Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT02730377
Sponsor trial ID:	NN2211-4232
Official title of study:	LIRA-PRIME: Efficacy in controlling glycaemia with Victoza® (liraglutide) as add-on to metformin vs. OADs as add-on to metformin after up to 104 weeks of treatment in subjects with type 2 diabetes inadequately controlled with metformin monotherapy and treated in a primary care setting
Document date:	14 January 2020

16.1.1 Protocol and protocol amendments

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Redacted protocol
Includes redaction of personal identifiable information only.

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Protocol

Trial ID:NN2211-4232

LIRA-PRIME: Efficacy in controlling glycaemia with Victoza® (liraglutide) as add-on to metformin vs. OADs as add-on to metformin after up to 104 weeks of treatment in subjects with type 2 diabetes inadequately controlled with metformin monotherapy and treated in a primary care setting

A 104-week randomised, phase 4, two-arm, open-label, active-controlled, multicentre, multinational, parallel-group trial

Trial phase: 4

Protocol originators
Clinical trial management
Novo Nordisk A/S

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List of abbreviations

ADA	American Diabetes Association
AE	adverse event
BG	blood glucose
CRF	case report form
DPP-4	Dipeptidyl peptidase 4,
eCRF	electronic case report form
FAS	full analysis set
FPG	fasting plasma glucose
FSFV	first subject first visit
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide-1
HbA_{1c}	glycosylated haemoglobin
IEC	independent ethics committee
IRB	institutional review board
IWRS	interactive web response system
MESI	medical event of special interest
OAD	oral antidiabetic drug
SAE	serious adverse event
SGLT-2	Sodium/glucose cotransporter 2
SDV	source data verification
SmPC	summary of product characteristics
SUSAR	suspected unexpected serious adverse reaction
T2D	type 2 diabetes
UTN	Universal Trial Number

1 Summary

Objectives and endpoints:

Primary objective:
To compare the efficacy in controlling glycaemia with Victoza® (liraglutide) as add-on to metformin vs. oral antidiabetic drugs (OADs) as add-on to metformin after up to 104 weeks of treatment in subjects with type 2 diabetes (T2D) treated in primary care, inadequately controlled with metformin monotherapy.

Secondary objective:
To compare efficacy and safety of Victoza® as add-on to metformin vs. OADs as add-on to metformin after up to 104 weeks of treatment in subjects with type 2 diabetes (T2D) treated in primary care, inadequately controlled with metformin monotherapy.

Primary endpoint:
Time to inadequate glycaemic control defined as $HbA_{1c} > 7.0\%$ (53 mmol/mol) at two scheduled consecutive visits after the first 26 weeks of treatment and up to 104 weeks.

Key supportive secondary endpoints:

- Number of subjects who at 104 weeks or at premature treatment discontinuation achieve (Yes/No):
  - $HbA_{1c} \leq 6.5\%$ (48 mmol/mol)
  - $HbA_{1c} \leq 7.0\%$ (53 mmol/mol) without weight gain
- Change from baseline at 104 weeks or at premature treatment discontinuation in:
  - Fasting plasma glucose (FPG)
  - Body weight

Trial design:

This is a 104-week randomised, two-arm, open-label, active-controlled, multicentre, multi-national, parallel-group, phase 4 trial.

Trial population:

It is planned to randomise 1994 subjects.

Key inclusion criteria:

- Male or female ≥ 18 years of age at the time of signing informed consent.
- Subjects diagnosed (clinically) with type 2 diabetes ≥ 90 days prior to the screening visit.
- Stable daily dose of metformin as monotherapy ≥ 1500 mg or maximum tolerated dose within 60 days prior to the screening visit.

- HbA_{1c} 7.5-9.0% (59-75 mmol/mol) (both inclusive) and measured within the last 90 days prior to the screening visit.

Key exclusion criteria:

- Female who is pregnant, breast-feeding or intends to become pregnant or is of childbearing potential and not using adequate contraceptive methods (adequate contraceptive measures as required by local regulation or practice).
- Receipt of any investigational medicinal product within 30 days before the screening visit.
- Treatment with any medication for the indication of diabetes other than metformin in a period of 60 days before the screening visit. An exception is short-term treatment (≤7 days in total) with insulin in connection with intercurrent illness.
- Any disorder, which in the investigator's opinion might jeopardise subject's safety or compliance with the protocol.

Definition of primary care:
This trial will be conducted in a primary care environment which is defined as a non-endocrinologist, non-diabetologist clinic/practice/surgery or equivalent that provides continuing care to persons with any undiagnosed sign, symptom or health concern not limited by problem origin (biological, behavioural or social), organ system or diagnosis. The primary care practice may be the patient's first point of contact with the health care system.

The doctors/physicians that work in primary care are often referred to as general practitioners (GPs), primary care doctors/physicians and family doctors/physicians. The primary care practice may include a team of physicians and other health care professionals.

The definition of primary care is adapted from the definition used by the American Academy of Family Physicians (AAFP)[1].

