% (53 mmol/mol)*
    - HbA1c ≤ 6.5% (48 mmol/mol)*
    - HbA1c < 7.0% without weight gain
    - HbA1c < 7.0% without treatment emergent severe or blood glucose (BG) confirmed symptomatic hypoglycaemic episodes
- Change from baseline after 26 weeks of treatment in:
    - Self-Measured Blood Glucose (SMBG) 7-point profile
        - 7-point profile (individual points in the profile)

- Mean of 7-point profile
- Mean of postprandial 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.

- Fasting plasma glucose (FPG)
- Waist circumference
- Body weight*
- Body mass index (BMI)
- Blood pressure (systolic and diastolic)

- Fasting C-peptide, fasting insulin, fasting glucagon, proinsulin, proinsulin/insulin, HOMA-B, HOMA-IR after 26 weeks of treatment
- 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 26 weeks of treatment

4.2.2.2 Secondary safety endpoints

- Number of treatment emergent adverse events during 26 weeks of treatment*
- Number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during 26 weeks of treatment
- Number of treatment emergent nocturnal severe or BG confirmed symptomatic hypoglycaemic episodes during 26 weeks of treatment
- Number of treatment emergent hypoglycaemic episodes according to ADA definition during 26 weeks of treatment
- Change from baseline after 26 weeks of treatment:
  - Clinical evaluations:
    - Physical examination
    - Eye examination

- Electrocardiogram (ECG)
- Pulse

- Laboratory assessments:
  - Biochemistry
  - Haematology
  - Calcitonin

The above mentioned primary endpoint, secondary efficacy endpoints and secondary safety endpoints will also be evaluated separately for 52 weeks of treatment.

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

Note; the following secondary safety endpoint for 52 weeks is also selected as key secondary endpoint and mentioned in section 1; number of treatment emergent adverse events during 52 weeks of treatment.

5 Trial design

5.1 Type of trial

This is a 26-week randomised, parallel, two-arm, open-label, multi-centre trial comparing the efficacy and safety of liraglutide 1.8 mg/day to liraglutide 0.9 mg/day in Japanese subjects with T2DM. The liraglutide 1.8 mg/day treatment arm will be continued for a total of 52 weeks after randomisation for monitoring of safety and glycaemic control over 52 weeks.

Subjects on 1 OAD with an HbA1c level of 7.5-10.0%, both inclusive, will be eligible for the trial. At Visit 2 the pre-trial OAD will be discontinued and liraglutide 0.9 mg/day will be initiated for a 12 week run-in period. Subjects with an HbA1c ≥7.0% at the end of run-in period will be randomised to the two treatment arms: continuing liraglutide 0.9 mg/day or dose escalation to liraglutide 1.8 mg/day, see Figure 5–1. Subjects not meeting the randomisation criterion of HbA1c ≥7.0% after run-in will not continue in the trial.

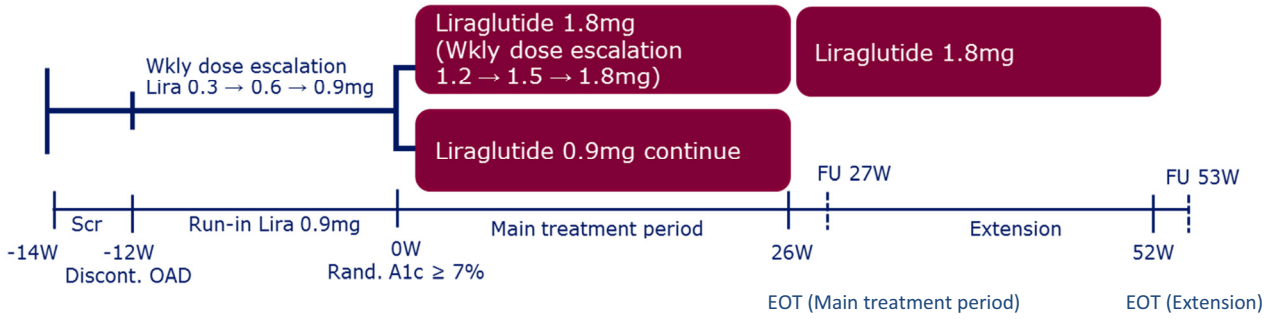


Figure 5–1 Trial design

Subjects will be randomised in a 1:1 manner, using a centralised allocation via an interactive voice/web response system (IV/WRS) to receive liraglutide 0.9 mg/day or dose escalation to liraglutide 1.8 mg/day.

Based on an anticipated screening failure rate and drop-out rate in the run-in period of both 15%, as well as an anticipated proportion of 50% of subjects meeting the randomisation criterion, 1301 subjects will be screened.

The total trial duration for the 1.8 mg/day treatment arm will be approximately 67 weeks, consisting of 2 weeks screening period, a 12 weeks run-in period, a 26-week main treatment period, an extension period of 26 weeks and a follow-up visit. The total trial duration for the 0.9 mg/day treatment arm will be approximately 41 weeks, consisting of 2 weeks screening period, a 12 weeks run-in period, a 26-week treatment period, and a follow-up visit.

5.2 Rationale for trial design

An open-label, randomised trial has been chosen due to the need for dose escalation in the 1.8 mg/day treatment arm after randomisation and unchanged dose in the 0.9 mg/day treatment arm. Blinding the trial by using a double dummy design would mean an unacceptable burden to the subjects and increase the trial design complexity, thereby increasing the risk of subjects withdrawing from the trial or being non-compliant. The double dummy design is therefore not considered acceptable for this trial. The primary endpoint HbA1c is a laboratory parameter and consequently the probability of assessment bias is limited.

Duration of run-in period is considered adequate to obtain a stable effect of liraglutide 0.9 mg/day on HbA1c (randomisation criterion).

Based on the data from the clinical development programme for liraglutide, the duration of 26 weeks of treatment is considered adequate for obtaining meaningful information on efficacy and safety, in accordance with the trial objectives for the comparison between liraglutide 1.8 mg/day and liraglutide 0.9 mg/day.

The total duration of liraglutide 1.8 mg/day treatment (52 weeks) was chosen in order to investigate long-term safety of liraglutide 1.8 mg/day according to local requirement.

5.3 Treatment of subjects

Subjects who enter the trial will discontinue pre-trial OAD and receive monotherapy with liraglutide. Liraglutide should be injected subcutaneously once daily in the thigh, upper arm or abdomen. Dosing can be done in the morning or the evening, but should be approximately at the same time of the day throughout the trial for the individual subject. Trial product will be provided in a prefilled device.

Antidiabetic drugs other than liraglutide are not to be used during the trial.

During the run-in period liraglutide will be initiated with 0.3 mg/day and subsequent 0.3 mg weekly dose escalation to a maximum dose of 0.9 mg/day (see Table 5-1).

Dose reduction to 0.6 mg/day of liraglutide due to AEs (for 7 days or less in total) is allowed at the investigator's discretion during the run-in period.

Table 5-1 Liraglutide dose escalation in run-in period

	1st week	2nd week	3rd week	Remaining run-in period
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)	0.9 mg/day (150 µL=15 clicks)

After the 12 week run-in period subjects who are eligible for randomisation will be randomised to either continuation of liraglutide 0.9 mg/day or further dose escalation to liraglutide 1.8 mg/day.

Subjects who are randomised to the liraglutide 0.9 mg/day treatment arm will continue their treatment unchanged for the 26-week treatment period. In the treatment period no dose reduction of the 0.9 mg/day dose is allowed except temporarily for safety reasons.

Subjects who are randomised to the liraglutide 1.8 mg/day treatment arm will have their dose escalated to 1.2 mg/day after randomisation and enter the dose escalation period of 2 weeks with 0.3 mg weekly dose escalation to a maximum dose of 1.8 mg/day (see Table 5-2). If subjects do not tolerate an increase in dose during dose escalation, this dose escalation period can be extended, but should not extend 1 week (7 days) in total. During dose escalation period, tentative dose reduction will be allowed(1.8 mg/day to 1.5 mg/day or 1.5 mg/day to 1.2 mg/day, dose reduction to lower than 1.2 mg/day is not allowed)except temporarily for safety reasons, as long as the total recommended dose escalation period is within 4 weeks. All subjects in the 1.8 mg/day treatment arm must be at the target dose of 1.8 mg/day 28 days after randomisations at the latest. The Investigator must emphasise to subjects the necessity of reaching the target dose of 1.8 mg.

Table 5-2 Liraglutide dose escalation in 1.8 mg/day treatment arm

	1st week	2nd week	3rd week	Remaining treatment period
Liraglutide	1.2 mg/day (200 µL=20 clicks)	1.5 mg/day (250 µL=25 clicks)	1.8 mg/day (300 µL=30 clicks)	1.8 mg/day (300 µL=30 clicks)

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, however, if possible this should not extend more than 7 days or less in total from end of dose escalation to end of treatment. The Investigator must emphasise to subjects the necessity of maintaining the target dose of 1.8 mg. If subjects do not tolerate the target dose they must be withdrawn from the trial due to safety concern, reporting the AE that led to the withdrawal..

Subjects randomised to the liraglutide 1.8 mg/day treatment arm will after the 26-week main treatment period enter a 26-week extension period and continue treatment with liraglutide 1.8 mg/day until 52 weeks post-randomisation.

5.4 Treatment after discontinuation of trial product

After the end of treatment (after 12 weeks of run-in period [for subjects who are ineligible for randomisation], 26 weeks of trial treatment period [for subjects in 0.9 mg/day treatment arm] or 52 weeks of trial treatment period [for subjects in 1.8 mg/day treatment arm]) or at withdrawal, no trial products will be provided to the subjects.