Assessments:

- HbA_{1c}
- Fasting plasma glucose
- Body weight
- Hypoglycaemic episodes

Trial products:

Victoza®:

- Victoza® (liraglutide 3.0 mL;6.0 mg/mL)

Oral antidiabetic drugs (OADs):

- Alpha-glucosidase inhibitors
- DPP-4 inhibitors
- Meglitinides
- SGLT-2 inhibitors
- Sulphonylureas
- Thiazolidinediones

2 Flow chart

Trial Periods	**Screening**[1]	**Random isation**	**Treatment**									**End of treatment**	**Follow up**
Visit type	**S**	**S**	**P/S**[2]	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**P**
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Timing of visit, Weeks	**Up to -2**	**0**	**2**	**4**	**16**	**26**	**38**	**52**	**65**	**78**	**91**	**104**	**105**
Visit window, Days			**±7**	**±4**	**±10**	**±10**	**±10**	**±10**	**±10**	**±10**	**±10**	**±4**	**+4**
Informed consent	x												
In/exclusion criteria	x												
Randomisation		x											
IWRS session	x	x											
Withdrawal criteria[3]			x	x	x	x	x	x	x	x	x	x	
Medical history /Concomitant illness	x												
Concomitant medication	x	x	x	x	x	x	x	x	x	x	x	x	x
Demography	x												
Diagnosis of diabetes	x												
Diabetes complications	x							x				x	
Diabetes treatment history	x												
Smoking status	x												
Pregnancy urine test	x	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	x	
Handout ID card	x												
Height		x											
Body weight		x		x	x	x	x	x	x	x	x	x	
Blood sampling		x		x	x	x	x	x	x	x	x	x	
- Fasting plasma glucose		x		x		x		x				x	
- HbA_{1c}		x			x	x	x	x	x	x	x	x	
- Lipids		x						x				x	
- Biochemistry		x						x				x	
- Haematology		x						x				x	
Attend visit fasting		x		x		x		x				x	

Trial Periods	**Screening**[1]	**Randomisation**	**Treatment**									**End of treatment**	**Follow up**
Visit type	**S**	**S**	**P/S**[2]	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**P**
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Timing of visit, Weeks	**Up to -2**	**0**	**2**	**4**	**16**	**26**	**38**	**52**	**65**	**78**	**91**	**104**	**105**
Visit window, Days			**±7**	**±4**	**±10**	**±10**	**±10**	**±10**	**±10**	**±10**	**±10**	**±4**	**+4**
Systolic and diastolic blood pressure, sitting		x		x	x	x	x	x	x	x	x	x	
Pulse, sitting		x		x	x	x	x	x	x	x	x	x	
Handout diary and instruct in use[5]		x		x	x	x	x	x	x	x	x		
Handout blood glucose meter and instruct in use		x											
Prescription of trial product		x		x	x	x	x	x	x	x	x		
Information about trial product handling		x	(x)[4]	(x)[4]	(x)[4]	(x)[4]	(x)[4]	(x)[4]	(x)[4]	(x)[4]	(x)[4]		
Drug accountability				x	x	x	x	x	x	x	x	x	
Adverse events		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
Technical complaints			x	x	x	x	x	x	x	x	x	x	
End of treatment												x	
End of trial													x
Sign off Casebook													x

Abbreviations: IWRS: Interactive web response system; P/S: Phone contact/Site visit; S: Site visit; P: Phone contact

[1] Procedures and assessments relating to visit 1 may be conducted at visit 2 prior to randomisation. Trial related procedures (including requesting the subject to be fasting) are not allowed before signing of informed consent

[2] Visit 3 can be performed as either a phone contact or a site visit at the discretion of the investigator.

[3] Subjects withdrawing from the trial should attend end of treatment visit as soon as possible.

[4] Information about and training in trial product handling to be given at the discretion of the investigator.

[5] Diaries should be reviewed at every visit. Relevant data should be reported into the eCRF.

3 Background information and rationale for the trial

3.1 Background information

The trial will be conducted in compliance with this protocol, ICH GCP[2] and applicable regulatory requirements, and in accordance with the Declaration of Helsinki[3].

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

Information about Victoza® (liraglutide) (hereafter referred to as Victoza®) and oral antidiabetic drugs (OAD's) used as comparators is available in the approved local label documents.

The HbA_{1c} lowering effect of Victoza® in subjects with type 2 diabetes (T2D) is well established. The completed phase 3 and phase 4 trials with Victoza® have tested Victoza® in most treatment scenarios used for patients with T2D including combination with metformin[4]. In all these treatment scenarios the efficacy of Victoza® was demonstrated and there were no major safety concerns. Furthermore, Victoza® has been shown to be safe and efficacious in subjects with moderate renal impairment[5].

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

3.2 Rationale for the trial

The deterioration of glycaemic control over time in T2D, driven by progressive deterioration of pancreatic β-cell function, may require continuous intensification of antidiabetic treatment in order to provide optimal glycaemic care. In addition, in patients suffering from chronic diseases such as T2D, non-compliance to prescribed treatment can be associated with poor treatment outcomes. Generally, treatment compliance and adherence decrease with increasing complexity of the treatment regimen, e.g. add-on of a third antidiabetic drug[6]. Thus, the durability of the glycaemic control of the antidiabetic drugs added when metformin monotherapy no longer provides adequate glycaemic control is important. GLP-1 receptor agonists (RAs) are recommended as a potential second line treatment in the American Diabetes Association (ADA) and the European Association for the study of Diabetes (EASD) position statement[7]. However, the durability of the glucose-lowering effect of GLP-1 receptor agonists is not described in the position statement.

Data have suggested that GLP-1 may increase β-cell mass and function in animal models[8,9]. Further, GLP-1 RAs may improve β-cell function and growth in human subjects. One trial reported that in patients with T2D Victoza® provided robust enhancement of β-cell function that was sustained over 48 weeks[10]. Therefore, early introduction of Victoza® may promote durability of glycaemic control.

The majority of patients with T2D are treated in the primary care setting, however, most clinical trials are conducted in secondary care units. This may make the generalisability of the trial results - ie. whether the results can be reasonably applied to routine primary care practice - challenging[11,12].

The objective of this trial is to compare the efficacy in controlling glycaemia with Victoza® as add-on to metformin vs. OADs as add-on to metformin after up to 104 weeks of treatment in subjects with type 2 diabetes treated in primary care, inadequately controlled with metformin monotherapy.

4 Objectives and endpoints

4.1 Objectives

Primary objective:

To compare the efficacy in controlling glycaemia with Victoza® (liraglutide) as add-on to metformin vs. OADs as add-on to metformin after up to 104 weeks of treatment in subjects with T2D treated in primary care, inadequately controlled with metformin monotherapy.

Secondary objective:

To compare efficacy and safety of Victoza® as add-on to metformin vs. OADs as add-on to metformin after up to 104 weeks of treatment in subjects with type 2 diabetes (T2D) treated in primary care, inadequately controlled with metformin monotherapy.

4.2 Endpoints

4.2.1 Primary endpoint

Time to inadequate glycaemic control defined as $HbA_{1c} > 7.0\%$ (53 mmol/mol) at two scheduled consecutive visits after the first 26 weeks of treatment and up to 104 weeks.

4.2.2 Secondary endpoints

4.2.2.1 Supportive secondary endpoints

- Time to premature treatment discontinuation (for any reason including inadequate glycaemic control)
- Change from baseline in HbA_{1c} at 104 weeks or at premature treatment discontinuation
- Number of subjects who at 104 weeks or at premature treatment discontinuation achieve (Yes/No):
    - $HbA_{1c} \leq 6.5\%$ (48 mmol/mol) *
    - $HbA_{1c} \leq 7.0\%$ (53 mmol/mol) without weight gain *
    - $HbA_{1c} \leq 7.0\%$ (53 mmol/mol) without treatment emergent severe hypoglycaemic episodes or blood glucose confirmed symptomatic hypoglycaemic episodes
    - $HbA_{1c} \leq 7.0\%$ (53 mmol/mol) without weight gain and no treatment emergent severe hypoglycaemic episodes or blood glucose confirmed symptomatic hypoglycaemic episodes
- Change from baseline at 104 weeks or at premature treatment discontinuation will be evaluated for:
    - Fasting plasma glucose (FPG) *
    - Body weight *
    - BMI
    - Systolic and diastolic blood pressure
- Number of severe hypoglycaemic episodes
- Number of severe or blood glucose confirmed symptomatic hypoglycaemic episodes
- Number of documented symptomatic hypoglycaemic episodes (ADA)
- Number of serious adverse events (SAEs)
- Number of AEs leading to permanent discontinuation of trial product
- Change from baseline at 104 weeks or at premature treatment discontinuation will be evaluated for:
    - Lipids
    - Biochemistry
    - Haematology
    - Pulse

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

5 Trial design

5.1 Type of trial

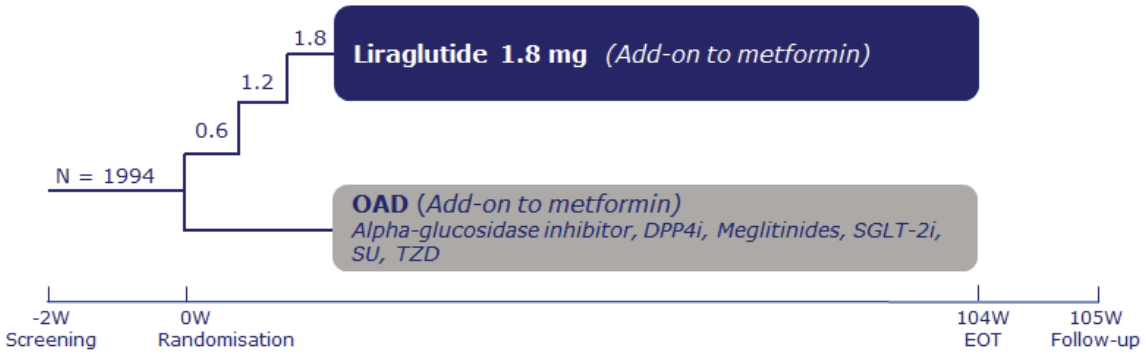
This is a 104-week randomised, two-arm, open-label, active-controlled, multicentre, multi-national, parallel-group, phase 4 trial.

The trial will be conducted in the primary care setting. Please refer to definition in section 5.2

Subjects' eligibility is based on the subjects' medical history including $HbA_{1c,}$ measured up to 90 days before screening.

Subjects will be randomised to one of two treatment arms: Victoza® or OAD. The OAD (see list below in section 5.4) will be chosen at the discretion of the investigator. Trial product will be prescribed by the investigator and dispensed by pharmacy or similar (see section 9).

The maximum trial duration for the individual subjects will be up to approximately 107 weeks. The trial includes an up to 2-week screening period, followed by an up to 104-week randomised treatment period and a 1-week follow up period after end of treatment. Please see Figure 5–1 for a schematic overview of the trial.