At the end of treatment with trial product, the subject should be switched to a suitable marketed product at the discretion of the investigator.

5.5 Rationale for treatment

Liraglutide dose of 1.8 mg/day is the approved maximum maintenance dose for treatment of T2DM outside of Japan, and 0.9 mg/day is the currently approved maximum dose in Japan.

The dosage and administration of liraglutide 0.9 mg/day (in run-in period and treatment period in liraglutide 0.9 mg/day treatment arm) is set in accordance with the J-PI for Victoza®.

In liraglutide 1.8 mg/day treatment arm, in order to improve the tolerability of the 1.8 mg dose, a slow, stepwise dose escalation, i.e., 0.3 mg weekly dose escalation and allowance of 1 week extension of dose escalation period, is applied.

For the rationale for treatment duration, see section 5.2.

6 Trial population

6.1 Number of subjects

Number of subjects planned to be screened (i.e. documented informed consent): 1301

Number of subjects planned to be included in the run-in period, starting liraglutide treatment: 1106

Number of subjects planned to be randomised: 470 (235 per arm)

Number of subjects expected to complete the 26 week main treatment period: 423 (withdrawal rate of 10%)

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 ≥20 years of age at the time of informed consent.
3. Type 2 diabetes subjects (diagnosed clinically) ≥ 6 months prior to screening.
4. HbA1c 7.5-10.0 % [58 mmol/mol-86 mmol/mol] (both inclusive).
5. BMI ≥20 kg/m^2.
6. Subjects on stable therapy with one OAD (stable therapy is defined as unchanged medication and unchanged dose) for ≥ 60 days before screening according to approved Japanese labelling.

Rationale for the 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.[41]
- Criteria 3 and 4 are chosen according to the objective of the trial. Being diagnosed for 6 months or more is included in order to ensure correct diagnosis and metabolic stabilisation. HbA1c range (7.5-10.0 %) is chosen to include subjects whose glycaemic control is not adequate on OAD monotherapy and treatment with liraglutide is considered possible. The upper limit of HbA1c is chosen in order to exclude subjects with unacceptable glycaemic control who need a more intensive therapy. The lower limit of HbA1c is chosen as this trial includes a run-in period of treatment with liraglutide 0.9 mg/day to identify subjects who do not obtain adequate glycaemic control (HbA1c < 7.0%) on this dose level.
- Criterion 5 is chosen in order to assure that subjects' 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 since this trial per guideline should be a monotherapy trial and a minimum of treatment at entry is optimal for not risking excess hyperglycaemia. Sixty (60) days of pre-trial OAD treatment are required to ensure that the subject's condition is stabilised.

6.3 Exclusion criteria

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

1. Known or suspected hypersensitivity to trial products or related products.
2. Previous participation in this trial. Participation is defined as signed informed consent.
3. Female who is pregnant, breast-feeding or intend to become pregnant or of child-bearing potential not using adequate contraceptive methods (adequate contraceptive measures as required by local regulation or practice).
4. Receipt of any investigational medicinal product within 30 days prior to screening.
5. Previous treatment with insulin (except for short-term treatment in connection with intercurrent 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 eGFR <60ml/min as per CKD-EPI.
10. Screening calcitonin ≥50 ng/l.

11. History of pancreatitis (acute or chronic).
12. Personal or family history of MTC or MEN 2.
13. Subjects presently classified as being in NYHA Class IV (see Appendix B).
14. Within the past 180 days any of the following: myocardial infarction, stroke or hospitalisation for unstable angina and/or transient ischemic attack.
15. Inadequately treated hypertension, 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 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 run-in.
17. Diagnosis of malignant neoplasms within the last 5 years (except basal and squamous cell skin cancer, polyps and in-situ carcinomas).
18. Any condition which, in the opinion of the investigator might jeopardise subject's safety or compliance with the protocol.

Rationale for the Exclusion Criteria:

- Criteria 1, 8-18 are chosen to ensure the safety of the subjects.
- Criterion 2 is chosen in order to exclude subjects who were 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 because the safety of liraglutide in pregnancy has not yet been established.
- Criteria 4-7 are chosen to minimise factors that may influence the results.

6.4 Randomisation criterion

To be randomised, the randomisation criterion must be answered "yes".

1. HbA1c as assessed at the randomisation visit greater than or equal to 7.0% (based on the laboratory sample performed at Visit 7).

6.5 Withdrawal criteria

The subject may withdraw at will at any time.

The subject may be withdrawn from the trial at the discretion of the investigator due to a safety concern.

Subjects not tolerating the target dose 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 violation of the randomisation criteria
2. Withdrawal of consent to proceed in the trial
3. Pregnancy
4. Intention of becoming pregnant
5. Use of any other antidiabetic medication during the trial
6. Any of the calcitonin samples analysed by the central laboratory are ≥ 50 ng/L (see Appendix A)
7. If the investigator suspects acute pancreatitis, all drugs suspected to relate to this condition should be discontinued until confirmatory tests have been conducted and appropriate treatment should be initiated. Subjects that are diagnosed with acute pancreatitis (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]), must be withdrawn from the trial (see section 8.4.9).
8. Receipt of any investigational medicinal products after screening other than trial product
9. If the fasting 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) during the first 6 weeks after initiation of run-in
   - 13.3 mmol/L (240 mg/dl) from week 7 to week 12 after initiation of run-in
   - 11.1 mmol/l (200 mg/dl) after randomisation

   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 . If there is no intercurrent cause for the hyperglycaemia, and FPG exceeds the limits stated above, the subject must be withdrawn.

Rationale for the Withdrawal Criteria

- Criterion 1 is applied to withdraw the subjects enrolled or randomised in error.
- Criterion 2 is applied since subjects can withdraw at will at any time.
- Criterion 3 and 4 are applied because the safety of liraglutide in pregnancy has not yet been established.
- 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 the ethical and safety viewpoints.

6.6 Subject replacement

Subjects who are withdrawn will not be replaced.

6.7 Rationale for trial population

Japanese subjects with T2DM who are inadequately controlled on OAD monotherapy are eligible for inclusion in the trial.

The trial is designed with a run-in phase to identify subjects inadequately controlled with the currently approved dose level for liraglutide in Japan.

Eligible subjects are presenting with an HbA1c level of 7.5-10.0 %.

The HbA1c range of 7.5-10.0 % is chosen to include a T2DM population on OAD monotherapy, who are not optimally controlled on their current treatment and may benefit from treatment with liraglutide. The lower limit of the HbA1c range is set to 7.5% as this trial includes a run-in period of treatment with liraglutide 0.9 mg/day to identify subjects who do not obtain adequate glycaemic control (HbA1c < 7.0%) on this dose level. Subjects are thus required to have an HbA1c ≥ 7.0% at the end of run-in period (i.e. at randomisation). The efficacy of liraglutide 0.9 mg on glycaemic control was confirmed in the completed clinical trials (NN2211-1700, 1701, 3924 and 3925), and if the inclusion criterion included the HbA1c range 7.0 to 7.5% a significant proportion of subjects would have HbA1c below 7.0% after the run-in period and would not continue in the trial.

The randomisation criterion HbA1c ≥7.0% is chosen to randomise a T2DM population inadequately controlled on liraglutide 0.9 mg/day.

Subjects on OAD monotherapy are chosen since this trial per guideline should be a monotherapy trial and a minimum of treatment at entry is optimal for not risking excess hyperglycaemia.

As weight loss has been observed in global trials with liraglutide 1.8 mg a BMI ≥20 kg/m^2 has been chosen in order to assure that subjects' BMI will not change to the low BMI category.

7 Milestones

Planned duration of recruitment period (FSFV – LSFV): 52 weeks (28-Jul-2015 to 26-Jul-2016)

Planned date for FSFV: 28-Jul-2015

Expected/planned date for LSLV: 07-Nov-2017

The end of the clinical trial is defined as LSLV.

Recruitment must be closed as soon as the planned number of subjects to be randomised is achieved.

The screening and randomisation rate will be followed closely via the interactive voice/web IV/WRS in order to estimate when to stop screening. All investigators will be notified immediately when the recruitment period ends, after which no further subjects may be screened and the IV/WRS will be closed for further screening.

Trial registration:
Information of the trial will be disclosed at clinicaltrials.gov and novonordisk-trials.com and the Clinical Trials Information/JapicCTI site (clinicaltrials.jp). According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure[42], it will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE)[43], the Food and Drug Administration Amendment Act (FDAAA)[44], European Commission Requirements[45,46] 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

Throughout the trial, the investigator should ensure working in accordance with ICH GCP[1] and local regulations. The investigator must ensure that trial procedures are performed as described in the protocol. Any discrepancies will result in protocol deviations and the investigator must take appropriate actions to avoid recurrence of the detected discrepancies.

In addition, the investigator must keep a log of staff and a delegation of task (s) at site. Investigator must sign the log of staff and the delegation of task(s) at site at the time of delegation of tasks.

8.1.1 Informed Consent

Investigators must obtain informed consent for each subject before any trial related procedures. For information on informed consent procedure, please see section 18.1.

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

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

8.1.2 Screening (Visit 1)

For procedures and assessments performed at screening, please see flow chart (section 2).

Screening will take place within 2 weeks prior to run-in visit (Visit 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.
A screening session must be made in the IV/WRS.

To minimise blood sampling from trial subjects, all efforts should be made to ensure that other screening parameters have been evaluated prior to blood sampling.

Subjects will continue on their current diabetes treatment until run-in visit (Visit 2) and they will not be supplied with any trial products until then.

Once all data relating to Visit 1 have been obtained, these must be reviewed by the investigator to ensure that the subject is eligible to continue the trial prior to performing any procedures related to Visit 2.