W = weeks, EOT = End of treatment, OAD = Oral antidiabetic drug, DPP-4i = Dipeptidylpeptidase 4 inhibitor, SGLT-2i = sodium/glucose cotransporter 2 inhibitor , SU = Sulphonylurea, TZD = thiazolidinediones

Figure 5–1 Schematic overview of the trial design

5.2 Definition of primary care

This trial will be conducted in a primary care environment which is defined as a non-endocrinologist, non-diabetologist clinic/practice/surgery or equivalent that provides continuing care to persons with any undiagnosed sign, symptom or health concern not limited by problem

origin (biological, behavioural or social), organ system or diagnosis. The primary care practice may be the patient's first point of contact with the health care system.

The doctors/physicians that work in primary care are often referred to as general practitioners (GPs), primary care doctors/physicians and family doctors/physicians. The primary care practice may include a team of physicians and other health care professionals.

The definition of primary care is adapted from the definition used by the American Academy of Family Physicians (AAFP)[1]

5.3 Rationale for trial design

A randomised, parallel-group trial design with two treatment arms has been chosen to avoid bias. A 104-week duration has been chosen as this was deemed appropriate for assessing time to inadequate glycaemic control. Due to the duration of the trial and the prescription of trial drug by the investigator an open-label design has been chosen as a double-dummy design was deemed unfeasible.

5.4 Treatment of subjects

After randomisation, subjects in the Victoza® arm will initiate treatment with 0.6 mg/day with subsequent dose escalation according to approved local label up to final dose of 1.8 mg/day at the discretion of the investigator. A maintenance dose of 1.2 mg is accepted if the subject's HbA_{1c} is < 7.0% (53 mmol/mol), however, escalation to 1.8 mg should be attempted if the subjects' HbA_{1c} is ≥ 7% (53 mmol/mol).

Subjects randomised to the OAD arm will initiate treatment with one OAD selected at the discretion of the investigator and, if relevant for the specific OAD, will escalate the dose to the maximum approved or maximum tolerated dose according to approved local label at the discretion of the investigator. A maintenance dose below the maximum approved or maximum tolerated dose is acceptable if the subject's HbA1c is < 7.0% (53 mmol/mol). However, escalation to the maximum approved or maximum tolerated dose should be attempted, at the discretion of the investigator, if the subjects' HbA1c is ≥ 7% (53 mmol/mol). Subjects randomised to the OAD arm must remain on the same OAD throughout the trial.

After randomisation, subjects must remain on the same antidiabetic drugs throughout the trial.

Subjects will receive Victoza® or the OAD treatment for a maximum of 104 weeks.

Victoza® and the OADs will be handled and dispensed by local pharmacies or similar means in accordance with local regulations and will be reimbursed by Novo Nordisk throughout the individual subject´s trial participation.

Subjects can receive the following antidiabetic drugs:

- **Victoza®**

- **Oral antidiabetic drugs:** The OADs included in this trial are:
  - Alpha-glucosidase inhibitors
  - Dipeptidyl peptidase 4 (DPP-4) inhibitors
  - Meglitinides
  - Sodium/glucose cotransporter 2 (SGLT-2) inhibitors
  - Sulphonylureas
  - Thiazolidinediones

Victoza® and OADs must be used in accordance with approved local labels at the discretion of the investigator. Fixed dose antidiabetic combination products (e.g. metformin plus DPP-4 inhibitor combinations) are not allowed in this trial.

Subjects should start the treatment they are randomised to as soon as possible and preferably no later than 5 days after randomisation.

Background medication: Metformin is considered background medication. The background metformin treatment must be maintained at the pre-trial dose and frequency during the entire trial treatment period unless there is a safety concern. Metformin is not provided or reimbursed by Novo Nordisk.

5.5 Treatment after discontinuation of trial product

Subjects meeting any withdrawal criteria must be withdrawn from the trial and stop treatment with trial product. After trial discontinuation the investigator is responsible for further treatment of the subject. Novo Nordisk will not provide or reimburse treatment after trial discontinuation.

5.6 Rationale for treatment

Victoza® and OADs will be used according to local approved labels in order to compare the real life efficacy in the two treatment arms. The OAD will be chosen at the discretion of the investigator in order to compare Victoza® to the OADs most relevant for the individual patient.

Background metformin has been chosen as this is the recommended first line treatment for type 2 diabetes. Metformin treatment must be maintained at the pre-trial dose and frequency during the trial treatment period in order to be able to compare the efficacy of Victoza® and OADs.

6 Trial population

6.1 Number of subjects

Number of subjects planned to be randomised: 1994

Number of subjects expected to complete the trial (defined as treated with trial product for 104 weeks): 462

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 ≥ 18 years of age at the time of signing informed consent.

3. Subjects diagnosed (clinically) with type 2 diabetes ≥ 90 days prior to the screening visit.

4. Stable daily dose of metformin as monotherapy ≥ 1500 mg or maximum tolerated dose within 60 days prior to the screening visit.

5. HbA_{1c} 7.5-9.0% (59-75 mmol/mol) (both inclusive) and measured within the last 90 days prior to the screening visit.