8.1.2.1 Screening failures

For screening failures the screening failure form in the electronic case report form (eCRF) must be completed with the reason for not continuing in the trial. 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 12.2. Screening failures experiencing an AE that would qualify for adjudication (see section 12.7.2) will not be adjudicated as no trial product has been administered.

A screening failure session must be made in the IV/WRS. When all data has been monitored and all queries have been resolved, the case book must be signed.

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

8.1.3 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.

In case a subject attends a fasting visit in a non-fasting state, all non-fasting assessments should be performed and the subject should be asked to return to the site the day after in a fasting state to have fasting assessments done. If not possible the day after, re-scheduling should preferably be within the visit window for the relevant visit.

8.1.4 Run-in visit (Visit 2)

If the subject is found to be eligible after a review of the assessments and laboratory samples performed at screening (Visit 1), the subject will continue in the 12 week run-in period and receive trial products. No other anti-diabetic treatment is allowed during run-in period, therefore the subject will be instructed to discontinue pre-trial OAD on the day of Visit 2, i.e. last dose should be taken the day before Visit 2.

8.1.4.1 Run-in failures

If the Subject is not eligible to be randomised, i.e. has met one of the withdrawal criteria or not met the randomisation criterion, then the Subject will be considered a run-in failure. For run-in failures,

randomisation visit (Visit 8) will be End of treatment (EOT) and Visit 9 will be follow-up visit and this follow-up visit should be made 7-10 days after Visit 8 in contrast to the randomised subjects.

A run-in failure session must be made in the IV/WRS system and a run-in failure form must be completed in the eCRF together with the reason for not continuing in the trial. Subjects should be requested to return all used, partly used and unused trial product.

Medical events of special interest (MESIs), serious adverse events (SAEs), adverse events (AEs) requiring special forms in the eCRF and non-SAEs from run-in failures must be transcribed by the Investigator into the eCRF. The last date of trial product must be captured. Follow-up of adverse events should be carried out according to section 12.3.

When data has been monitored and queries have been resolved the case book must be signed in the eCRF.

8.1.5 Randomisation

If the subject meets the randomisation criterion after a review of the laboratory sample performed at Visit 7, then the subject will be randomised into one of the 2 treatment groups by using IV/WRS at randomisation visit (Visit 8), see section 10.

The subject will keep the same subject number as allocated at screening.

The subject must attend Visit 8 fasting. For definition of fasting please refer to section 8.1.3.

For randomisation visit procedures, please see flow chart (section 2).

8.1.6 Visit

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

It is the responsibility of the investigator to ensure that all site visits and phone contacts occur according to the flowchart in order to secure consistency in data over time it is encouraged that assessments are performed consistently (e.g. using the same type of equipment and trial site staff with alike qualifications) during the trial.

8.1.7 End of treatment (EOT) visit and follow-up visit

End of treatment at Visit 16 and subsequent follow-up visit (Visit 17) are only relevant for 0.9 mg/day treatment arm. The subjects with 1.8 mg/day treatment arm will attend normal Visit 16 at week 26 and will not attend Visit 17.

For 1.8 mg/day treatment arm, EOT will be Visit 23 and follow-up visit will be Visit 24.

8.1.8 Withdrawal

If a subject is withdrawn from the trial, the investigator must aim to undertake procedures similar to those for end of treatment visit (0.9 mg /day treatment arm: Visit 16, 1.8 mg/day treatment arm: Visit 23) as soon as possible after the last dose of trial product and the follow up visit (0.9 mg /day treatment arm: Visit 17, 1.8 mg/day treatment arm: Visit 24) should be performed 7-10 days after end of treatment visit. The subject should be requested to return all subject diaries and remainder of trial product to the site.

The end of trial form must be completed, and final drug accountability must be performed even if the subject is not able to come to the trial site. A withdrawal session must be made in the IV/WRS. When all data has been monitored and all queries have been resolved, the case book must be signed.

Although a subject is not obliged to give his/her reason(s) for withdrawing 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 or found as a result of a screening procedure which also includes assessments performed between Visit 1 and Visit 2 and at Visit 2. All concomitant illnesses should be reported including information on diabetes and diabetes complications.

Medical history is a medical event that the subject has experienced in the past. Only relevant medical history related to the evaluation of this trial should be reported at the investigator's discretion.

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

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.

8.2.2 Concomitant medication

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

Details of any concomitant medication must be recorded in the eCRF at the first visit.

The information collected for each concomitant medication should include trade name or generic name, indication, start date and stop date or continuation and total daily dose (applicable only for antidiabetic medication).

Any changes in concomitant medication must be recorded at each visit as they occur, including antidiabetic treatment prescribed at the end of the trial. 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.

8.2.3 Demography

Demography will be recorded in the IV/WRS system at screening visit (Visit 1) and consists of:

- Date of birth
- Sex

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

- Race (according to local regulation)

8.2.4 Diagnosis of diabetes

The date of diagnosis of type 2 diabetes should be recorded in the medical history/concomitant illness form at screening visit (Visit 1).

8.2.5 Diabetes complications

Diabetes complications should be recorded in the medical history/concomitant illness form at screening visit (Visit 1).

8.2.6 Diabetes treatment history

The details of pre-trial OAD should be recorded in concomitant medication form at screening visit (Visit 1).

8.2.7 Smoking status

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

8.2.8 New York Heart Association classification

The functional capacity of subjects with heart disease should be assessed according to the NYHA classification (please see Appendix B) and either class I, II, III, IV or 'none' should be captured in the eCRF. The assessment must be in accordance with relevant exclusion criterion.

8.3 Assessments for efficacy

8.3.1 Blood sample

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

Glucose metabolism:

- HbA1c
- Fasting plasma glucose (FPG)
- Fasting insulin
- Fasting C-peptide
- Fasting glucagon
- Proinsulin

HOMA-B and –IR and proinsulin/insulin ratio will be calculated on glucose metabolism parameters to assess beta-cell function and insulin resistance.

Lipids (all fasting):

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

8.3.2 Self-measured blood glucose (SMBG)

At visit 1, subject will receive blood glucose (BG) meter to use for all SMBG measurements during the trial. Subject will receive written directions for use and demonstration on how to use the device including the performance of regular calibrations according to the manufacturer's instructions. As necessary, sites should repeat the directions for use to the subject at subsequent visits. Subjects must be instructed to use the BG meter for all measurements of BG as defined in the protocol.

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 subject should be instructed how to record the results of the SMBG values in the provided diaries as agreed with the investigator. Subject should only record the SMBG values based on measurements obtained with the provided BG meter. The subjects must be instructed to contact the investigator in case of low or high SMBGs.

For all SMBG values that meet the definition of a hypoglycaemic episode (see section 8.4.6), relevant information must be registered in the subject diary and a hypoglycaemic episode form must be completed in the eCRF.

7 point self-measured blood glucose profile

The subject will be instructed to perform a 7-point SMBG profile 5 times during the trial preferably within the week prior to site visit according to the flowchart (section 2) , on days where the subject does not anticipate unusual strenuous exercise.

The plasma glucose levels should be measured and recorded in the diary (including date, actual clock time,value) at the following time points always starting with the first.

- Before breakfast
- 90 min after start of breakfast
- Before lunch
- 90 minutes after start of lunch
- Before dinner
- 90 min after start of dinner
- At bedtime

8.3.3 Body measurement

8.3.3.1 Height

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

8.3.3.2 Body weight

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

Preferably the same set of scales should be used throughout the trial.

8.3.3.3 BMI

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])

8.3.3.4 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 should be performed and recorded in the eCRF. The waist circumferences will be measured in cm using a non-stretchable measuring tape (measuring tapes will be provided to the sites by Novo Nordisk). It should be recorded to the nearest ½ cm 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.

8.3.4 Blood pressure

Blood pressure (Systolic and diastolic blood pressure) will be measured at the visits specified in the flowchart (section 2).

Blood pressure must be measured after the subject has been resting for at least 5 minutes and by using the standard clinical practice at the site.

For blood pressure measurements at the screening visit (Visit 1), three measurements must be performed and all three values must be entered into the eCRF. The mean value will be calculated by the eCRF and must be in accordance with the relevant exclusion criterion.

It is recommended to use the same arm and the same device and cuff as used at the first visit for the subsequent measurements. For the subsequent visits, only one measurement needs to be performed.

If the investigator suspects white-coat hypertension at the screening visit (Visit 1), one re-assessment of the systolic and diastolic blood pressure (as described above) is allowed and the mean of the three new measurements will be conclusive. These repeated measurements must be performed prior to any other study activities at the run-in visit to confirm eligibility.

8.4 Assessments for safety

8.4.1 Adverse events (AEs)

All AEs must be collected and reported according the procedure described in section 12.

8.4.1.1 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
- Neoplasm
- Thyroid disease

In case any of these events fulfil the criteria for a SAE, please report accordingly. See section 12.1.

Certain events occurring in subjects eligible for the trial will be evaluated by an external and independent Clinical Safety Event Adjudication Committee in accordance with section 12.7.2.

Cardiovascular events

Cardiovascular events that are suspected as being related to:

- **Acute coronary syndrome**

All types of myocardial infarction (MI) or hospitalisation for unstable angina, for further information see Appendix C. If an event of acute coronary syndrome (ranging from unstable angina pectoris to MI) 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
- 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 gall-stones
    - History of pancreatitis
    - Family history of pancreatitis
    - Trauma

Thyroid disease

Subjects scheduled for thyroidectomy (partial or total) for any reason during the trial, must be instructed to inform the investigator prior to their operation. If an event of thyroid disease, including any thyroid neoplasms is observed during the trial, this must be recorded as an AE and on a specific thyroid disease event form in the eCRF. The following information must be reported if available:

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

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

8.4.2 Blood samples

Blood samples must be drawn according to flow chart (section 2) and will be analysed at the central 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

- Calcitonin (please refer to the Appendix A for actions to be taken if calcitonin is ≥ 10 ng/L)

8.4.3 Electrocardiogram (ECG) – 12 lead

A 12-lead ECG must be performed and interpreted locally by the Investigator and 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)

A 12-lead ECG should be obtained at screening visit (Visit 1) or between Visit 1 and run-in visit (Visit 2). The result must be available prior to performing any procedures related to Visit 2.

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

8.4.4 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 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)

Any abnormalities found as a result of a screening procedure which also includes assessments performed between Visit 1 and Visit 2 should be recorded as a concomitant illness. Any new abnormal, clinically significant finding during the trial and any clinically significant worsening from Fundoscopy/fundus photography performed at baseline (up to Visit 2) must be reported as an AE (see section 12).

Fundoscopy/fundus photography performed within 90 days prior to run-in visit is acceptable. If a funduscopy/fundusphotography 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.

8.4.5 Physical Examination

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

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

- Lymph node palpation

The interpretation must follow the categories:

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

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

8.4.6 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 in the subject diary. These must be transcribed into the eCRF (hypoglycaemic episode form) throughout the trial from visit 1 to Visit 9 (for subjects who are not randomised)/Visit 17 (for 0.9 mg/day treatment arm)/Visit 24 (for 1.8 mg/day treatment arm) as according to the flowchart (section 2).

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:
  - Who assisted in the treatment of the hypoglycaemic episode (ie family/friend/co-worker or similar, paramedic, doctor or other, please specify)
  - Where the treatment was administered (ie 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 (ie oral carbohydrates, glucagon, IV glucose or other, please specify)

  - Were symptoms alleviated by the administration of treatment?
  - Factors contributing to the episode (ie physical activity, missed meal, diet changed, medication error (ie overdose, mix-up between products), 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?[47]
    - Autonomic: sweating, trembling, hunger or palpitations
    - Neuroglycopenic: confusion, drowsiness, speech difficulty, visual disturbances, odd behaviour, impaired balance or incoordination
    - General malaise: headache or malaise
  - Did the subject experience other symptoms? Please specify
  - Further description of the episode
- Type, date and time of last trial product and other antidiabetic drug administration prior to episode
- Date and time of last main meal prior to episode
- Whether the episode occurred in relation to physical activity

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

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

For all FPG values measured by central laboratory that meet the definition of a hypoglycaemic episode, a hypoglycaemic episode must be recorded in a hypoglycaemic episodes form.

8.4.7 Pulse

Pulse (beats per minute) should be recorded in the eCRF at site visits after resting for 5 minutes in a sitting position.

8.4.8 Pregnancy test

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

Urine pregnancy tests will be performed at site during the trial for females of childbearing potential if a menstrual period is missed (unless this is a part of the mode of action of the contraceptive method) or if pregnancy is suspected.

If at the 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, who have been without menses for at least 1 year. This must be documented in the subject's medical record and eCRF.

8.4.9 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. If acute pancreatitis is ruled out trial product should be re-initiated. If the discontinuation period is for three days and more, the trial product should be restarted with a dose of 0.3 mg/day, and dose escalation procedure described in section 5.3 should be followed.

Appropriate treatment and careful monitoring of the subject should be initiated if pancreatitis is confirmed (as a minimum 2 of 3):

- severe acute abdominal pain
- amylase and/or lipase >3x upper normal range (UNR)
- characteristic findings on relevant imaging (e.g. CT/MRI/ultrasound)

The event must be recorded as an AE and on a specific Pancreatitis event form in the eCRF and will undergo assessment by the Event adjudication committee (EAC) (see section 12.7.2).

8.5 Laboratory assessments

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

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 will be made available by the central laboratory. Laboratory reports must be reviewed, dated and signed by the Investigator on the day of evaluation. It must be specified whether out of range results are clinically significant.

If any clinically significant abnormalities will be found as a result of screening procedures which also includes assessments performed between Visit 1 and Visit 2 and at Visit 2 then these must be recorded on the concomitant illness/medical history form in the eCRF. Any clinically significant deterioration of a pre-existing condition as well as any new clinically significant signs or symptoms should be reported as an AE in accordance with section 12.

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.

8.6 Other assessments

8.6.1 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 should instruct subjects to record the following in the diary:

- Date and value of all SMBG and also actual clock time of the 7-point SMBG measurements
- Date, dose and injection site for first dose of trial product
- Dose of trial product one day prior to visit/phone contact during dose escalation
- Date for last dose of trial product
- Hypoglycaemic episodes
- Medical problems
- Changes in concomitant medication

The Investigator and/or delegate or site staff is 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

It is the responsibility of the investigator to review the diary for possible AEs (see section 12), hypoglycaemic episodes (see section 8.4.6) and concomitant medication (see sections 8.2.2).

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.

8.7 Subject compliance

Throughout the trial, the investigator will remind the subjects to follow the trial procedures and requirements to ensure subject compliance. To ensure subject compliance, the investigator will at each visit assess the subject's compliance by evaluating the glycaemic control, adherence to the visit schedule, drug accountability and completion of the subject's diary. If a subject is found to be non-compliant, the investigator will remind the subject of the importance of following the instructions given including taking the trial products as prescribed and the 7-points SMBG profiles.

Treatment compliance will be assessed by monitoring of drug accountability. Prior to visits where drug accountability is performed the subject will be asked to return all used, partly used and unused investigational medicinal products (IMPs). The investigator must assess the amount of IMPs returned compared to what was dispensed at the last dispensing visit and, in case of discrepancies, question the subject.

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

Liraglutide must not be used, if it does not appear clear and colourless or almost colourless.

9.1 Trial products

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

Trial product	Strength	Dosage form	Route of administration	Delivery device
Liraglutide 6.0mg/mL (Investigational medicinal products: [IMPs])	6.0 mg/mL	Solution for injection	Subcutaneous injection (s.c.)	3 mL FlexPen®

9.2 Labelling

The trial products will be labelled in accordance with Annex 13[49], local regulations and trial requirements. Please refer to the TMM provided by Novo Nordisk for details regarding standard packages and handling of trial product.

Each trial site will be supplied with sufficient trial products for the trial on an on-going basis controlled by the IV/WRS. 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 each dispensing visit.

9.3 Storage

Liraglutide (both not in-use and in-use) must not be exposed to excessive heat or direct light.

Srorage condition for Liraglutide:

Trial product	Storage conditions (not-in-use)	In-use conditions	In-use time*
Liraglutide 6.0mg/mL	• Store in a refrigerator between 2°C to 8°C • Protect from light • Do not freeze	• Store at room temperatures not above 30°C • Protect from light • Do not freeze	• Use within 30 days

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

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. A temperature log must be kept to document storage within the right temperature interval and storage facilities should be checked frequently.

The investigator, the head of the study site or the trial product storage manager (if assigned by the head of the study site) must inform Novo Nordisk **immediately** if any trial product has been stored outside specified conditions (e.g. outside temperature range) and register the product as out of temperature in the IV/WRS.

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 and/or the head of the study site or the trial product storage manager if assigned by the head of the study site.

The trial product will be dispensed to each subject as required according to treatment group. The IV/WRS will allocate trial product DUN to the subject at each dispensing visit. The correct DUN must be dispensed to the subject.

The investigator, the head of the study site or the trial product storage manager (if assigned by the head of the study site) will perform drug accountability using the IV/WRS drug accountability module. Only dispensed DUNs returned by the subject (used/partly used or unused) are accounted for.

Subjects are instructed to return all used, partly used and unused trial product including empty packaging material at each dispensing visit and at the end of treatment 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.

Destruction of trial products will be done according to local law after accountability is finalised at site and reconciled by monitor. Destruction of trial products must be documented.

9.5 Auxiliary supplies

The DFU will be supplied by Novo Nordisk A/S, Denmark and the following auxiliary supplies will be supplied by Novo Nordisk Pharma Ltd. in accordance with the TMM. The trial sites are allowed to purchase and supply themselves with auxiliary supplies, if possible.

- Needles for the device
- Blood glucose meters (BG meters) and BG meter auxiliaries
- Glucose for treating a hypoglycaemia
- Urine pregnancy test kit

10 Interactive voice/web response system

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

IV/WRS is used for:

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

It is important that at all times during the trial only DUNs allocated by the IV/WRS are dispensed to the Subject.

If a Subject requires additional trial product between dispensing visits, the site must perform an additional dispensing session in IV/WRS.

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

11 Randomisation procedure

The trial is an open-labelled trial. A randomisation will be conducted at the randomisation visit (Visit 8). The subjects meeting randomisation criterion will be randomised at the ratio of 1:1 to liraglutide 0.9 mg/day or dose escalation to liraglutide 1.8 mg/day.

Randomisation will be performed using the IV/WRS system (section 10).

12 Adverse events, and technical complaints and pregnancies

12.1 Definitions

Adverse event

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

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

An AE includes:

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

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

- Pre-existing conditions, including those found as a result of screening procedures which also includes assessments performed between Visit 1 and Visit 2 and at Visit 2 (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 8.4.6.

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 an SAE.

Medical event of special interest

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

- Medication errors concerning trial products:
  - Administration of wrong drug
    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, however the administered dose must deviate from the intended dose to an extend where clinical consequences for the trial subject were likely to happen as judged by the investigator, although not necessarily did happen.