6. Patients in which Victoza® and OAD treatment are indicated according to approved local label.

6.3 Exclusion criteria

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

1. Previous participation in this trial. Participation is defined as signed informed consent.

2. Female who is pregnant, breast-feeding or intends to become pregnant or is of childbearing potential and not using adequate contraceptive methods (adequate contraceptive measures as required by local regulation or practice).

3. Receipt of any investigational medicinal product within 30 days before the screening visit.

4. Treatment with any medication for the indication of diabetes other than metformin in a period of 60 days before the screening visit. An exception is short-term treatment (≤7 days in total) with insulin in connection with intercurrent illness.

5. Any disorder, which in the investigator's opinion might jeopardise subject's safety or compliance with the protocol.

6.4 Withdrawal criteria

The subject may withdraw at will at any time. The subject´s request to discontinue must always be respected. The subject may be withdrawn from the trial at the discretion of the investigator due to a safety concern.

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.

2. Pregnancy or intention of becoming pregnant.

3. Participation in another clinical trial throughout the trial

4. Use of any antidiabetic medication during the trial other than background metformin, and randomised antidiabetic treatment except short-term insulin (≤7 days in total) treatment in connection with intercurrent illness.

5. Inadequate glycaemic control defined as HbA_{1c} > 7.0% (53 mmol/mol) at two scheduled consecutive visits after the first 26 weeks of treatment. First possible discontinuation due to this criterion is at week 38.

If a subject becomes pregnant or intends to become pregnant, trial products must be discontinued immediately and the subject should attend the end of treatment visit.

6.5 Subject replacement

Subjects who are withdrawn from the trial will not be replaced.

6.6 Rationale for trial population

Subjects with T2D who are inadequately controlled on metformin monotherapy are eligible for the trial. Subjects on metformin monotherapy are chosen since this is the current first line treatment of T2D recommended by the ADA and EASD.

The inclusion criteria are chosen to include a population of patients with T2D treated with metformin monotherapy, who are inadequately controlled and may benefit from treatment with Victoza® or an OAD in addition to metformin treatment. Stable pre-trial treatment prevents recent dose changes affecting trial endpoints. A minimum of exclusion criteria is chosen in order to reflect a real life setting.

6.7 Pre-trial HbA_{1c}

For evaluating whether a subject meets inclusion criterion 5, the requirements for documentation are:

- The most recent available HbA_{1c} obtained by a health care professional and documented in the medical records.
- Only HbA_{1c} measured within the last 90 days prior to the screening visit can be used.

Informed consent must be obtained prior to performing any trial related HbA_{1c} measurement.

7 Milestones

Planned duration of recruitment period: 52 weeks

End of trial is defined as Last Subject Last Visit.

Recruitment:
All investigators will be notified immediately when the recruitment period ends, after which no subjects may be screened.

Trial registration:
Information of the trial will be disclosed at clinicaltrials.gov and novonordisk-trials.com. According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure[13], it will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE)[14], the Food and Drug Administration Amendment Act (FDAAA)[15], European Commission Requirements[16,17] and other relevant recommendations or regulations. If a subject requests to be included in the trial via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the subject. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

8 Methods and assessments

The following sections describe the assessments and procedures. These are also included in the flow chart (see section 2) along with their timing.

8.1 Visit procedures

8.1.1 Informed consent

Informed consent must be obtained before any trial related activity; see section 18.2.

8.1.2 Investigator site logs

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.

8.1.3 Screening

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. A screening session must be performed in IWRS (see section 10). Each subject will be assigned a unique 6-digit subject number which will remain the same throughout the trial.

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

8.1.4 Randomisation

A randomisation session must be performed in IWRS (see section 10).

8.1.5 Withdrawals

If a subject is withdrawn from the trial, the investigator must aim to undertake procedures similar to those for visit 12 as soon as possible if acceptable to the subject. 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. In addition the follow-up telephone contact (visit 13) should be completed approximately 1 week after the early treatment discontinuation visit if possible. After that 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.

8.1.6 Site visits

It is the responsibility of the investigator to have an appointment with the subjects for the site visits. If a site visit is missed and it is not possible to re-schedule, the investigator should ensure that relevant information is collected for example over the phone.

8.1.7 Visits attended fasting

At the time points specified in section 2, subjects must attend the visits fasting for blood sampling. Fasting is defined as at least eight hours without food and liquids, except for water and any prescribed medication other than trial products and background metformin treatment.

8.1.8 Missed visits

Should a visit be missed, every effort should be made to re-schedule the visit within the allowed visit window. If this is not possible, the visit should be re-scheduled at the earliest possible date before the next visit.

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. **Medical history** is a medical event that the subject has experienced in the past.

Procedures and assessments performed at visit 1 and/or 2 are considered screening procedures. The results of these procedures should be considered pre-existing conditions and should be reported as medical history or concomitant illness

Relevant concomitant illness/medical history related to diabetes should be transcribed to the eCRF.

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

Any relevant change to a concomitant illness should be recorded during the trial. A clinically significant worsening of a concomitant illness must be reported as an AE, if the event meets the SAE criteria or is an AE leading to permanent treatment discontinuation according to section 12.2.

8.2.2 Concomitant medication

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

Concomitant medications used to treat an SAE, an AE leading to permanent treatment discontinuation or diabetes must be recorded in the eCRF. Details of diabetes medication must be recorded at the first visit. Changes in concomitant medication must be recorded at each visit as they occur.