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 disorders

For detailed information on AEs with additional data collection, see section 8.4.1.1.

Along with fatal events, certain events of interest will be adjudicated by an external independent 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 (Run-in failure: Visit 9, 0.9 mg/day treatment arm: Visit 17, 1.8 mg/day treatment arm: Visit 24). The events must be recorded in the applicable CRF forms in a timely manner, see timelines below and Figure 12–1.

During each contact with the trial site staff, the subject must be asked about AEs, 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:

- Company Core Data Sheet for Victoza® 6.0 mg/mL, Current version and any updates hereof

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

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

For 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 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. Both forms must be signed within 7 calendar days from the date the information was entered in the eCRF. 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.
- **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.

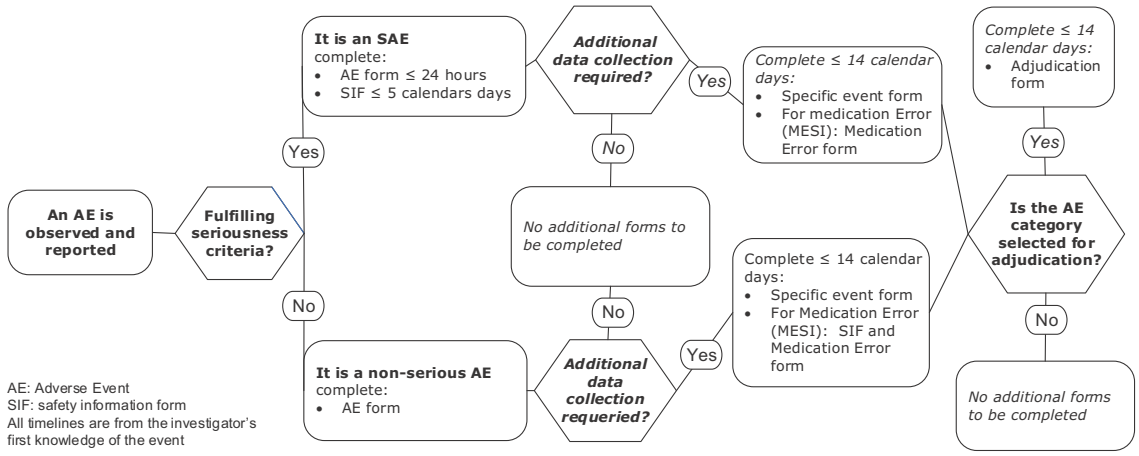


Figure 12–1 Initial reporting of AEs

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

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

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

12.4 Technical complaints and technical complaint samples

12.4.1 Reporting of technical complaints

All technical complaints on any of the following products:

- Liraglutide prefilled pen
- Needles for prefilled pen

which occur from the time of first usage of the product until the time of the last usage of the product, must be collected and reported to Customer Complaint Center, Novo Nordisk.
Contact details (fax, e-mail and address) are provided in Attachment I to the protocol.
The investigator must assess whether the technical complaint is related to any AEs, SAEs, and/or MESI.

Technical complaints must be reported on a separate technical complaint form. A technical complaint form for each batch, code or lot number or for each DUN must be completed.
The investigator must complete the technical complaint form in the eCRF within the following timelines of the trial site obtaining knowledge of the technical complaint:

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

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

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

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

12.5 Pregnancies

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

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

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

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

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

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

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

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

   <u>Forms and timelines for reporting AEs:</u>
   Non-serious AEs:
   - Paper AE form* **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

When initiating treatment with liraglutide, the subject may, in some cases, experience loss of fluids/dehydration, e.g., in cases of vomiting, nausea or diarrhoea sometimes with a decrease in kidney function. It is important to avoid dehydration by drinking enough fluids.

From clinical trials and marketed use overdoses of liraglutide have been reported up to 40 times the recommended maintenance dose (72 mg). Events reported included severe nausea and severe vomiting. None of the reports included severe hypoglycaemia. All patients recovered without complications. In the event of overdosage, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

12.7 Committees related to safety

12.7.1 Novo Nordisk safety committee

Novo Nordisk will constitute an internal liraglutide safety committee to perform ongoing safety surveillance. The liraglutide safety committee may recommend unblinding of any data for further analysis, and in this case an independent ad hoc group will be established in order to maintain the blinding of the trial personnel.

12.7.2 Event adjudication committee (EAC)

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 an independent and a blinded manner.

The EAC is composed of permanent members covering required medical specialities. EAC members must disclose 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 EAC will have no authorisations to impact on trial conduct, trial protocol or amendments.

The EAC works in accordance with written guidelines included in the EAC Charter describing in details the composition, tasks, responsibilities, and work processes of the committee.

The events will be adjudicated according to FDA requirements[50].

The EAC will review copies in English (translated if necessary) of medical documentation received in the adjudication packages (for example X-ray, ECGs, ultrasound images, discharge summaries, pathology reports, and death certificates). The investigator should provide medical documentation within 4 weeks of event identification.

The supplier or EAC can evaluate an event not initially reported as a MESI for adjudication to be adjudicated. In this case the investigator must provide medical documentation as soon as possible, when receiving a request from Novo Nordisk or the Event Adjudication vendor.

The assessments made by the EAC will be included in the CTR as well as assessments made by the investigator. However, the adjudication made by an EAC, given its independence and in-depth analysis of each event, will be attributed with greater importance of the two. The outcomes of adjudication will be kept in the clinical trial database.

The following AEs will be adjudicated in this trial (Please also see Appendix C):

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

Event adjudication will be performed for AEs in subjects eligible for the trial including AEs with an onset date during the screening or run-in period. Event adjudication will not be performed for AEs in screening failures.

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

13 Case report forms

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

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

The following will be provided as paper CRFs:

- Pregnancy forms

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

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

13.1 Corrections to case report forms

Corrections to the 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.

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.

At the end of the trial the investigator must 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. When the final CTR is available the data will be archived by Novo Nordisk.

13.3 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.

The investigator must ensure that data are recorded in these forms as soon as possible and ensure that Novo Nordisk receives these forms within the required timeline (see section 12).

Print legibly, using a ballpoint pen. Ensure that all questions are answered, and that no empty data blocks exist. Ensure that no information is recorded outside the data blocks. Further guidance can be obtained from the instructions in the CRF.

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

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 CRFs, the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP[1], 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 eCRF (BMI is not source data verified as it is calculated in EDC).

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, dose of trial product one day prior to visit/phone contact during dose escalation, date, dose and injection site for first dose of trial product, date for last dose of trial product and hypoglycaemic episodes.

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

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

The monitor will ensure that the CRFs are completed 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. Data management may be delegated under an agreement of transfer of responsibilities to another data management unit within Novo Nordisk or an external Contract Research Organisation (CRO).

Appropriate measures, including encryption of data files containing person identifiable data, will be used to ensure confidentiality of subject data, when they are transmitted over open networks.

Data from central laboratories will be transferred electronically from the laboratory performing the analyses. In cases where data is transferred via non-secure electronic networks, data will be encrypted during transfer.

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

16 Computerised systems

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

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

17 Statistical considerations

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

All analyses of efficacy and safety endpoints will be based on the full analysis set (FAS). All efficacy endpoints will be summarised using the FAS and safety endpoints will be summarised using the safety analysis set (SAS).

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

Unless otherwise specified, all continuous measurements will be summarised descriptively at each visit by treatment using all observed data. 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.

An analysis of covariance (ANCOVA) model will be applied for the primary endpoint and continuous secondary endpoints after 26 weeks of treatment. The model includes treatment as fixed effect 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 10%. In accordance with industry guidance[51] endpoints will be assessed at frequent visits and also on subjects who withdraw prematurely. This will facilitate an analysis in accordance with ITT principles. Also, the combined information on frequent outcomes and information on reason for drop-out is assumed to account for the missing data anticipated.

If not otherwise specified, the value from the randomisation visit (Visit 8) will be used as the baseline value. If the value measured at the randomisation visit is missing and the assessment has

also been made at an earlier visit, then the non-missing value obtained at the preceding visit closest to Visit 8 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. In this trial, sensitivity analyses will be made to examine the robustness of the LOCF method.

17.1 Sample size calculation

The primary objective of this trial is to confirm superiority of liraglutide 1.8 mg/day vs. liraglutide 0.9 mg/day in controlling glycaemia after 26 weeks of treatment in Japanese subjects with T2DM inadequately controlled with liraglutide 0.9 mg/day.

Superiority in the primary endpoint for liraglutide 1.8 mg/day vs. liraglutide 0.9 mg/day will be considered confirmed if the upper bound of the two-sided 95% confidence interval for the estimated mean treatment difference in change from baseline in HbA1c is strictly below 0.0% or equivalently if the p-value for the two-sided test of

H_0 D=0 against H_A D≠0,

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

Based on experience from the NN2211-1842, NN2211-1700, NN2211-1701, NN2211-3924 and NN2211-3925 studies the following assumptions are made.

- 15% screening failure rate
- 15% drop-out rate in the run in period
- 50% chance that a subject at the end of the run-in will be randomised (i.e. HbA1c ≥7.0% at randomisation)

The sample size is determined using a t-statistic under the assumption of a two-sided test of size 5% and a standard deviation of SD=1.0%. From the above assumptions and based on a 1:1 randomisation, a sample size of 235 subjects in each treatment arm; in total 470 subjects was chosen to obtain sufficient exposure to liraglutide 1.8 mg in the Japanese diabetes population as well as having a reasonable estimation of efficacy. With this sample size it would be possible to detect a 0.3% treatment difference with a power of at least 90%. In order to reach the required sample size 1,301 subjects should be screened and 1,106 subjects should enter the run-in period.