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

If a change is due to an SAE or an AE leading to permanent treatment discontinuation, 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

The following demographic data must be recorded:

- Date of birth
- Sex
- Race
- Ethnicity

Investigators must document whether females are of childbearing potential.

8.2.4 Diabetes details

Details regarding diagnosis of diabetes (diabetes type and date of diagnosis), diabetes complications and diabetes treatment history (dose, start and stop date of current diabetes treatment) must be recorded in the eCRF at visit 1.

8.2.5 Smoking status

Details of smoking status must be recorded at the first visit. Smoking is defined as smoking at least one cigarette, cigar or pipe daily. The collected information should include whether or not the subject smokes or has smoked.

8.3 Assessments

8.3.1 Body measurements

Height should be assessed without shoes in centimetres or inches and recorded to nearest half centimeter or ¼ inch.

Body weight should be assessed in light clothes without shoes. It should be recorded in kg or lb and preferably using the same scale throughout the trial.

8.3.2 Vital signs

Diastolic blood pressure, systolic blood pressure and pulse should be assessed according to normal site procedures while the subject is sitting.

8.3.3 Hypoglycaemic episodes

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

All plasma glucose values:
- ≤ 3.9 mmol/L (70 mg/dL) or
- > 3.9 mmol/L (70 mg/dL) when they occur in conjunction with hypoglycaemic symptoms

should be recorded by the subject. These must be transcribed into the eCRF (hypoglycaemic episode form) throughout the trial from visit 2 to visit 13.

The record should include the following information:
- Date and time of hypoglycaemic episode
- The plasma glucose level before treating the episode (if available)
- Whether the episode was symptomatic
- Whether the subject was able to treat him/herself
- Date and time of last antidiabetic treatment administration prior to episode
- Type and dose of last antidiabetic treatment administration prior to episode
- Date and time of last main meal prior to episode
- Whether the subject was asleep when the episode occurred
  - If yes, whether the symptoms of the episode woke up the subject

The answer to the question: "Was 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[10].

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

If the question "Was subject able to treat him/herself?" is answered "No", the following information should be recorded:
- Who assisted in the treatment of the hypoglycaemic episode (i.e. family/friend/co-worker or similar, paramedic, doctor or other, please specify)
- Where the treatment was administered (i.e. at home/at friends/at work or similar, in an ambulance, emergency room/hospital or other, please specify)
- Type of treatment provided by other person (i.e. oral carbohydrates, glucagon, IV glucose or other, please specify)
- Were symptoms alleviated after administration of treatment?

- Factors contributing to the episode (i.e. physical activity, missed meal, diet changed, medication error (i.e. overdose, mix-up between products), 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?
  - Autonomic: sweating, trembling, hunger or palpitations
  - Neuroglycopenic: confusion, drowsiness, speech difficulty, visual disturbances, odd behaviour, impaired balance or incoordination
  - General malaise: headache or malaise
- Did the subject experience other symptoms? Please specify
- Description of the episode, if applicable

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

8.3.4 Self-measured blood glucose (SMBG)

At Visit 2, subjects will be provided with a blood glucose meter including lancets, plasma-calibrated test strips and control solutions as well as instructions for use. The subjects will be instructed on how to use the device, the instruction will be repeated as necessary during the trial.

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

Subjects should be instructed on how to record the results of the SMBGs in the diaries and to only record them in the diaries in case of hypoglycaemic episodes. All relevant data from the diary must be transcribed into the eCRF during or following the contact. If obtained via phone and a discrepancy is later detected, the values in the eCRF should be corrected.

8.3.5 Diaries

The subject must be provided with diaries at the specified visits (section 2). During the trial subjects should use the diary for the below:

- to record their blood glucose values in case of hypoglycaemic episodes
- to record any new concomitant medication during the trial
- to record dose changes to metformin, Victoza® or OAD treatment (date of change, new trial product dose and reason for dose change)
- to record any adverse events experienced by the subject

In addition, subjects should be instructed to note the date, time and blood glucose value (if available) if they experience a hypoglycaemic episode where they are not able to treat themselves.

Subjects are requested to bring the diary to each visit. The diary must be collected and retained at the site as source data, and the subject will receive a new diary.

The investigator must review the subject diaries to ensure the relevant entries are transcribed to the eCRF. If clarification of entries or discrepancies is needed, the subject must be questioned and a conclusion made in the medical record. Care must be taken not to bias the subject. To verify that the data have been reviewed, the investigator must sign and date the diaries or ensure the review is documented in the subject's medical record.

8.3.6 Pregnancy test

Sites will be provided with urine pregnancy test kits (urine-sticks). For female subjects who are of child-bearing potential (at the discretion of the investigator), a pregnancy test must be performed on site at screening. For females of child-bearing potential pregnancy test should be repeated at end of treatment and at any time during the trial, if a menstrual period is missed or pregnancy is suspected or as required by local regulations. The date and result of the pregnancy tests must be recorded in the subject's medical record and the results must be transcribed to the eCRF.

8.4 Laboratory assessments

The laboratory analyses listed below must be performed at a central laboratory and the results will be made available for the investigators. The investigator must sign and date the reports from the laboratory, to verify that the results have been reviewed, or ensure the review is documented in the subject's medical record. The laboratory report and evaluation are retained at the investigator's site as source documentation.

For laboratory report values outside the reference range, the investigator must specify whether the value is or is not clinically significant.