Considering 0% efficacy retention as the most conservative approach for the anticipated 10% of subjects discontinuing randomised treatment reduces the expected treatment difference to -0.27%, a total of 235 subjects per treatment arm will then yield a power of at least 83% (see Table 17-1).

Table 17-1 Powers for various combinations of SD and mean difference

	Mean difference (%) adjusted for subjects discontinuing randomised treatment (efficacy retention in % for subjects discontinuing randomised treatment)			
SD (%)	-0.27 (0%)	-0.276 (20%)	-0.285 (50%)	-0.30 (100%)
0.9	90.1	91.3	92.9	95.0
1.0	83.2	84.7	86.9	90.1
1.1	75.7	77.5	80.0	83.9

17.2 Definition of analysis sets

The following analysis sets are defined in accordance with the ICH-E9 guidance.[52]

- **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"

- **Safety Analysis Set (SAS):** includes all subjects receiving at least one dose of randomised treatment. Subjects in the safety analysis set will contribute to the evaluation "as treated"

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

Before data are released for statistical analysis, a review of all data will take place to identify protocol deviations that could potentially affect the results. Any decision to exclude any subject or observation from the statistical analysis is the joint responsibility of the members of the study group. The subjects or observations to be excluded, and the 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 the change from baseline in HbA1c after 26 weeks of treatment.

The change from baseline in HbA1c after 26 weeks of treatment will be analysed using an analysis of covariance (ANCOVA) model with treatment as a fixed effect and baseline HbA1c as a covariate.

Missing values after 26 weeks of treatment will be imputed applying last observation carried forward (LOCF) using HbA1c values at and after baseline.

Superiority of liraglutide 1.8 mg/day vs. liraglutide 0.9 mg/day will be considered as confirmed if the 95% confidence interval for the treatment difference (liraglutide 1.8 mg/day minus liraglutide 0.9 mg/day) for change from baseline in HbA1c 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.

Additionally, change from baseline in HbA1c after 52 weeks of treatment will be presented descriptively for the liraglutide 1.8 mg/day treatment arm.

Sensitivity analysis

Sensitivity analysis will be performed on FAS using the mixed model for repeated measurements (MMRM) method. All HbA1c values available post baseline at scheduled measurement times will be analysed in a linear mixed normal model using an unstructured residual covariance matrix for HbA1c measurements within the same subject. The model will include treatment and visit as fixed factors and baseline HbA1c as a covariate. Interactions between visit and treatment and between visit and baseline HbA1c will also be included in the model. The results of sensitivity analyses will be compared to the result of the standard ANCOVA method using LOCF for imputation of missing data.

17.4 Secondary endpoints

17.4.1 Secondary endpoints

17.4.1.1 Efficacy endpoints

Endpoints evaluated after 26 weeks of treatment

Responder for HbA1c

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

- HbA1c target < 7.0%[53]
- HbA1c target ≤ 6.5%[53, 54]

Analysis of each of the two responder endpoints will be based on a logistic regression model with treatment as factor and baseline HbA1c value as a covariate.

HbA1c responder endpoints without weight gain

Responder for HbA1c without weight gain after 26 weeks of treatment will be defined as HbA1c < 7.0% after 26 weeks of treatment and change from baseline in body weight after 26 weeks of treatment below or equal to zero. Analysis will be based on a logistic regression model with treatment as factor and baseline HbA1c and baseline body weight values as covariates.

HbA1c responder endpoints without treatment emergent severe or blood glucose (BG) confirmed symptomatic hypoglycaemic episodes

Responder for HbA1c without hypoglycaemic episodes after 26 weeks of treatment will be defined as HbA1c < 7.0% after 26 weeks of treatment and without severe or BG confirmed symptomatic episodes during 26 weeks of treatment. Analysis will be based on a logistic regression model with treatment as factor and baseline HbA1c values as a covariate.

Fasting plasma glucose (FPG)

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

Waist circumference

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

Body weight

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

Body Mass Index (BMI)

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

Self measured blood glucose (SMBG) 7-point profile

Three endpoints from the 7 point SMBG profile will be defined:

- 7-point profile (individual points in the profile)

- Mean of the 7-point profile, defined as the area under the profile (calculated using the trapezoidal method) divided by the measurement time
- Mean of postprandial 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 7-point SMBG profile data. The model will include treatment, time and interaction between treatment and time as fixed factors and subject as random effect . From the model mean profile by treatment and relevant treatment differences will be estimated and explored.

Change from baseline after 26 weeks of treatment in mean of the 7-point profile and post-prandial increment endpoints will be analysed separately using the standard ANCOVA model.

Blood pressure (systolic and diastolic)

Systolic and diastolic blood pressure will be summarized descriptively.

Fasting C-peptide, fasting insulin, fasting glucagon, proinsulin, proinsulin/insulin, HOMA-B, HOMA-IR

In addition to fasting C-peptide, fasting insulin, fasting glucagon, and proinsulin, three derived parameters will be calculated; proinsulin/insulin ratio, beta-cell function (HOMA-B) and insulin resistance (HOMA-IR).

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

- Beta-cell function (%) = 20·fasting insulin[µU/mL]/(FPG[mmol/L]-3.5)
- Insulin resistance (%) = fasting insulin [µU/ml]·FPG [mmol/l]/ 22.5

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

Fasting lipid profile

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

Endpoints evaluated after 52 weeks of treatment

All above listed efficacy endpoints will be summarised descriptively for the liraglutide 1.8 mg/day arm after 52 weeks of treatment.

17.4.1.2 Safety endpoints

Adverse events

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

A treatment emergent adverse event (TEAE) is defined as an event that has onset date on or after the first day of IMP administration and no later than seven days after the last day on IMP. If the event has onset date before the first day of IMP administration 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.

AEs will be summarised descriptively for each of the following periods separately:

- The run-in period: AEs with an onset date on or after Visit 2 and before the first day of exposure to randomised treatment will be reported as part of the run-in period.
- The 26 week treatment period: TEAEs with an onset date on or after the first day of exposure to randomised treatment and no later than seven days after Visit 16 (EOT26) will be reported as during 26 weeks of treatment.
- The 52 week treatment period: For the liraglutide 1.8 mg/day arm all TEAEs will be reported as during 52 weeks of treatment.

For each of the above periods, AE 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 AEs and of serious AEs 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 for each period.

Furthermore separate summary tables for each period will be presented based on system organ class and preferred terms for:

- All AEs
- Serious AEs

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

A listing for non-treatment emergent adverse events with onset date before Visit 2 will be presented. A listing will also be presented for non-treatment emergent adverse events collected after the treatment emergent period according to the definition of TEAE.

Classification of Hypoglycaemia:

Treatment emergent: hypoglycaemic episodes will be defined as treatment emergent if the onset of the episode occurs on or after the first day of IMP administration, and no later than 7 days after the last day on IMP. Here the first day of IMP administration is defined as the first day of exposure to randomised treatment.

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

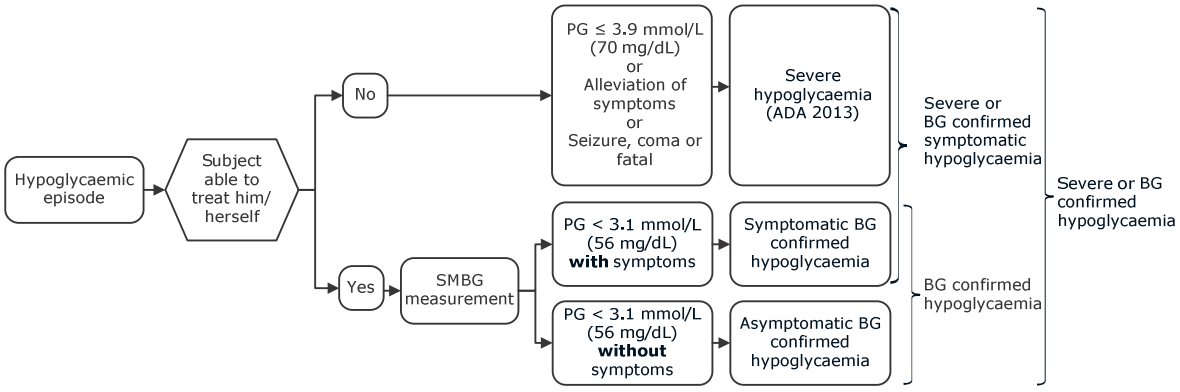
Hypoglycaemic episodes are classified according to the Novo Nordisk classification of hypoglycaemia (see Figure 17–1) and the ADA classification of hypoglycaemia (see Figure 17–2).

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)[55]. 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[48] or BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) **with** symptoms consistent with hypoglycaemia.



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

Figure 17–1 Novo Nordisk classification of hypoglycaemia

ADA classification[48] 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).

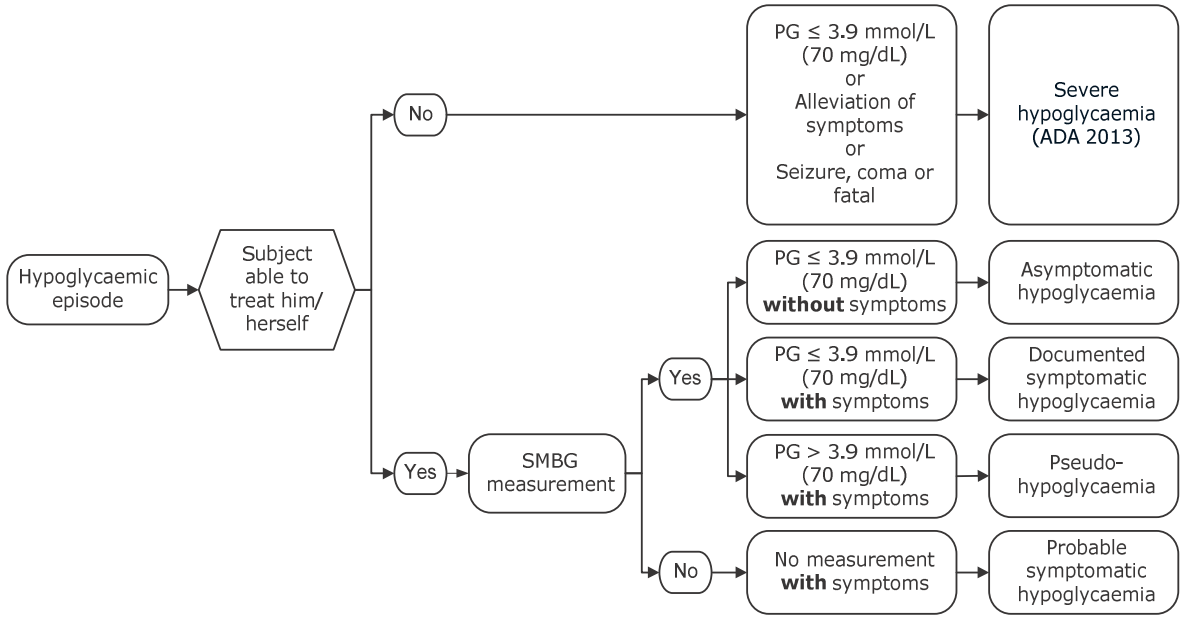


Figure 17–2 ADA classification of hypoglycaemia

Hypoglycaemic episodes will be summarised descriptively for each of the following periods separately:

- The run-in period: hypoglycaemic episodes where the onset date of the episode occurs on or after Visit 2 and before the first day of exposure to randomised treatment will be reported as part of the run-in period.
- The 26 week treatment period: treatment emergent hypoglycaemic episodes where the onset date of the episode occurs on or after the first day of exposure to randomised treatment and no later than seven days after Visit 16 (EOT26) will be reported as during 26 weeks of treatment.
- The 52 week treatment period: For the liraglutide 1.8 mg/day arm all treatment emergent hypoglycaemic episodes will be reported as during 52 weeks of treatment.

For each of the periods listed above, data on hypoglycaemic episodes are presented above 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 symptomatic hypoglycaemic episodes, nocturnal severe or BG confirmed symptomatic hypoglycaemic episodes and the ADA classification of hypoglycaemia.

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

Pulse

Pulse will be summarized descriptively.

Clinical evaluations (physical examination, eye examination and ECG)

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

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

Laboratory assessments

All laboratory parameters will be summarised descriptively.

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

- Shift tables from baseline to after 26 weeks of treatment and 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.

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

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

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 gender.

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).

18 Ethics

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. Liraglutide will be initiated liraglutide 0.9 mg/day treatment during the run-in period. Randomisation criterion has been defined in order to identify subjects inadequately controlled on liraglutide 0.9 mg/day. Furthermore withdrawal criteria have been defined to ensure that subjects are considered for discontinuation if the subjects have unacceptable glycaemic control during trial participation.

Subjects will be treated within a regimen anticipated to be better than or equal to the treatment they receive at the time of entry into the trial. Subject will need to spend more time, as additional visits to the clinic are required and some of assessments performed during the trial are done outside normal practice.

Liraglutide have shown to be effective in lowering blood glucose levels. It can therefore be expected that the subjects entering the trial with insufficiently controlled blood glucose will experience an improved glucose control during the trial. Subjects may benefit from the effect of treatment on weight, previously demonstrated for liraglutide. Another 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.

The trial drugs 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. Furthermore, subjects are fully informed about possible AEs and inconveniences and will be instructed to contact the investigator in case of any concerns regarding the trial participation.

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

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

18.1 Informed consent

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

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

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

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

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

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

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

18.2 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

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-investigator(s) (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 and dated by the investigator and/or head 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 task(s).

23 Reports and publications

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

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

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

One investigator will be appointed by Novo Nordisk to review and sign the clinical trial report (signatory investigator) on behalf of all participating investigators. The signatory investigator will be appointed based upon the criteria defined by the International Committee of Medical Journal Editors for research publications[56].

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[42].

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

At the end of the trial, one or more publications (abstracts, posters, manuscripts) 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.

24 Retention of clinical trial documentation

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

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

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

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

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

25 Institutional Review Boards and regulatory authorities

IRB:

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.

27 References

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Appendix A

Monitoring of Calcitonin

Trial ID: 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 type 2 diabetes mellitus

Trial Phase: 3b

1 Background

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

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

There are several known confounding factors affecting calcitonin levels, namely renal dysfunction, smoking, autoimmune thyroiditis and 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 and C-cell abnormalities - evaluation and follow-up

Subjects with a personal or family history of medullar thyroid cancer (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN 2) or with a screening calcitonin ≥ 50 ng/L will be excluded from the trial.

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

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

2.1 Calcitonin ≥ 100 ng/L

The subject (even if a screen failure) should immediately be referred to a thyroid specialist for further evaluation and the trial treatment should be discontinued.

The subject can remain in the trial, however, all drugs suspected to relate to this condition should be discontinued until appropriate treatment has been initiated. If it is a screening value the subject cannot be entered into run-in period.

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

2.2 Calcitonin ≥ 50 and < 100 ng/L

The subject (even if a screen failure) should be referred to a thyroid specialist for further evaluation and the trial treatment should be discontinued.

The subject can remain in the trial however, all drugs suspected to relate to this condition should be discontinued until appropriate treatment has been initiated. If it is a screening value the subject cannot be entered into run-in period.

These values were found in 0.14% of the population with thyroid nodular disease published by Costante et al. Diagnostic evaluation will likely include ultrasound examination and if available and if there is no contraindication, subjects should undergo a pentagastrin stimulation test. Subjects with

positive pentagastrin stimulation tests will be considered to undergo surgery. In the US and other countries where pentagastrin is not available, thyroid ultrasound and fine needle aspiration biopsy may add important clinical information informing the need for surgery.

2.3 Calcitonin ≥ 20 and <50 ng/L

The subject can continue in the trial. Repeat testing of calcitonin at next protocol scheduled calcitonin visit. If the subject is a screen failure or if the value is the last one taken in the trial, the subject should be referred to a thyroid specialist for further evaluation.

These values are expected to be found in up to 1% of subjects. Based on data from Costante et al[1], the predictive value of calcitonin levels ≥ 20 and < 50 ng/L for clinically significant C-cell disease begins to fall. However, up to 25% of these subjects had a positive pentagastrin stimulation test. The likelihood of having a medullary carcinoma >1 cm with calcitonin in this range is extremely low.

2.4 Calcitonin ≥ 10 and < 20 ng/L

The subject can continue in the trial. Repeat testing of calcitonin at next protocol scheduled calcitonin visit. If the subject is a screen failure or if the value is the last one taken in the trial, the subject should be referred to a thyroid specialist for further evaluation.

Costante et al[1] had 216 (3.7%) patients in this category. One patient out of the 216 had a subsequent basal (unstimulated) calcitonin of 33 ng/L, and had C-cell hyperplasia at surgery, a lesion of unknown clinical significance. Two other studies used a cutoff of CT > 10 ng/L to screen for C-cell disease, but they do not provide sufficient information on patients with basal CT >10 and <20 ng/L to allow conclusions.[2,3]

3 References

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Appendix B

New York Heart Association Criteria for Functional Capacity

Trial ID: 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 type 2 diabetes mellitus

Trial Phase: 3b

1 Criteria for Functional Capacity

Functional Capacity[1]	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

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Appendix C

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

Trial ID: 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 type 2 diabetes mellitus

Trial Phase: 3b

1 Events with additional data collection and events requiring adjudication

Events with additional data collection and/or events requiring adjudication	Definitions	Rationale	Event Adjudication Committee
Fatal events	All fatal events should be reported including all-cause mortality: • Cardiovascular death • Non-cardiovascular death • Undetermined cause of death	An FDA guidance document[1] requests that Sponsors demonstrate the cardiovascular safety profile of any new therapy for type 2 diabetes in order to ensure, that the new therapy does not increase the cardiovascular risk to an unacceptable extent.	All events will be adjudicated.
Acute coronary syndrome (myocardial infarction (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 order to ensure, that the new therapy does not increase the cardiovascular risk to an unacceptable extent.	All cases of heart failure requiring hospitalisation, defined as an admission to an impatient unit or a visit to an emergency department that results in a least a 24 hours 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. Pancreatitis (including necrotising pancreatitis) is an identified risk according to the Company Core Data Sheet (CCDS) for liraglutide. 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	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 and should not be reported as a Neoplasm)		
Thyroid disease	All disorders of thyroid gland (incl. thyroid neoplasms) must be reported. Please refer to the protocol for further details on the assessments.	Thyroid C-cells carcinogenicity has been reported in rats and mice treated with GLP-1 receptor agonists in non-clinical studies	All thyroid neoplasms will be adjudicated. Thyroid disease requiring thyroidectomy will be adjudicated.

2 Medical Events of Special Interest (MESI)

Medical Events of Special Interest	Definitions	Rationale	Event Adjudication Committee
Medication errors concerning trial products	• 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 over dose with the intention to cause harm (e.g., suicide attempt • Accidental administration of a lower or higher dose than intended.	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

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Global and country key Novo Nordisk staff

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

Content: Global key staff and Country key staff

Protocol Amendment

no 1
to Protocol, final version 2.0
dated 25-Mar-2015

Trial ID: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 type 2 diabetes mellitus

Trial phase: 3b

Applicable to Japan

Amendment originator:

[redacted]

[redacted], CMR Development Division, Novo Nordisk Pharma Ltd.