Laboratory materials, flow charts and a laboratory manual will be provided to each site. The documents will include instruction on handling, transportation and storage of the blood samples, as well as contact information for the laboratory.

The laboratory analyses are:

Glucose metabolism

- Fasting plasma glucose
- HbA_{1c}

Lipids

- Cholesterol
- High density lipoprotein (HDL) cholesterol
- Low density lipoprotein (LDL) cholesterol
- Triglycerides

Biochemistry

- Creatinine
- eGFR (calculated value)
- Alanine aminotransferase (ALT)
- Aspartate Aminotransferase (AST)
- Potassium
- Bilirubin
- Lipase
- Amylase

Haematology

- Haemoglobin

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

The laboratory equipment may provide analyses not requested in the protocol but produced automatically in connection with the requested analyses according to specifications in the laboratory standard operating procedures. Such data will not be transferred to the trial database, but abnormal values will be reported to the investigator. The investigator must review all laboratory results for concomitant illnesses and adverse events and report these according to this protocol see section 12.2.

8.5 Subject compliance

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

Treatment compliance: Treatment compliance will not be measured as the trial is designed to reflect everyday practice.

9 Trial supplies

Trial supplies comprise trial products and auxiliary supplies. Trial products must not be used by any person not included in the trial.

9.1 Trial products

Trial products used in this trial are:

Victoza®:

- Victoza® (liraglutide 3.0 mL;6.0 mg/mL)

Oral antidiabetic drugs (OADs):

- Alpha-glucosidase inhibitors
- DPP-4 inhibitors
- Meglitinides
- SGLT-2 inhibitors
- Sulfonylureas
- Thiazolidinediones

Trial products will be commercial products dispensed from pharmacies or similar means in accordance with local regulation/practice and hence trial product will not be supplied by Novo Nordisk. Dispensing of trial products will be based on Investigator prescriptions. The prescription must be in accordance with subject randomisation to either Victoza® or OAD treatment arm. Trial products will be reimbursed by Novo Nordisk throughout the individual subject´s trial participation.

It is the responsibility of the investigator that the patient is instructed in the use of trial drug during the trial and the expected adverse events.

Further information for trial products is available in approved local labels and package inserts.

Metformin is background treatment in this trial hence not trial product and will neither be supplied nor reimbursed by Novo Nordisk.

9.2 Labelling

Applicable for Russia, Serbia and Turkey

In accordance with local regulation the commercially supplied trial products will have a dispensing label with particulars added to the original container without obscuring the original labelling:

For Serbia the following particulars will be added:

- Name of sponsor
- Trial ID
- Subject number (this allows identification of the trial site, investigator and trial subject)
- For clinical trial use only

For Russia the following particulars will be added:

- Name of sponsor
- Trial ID
- Subject number (this allows identification of the trial site, investigator and trial subject)
- Investigator information
- For clinical trial
- Dispensing unit number (allocated by the pharmacy)

For Turkey the following particulars will be added:

- Name of sponsor
- Trial ID
- Subject number (this allows identification of the trial site, investigator and trial subject)
- Site number
- Investigator information
- For clinical trial use only
- Keep out of reach and sight of the children

Adding the dispensing label will be carried out by health care professional/trained specialist at a pharmacy or similar and documented.

Further information will be available in a country specific document describing the local process.

Applicable for Canada, India, Latvia, Lebanon and US

Commercially supplied trial products will not have any additional labelling.

9.3 Storage

Trial products are supplied commercially and hence will not be stored at site.

9.4 Drug accountability and destruction

Drug accountability is the responsibility of the investigator.

Drug accountability will be performed based on prescribed trial product by investigator. At each visit (except for visit number 3) the Investigator will prescribe trial product and at the next visit the subject will return to the site used, partly used and not used trial products dispensed from the pharmacy. At the site it will be documented what was prescribed and what the subject returned to the investigator at the next visit.

Through this procedure the investigator can verify that correct trial product has been dispensed.

Applicable for Canada, India, Latvia, Lebanon, Russia, Serbia and Turkey

Trial product (used/partly used or unused including empty packaging material) returned to the site can be stored without temperature monitoring.

Destruction of trial products must be documented.

Applicable for US

No requirement with regard to documentation of destruction of trial product

9.5 Auxiliary supplies

Auxiliary supplies to the subjects are:

- Blood glucose meters including lancets, plasma-calibrated test strips and control solutions. This will be provided by Novo Nordisk. User manual will be provided along with the blood glucose meter.

For subjects randomised to Victoza®, needles for pre-filled Victoza® pens will be supplied to subjects from pharmacies or similar means along with Victoza® and will be reimbursed by Novo Nordisk

10 Interactive web response system

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

IWRS is used for:

- Screening
- Screening failure
- Randomisation

IWRS user manuals will be provided to each trial site.

11 Randomisation procedure

The IWRS must be used for randomisation. Only eligible subjects are allowed to be randomised.

12 Adverse events, technical complaints and pregnancies

12.1 Definitions

Adverse event

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

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

An AE includes:

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

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

- Pre-existing conditions, including those found as a result of screening procedures (pre-existing conditions should be reported as medical history or concomitant illness).
- Pre-planned procedures unless the condition for which the procedure was planned has worsened from the first trial related activity after the subject has signed the informed consent.
- Non-serious hypoglycaemia is an AE, but is reported on a hypoglycaemic episode form instead of on an AE form, see section 8.3.3.