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1 Introduction including rationale for the protocol amendment

The purpose of this amendment is to update an exclusion criterion and further correct minor inconsistencies and errors. Exclusion criterion no. 5 will be updated to specify how previous insulin treatment should be handled when subject eligibility is assessed. A timeframe will be added to the current text in order to make the criterion more clear for the sites. This will not have any impact on already included subjects.

The following changes are implemented as well:

- Allowance of a time interval for the conduct of fundoscopy or fundus photography at visit 8, 16 and 23. This is intended to give operational flexibility to perform the fundoscopy or fundus photography.

- Withdrawal criteria no. 9 is updated since previous protocol didn't provide the detailed process if the fasting SMBG values taken on three consecutive days or if any of the FPG samples analysed by the central laboratory exceeds the limit given there is no intercurrent cause for the hyperglycaemia.

- Appendix A is updated to correct some inconsistencies with withdrawal criteria no.6 and to update algorithm of calcitonin monitoring to comply with revised company standards.

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

2 Changes

2.1 Section 1 Summary

Key exclusion criteria

- ~~Previous treatment with insulin (except for short-term treatment in connection with intercurrent illness including gestational diabetes).~~ *Treatment with insulin within 12 weeks prior to screening.*

2.2 Section 2 Flowchart

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
Hypoglycaemic episodes		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ECG	x[4]							x								x							
Eye examination[5]	x[5]							x								x							

Flow chart explanatory descriptions

Footnote No. 5: Fundoscopy or fundus photography performed within 90 days prior to run-in visit (V2) is acceptable, and results should be available prior to V2. *Eye examination obtained within 7 days prior to V8 and 28 days prior to V16 and 23 are acceptable.*

2.3 Section 6.3 Exclusion criteria

5. ~~Previous treatment with insulin (except for short-term treatment in connection with intercurrent illness including gestational diabetes).~~ *Treatment with insulin within 12 weeks prior to screening.*

2.4 Section 6.5 Withdrawal criteria

9. If the fasting 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) during the first 6 weeks after initiation of run-in
- 13.3 mmol/L (240 mg/dL) from week 7 to week 12 after initiation of run-in
- 11.1 mmol/L (200 mg/dL) after randomisation

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~~ *the subject should be called in as soon as possible for a confirmatory FPG sample to be analysed by central laboratory. The next scheduled site visit*

should not be awaited. If there is no intercurrent cause for the hyperglycaemia, and FPG exceeds the limits stated above, the subject must be withdrawn.

2.5 Section 8.4.4 Eye Examination

…Fundoscopy/fundus photography performed within 90 days prior to run-in visit is acceptable. If a funduscopy/fundusphotography 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 obtained within 7 days prior to V8 and 28 days prior to V16 and V23 are acceptable.

2.6 Protocol Appendix A

Section 1 Background

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

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

- renal dysfunction~~,~~
- smoking~~,~~
- autoimmune thyroiditis ~~and~~
- several drug classes (e.g. proton pump inhibitors, betablockers, H2-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.

Section 2 Calcitonin ~~and C-cell abnormalities – evaluation and follow-up~~ *monitoring*

~~Subjects with a personal or family history of medullar thyroid cancer (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN 2) or with a screening calcitonin ≥ 50 ng/L will be excluded from the trial.~~

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 entered into run-in period according to protocol section 6.3 and further if the calcitonin value is measured to be ≥ 50 ng/L after run-in visit (Visit2), the subjects must be withdrawn according to section 6.5 in the protocol.*

In case a subject has a~~n increased~~ calcitonin value ≥ 10 ng/L the algorithm outlined *in Figure 2-1 and described* below should be followed. The algorithm applies for all calcitonin values including screening values.

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

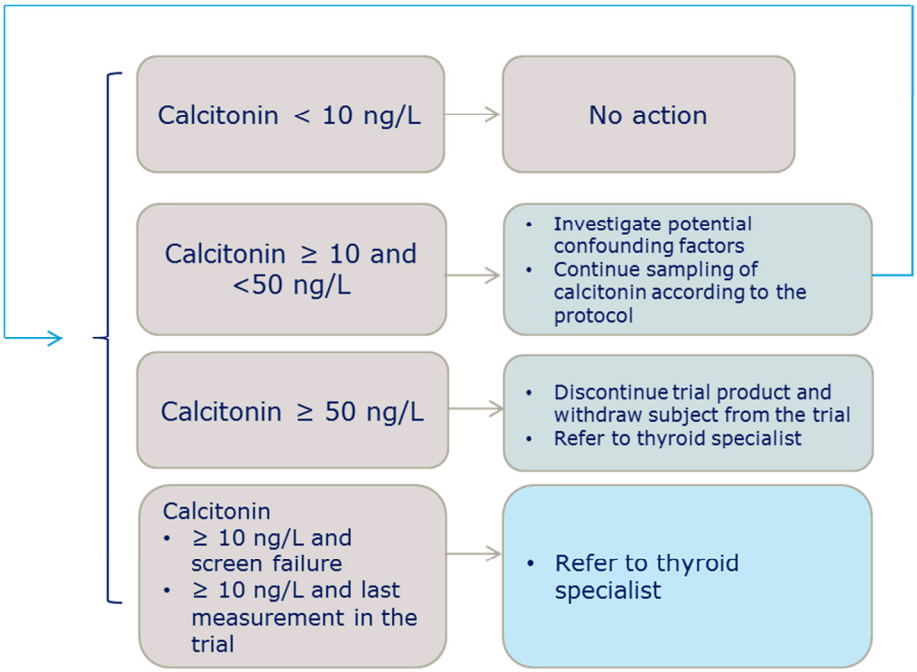

Figure 2-1 Flow of calcitonin monitoring

Section 2.1 Calcitonin ≥ 100 ng/L

Action: The subject (even if a screen failure) must immediately be referred to a thyroid specialist for further evaluation and ~~the trial treatment should be discontinued~~ *the subject must be withdrawn from the trial.*

~~The subject can remain in the trial, however, all~~*All medications*~~drugs~~ suspected to relate to this condition should be discontinued~~ until appropriate treatment has been initiated. If it is a screening value the subject cannot be entered into run-in period.~~

Background: These values were found in *9 (*0.15%*)* of a population *of 5817 patients* with thyroid nodular disease~~ published by Costante et al[1] and in one subject (on active comparator) in the liraglutide development program. For a calcitonin value of ≥100 ng/L, the subject should be assumed to have significant C-cell disease and a high likelihood of having medullary carcinoma of the thyroid.~~ *All of these patients were diagnosed with MTC resulting in a positive predictive value of 100%.*

Diagnostic evaluation should ~~consist of~~ *include:*

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

In case a subject is diagnosed with MTC, it is common clinical practice to explore the ~~F~~*f*amily history of MTC or MEN2 ~~should be evoked~~ and *perform a genetic test for* ~~a~~ RET proto-oncogene ~~analysis should be performed~~ *mutation*.

Section 2.2 Calcitonin ≥ 50 and < 100 ng/L

Action: The subject (even if a screen failure) should be referred to a thyroid specialist for further evaluation and~~ the trial treatment should be discontinued~~ t*he subject must be withdrawn from the trial*.

~~The subject can remain in the trial however,~~ *A*all ~~drugs~~ *medications* suspected to relate to this condition should be discontinued~~ until appropriate treatment has been initiated~~. ~~If it is a screening value the subject cannot be entered into run-in period.~~

Background: These values were found in *8 (*0.14%*)* of the population *of 5817 patients* with thyroid nodular disease~~ published by Costante et al[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~~ will likely~~ *should* include*:*

- *thyroid* ultrasound examination~~ and~~
- if available~~ and if there is~~ no contraindication,~~ subjects should undergo~~ a pentagastrin stimulation test. Subjects with positive pentagastrin stimulation tests ~~will~~ *should* be considered to undergo surgery.
- ~~In the US and other countries where~~*If* pentagastrin is not available, thyroid ultrasound and fine needle aspiration biopsy may add important clinical information informing the need for surgery.

~~**Section 2.3 Calcitonin ≥ 20 and <50 ng/L**~~

~~The subject can continue in the trial. Repeat testing of calcitonin at next protocol scheduled calcitonin visit. If the subject is a screen failure or if the value is the last one taken in the trial, the subject should be referred to a thyroid specialist for further evaluation.~~

~~These values are expected to be found in up to 1% of subjects. Based on data from Costante et al[1], the predictive value of calcitonin levels ≥ 20 and < 50 ng/L for clinically significant C-cell disease begins to fall. However, up to 25% of these subjects had a positive pentagastrin stimulation test. The likelihood of having a medullary carcinoma >1 cm with calcitonin in this range is extremely low.~~

~~**Section 2.4 Calcitonin ≥ 10 and < 20 ng/L**~~

~~The subject can continue in the trial. Repeat testing of calcitonin at next protocol scheduled calcitonin visit. If the subject is a screen failure or if the value is the last one taken in the trial, the subject should be referred to a thyroid specialist for further evaluation.~~

~~Costante et al[1] had 216 (3.7%) patients in this category. One patient out of the 216 had a subsequent basal (unstimulated) calcitonin of 33 ng/L, and had C-cell hyperplasia at surgery, a lesion of unknown clinical significance. Two other studies used a cutoff of CT > 10 ng/L to screen for C-cell disease, but they do not provide sufficient information on patients with basal CT >10 and <20 ng/L to allow conclusions.[2,3]~~

Section 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].