The following three definitions are used when assessing an AE:

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

- **Causality**

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

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

- **Final outcome**

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

Serious adverse event

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

Non-serious adverse event

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

Medical event of special interest

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

Medication errors concerning trial products:

- Administration of wrong drug.
- Wrong route of administration, such as intramuscular instead of subcutaneous.
- Administration of an overdose with the intention to cause harm (e.g. suicide attempt).
- Accidental administration of a lower or higher dose than intended, however the administered dose must deviate from the intended dose to an extent where clinical consequences for the trial subject were likely to happen as judged by the investigator, although they did not necessarily occur.

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 SAE (see section 12.1), MESI (see section 12.1), AEs leading to permanent discontinuation of trial product and pregnancies (see section 12.5) must be collected and reported. This includes events from first trial related activity after the subject has signed the informed consent until the end of trial (visit 13). The events must be recorded in the applicable eCRF forms in a timely manner, see timelines below and Figure 12–1.

During each contact with the investigator, the subject must be asked about AEs, for example by asking: "Have you experienced any problems since the last contact?" AEs are either observed by the investigator or reported by the subject.

The investigator will evaluate the need for reporting of AEs. The investigator must report the following AEs in the eCRF:

- All SAEs
- AEs leading to permanent discontinuation of investigational product
- MESIs

The investigator should report the diagnosis, if available. If no diagnosis is available, the investigator should record each sign as individual AEs using separate AE forms. The investigator must evaluate the severity and causality for each event.

For SAEs that could have resulted from hypoglycaemia (for example sudden death, seizure, trauma, fractures, fall, motor vehicle accident etc), the narrative should include information whether hypoglycaemia could have contributed to these events.

- The investigator must enter the AE in the eCRF and tick the seriousness box within 24 hours of obtaining knowledge of the SAE
- The safety information form must be completed within 5 days of obtaining knowledge of the SAE

If for some reason the eCRF is unavailable, the AE information should be reported to Novo Nordisk by fax, telephone, e-mail or courier within the same timelines.

Contact details (fax, telephone, e-mail and address) are provided to each site.

All SAEs, MESIs and AEs leading to permanent treatment discontinuation observed either by the investigator or the 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 **(**CCDS), Victoza®, 6.0 mg/mL, version 17.0 or any updates thereto
- Non Novo Nordisk A/S marketed products: European summary of product characteristics or other relevant labelling, current version or any updates thereto.

All SAEs, MESIs, AEs leading to permanent treatment discontinuation and AEs in connection with pregnancies must be recorded by the investigator on an AE form. The investigator should report the diagnosis, if available. If no diagnosis is available, the investigator should record each sign and symptom as individual AEs using separate AE forms.

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

MESIs, regardless of seriousness, must be reported using both AE form, safety information form and a medication error form. The medication error 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.

- **SAEs fulfilling the MESI criteria:** In addition to above, the medication error form **within 14 calendar days** of the investigator's first knowledge of the AE.

- **Non-serious AE fulfilling the MESI criteria:** The AE form, safety information form and medication error form **within 14 calendar days** of the investigator's first knowledge of the event.

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

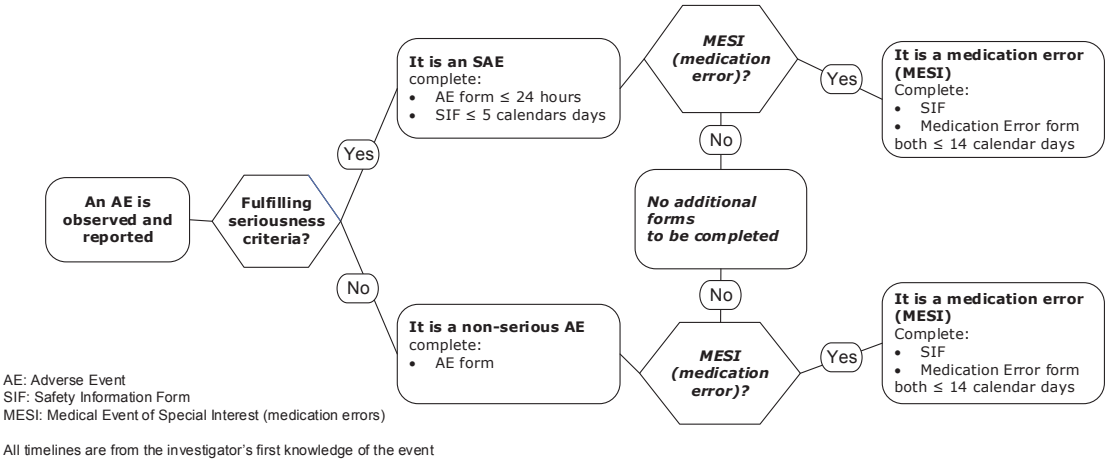


Figure 12–1 Initial reporting of AEs

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

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

12.3 Follow-up of adverse events

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

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

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

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

- **Non-serious AEs leading to permanent treatment discontinuation**: 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 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.- 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 Novo Nordisk products:

- Victoza®
- Needles for Liraglutide (Victoza®) prefilled pen-injector
- Repaglinid (NovoNorm® /Prandin® / GlucoNorm®) tablet

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.

All technical complaints on any non-Novo Nordisk OAD products:

- Alpha-glucosidase inhibitors
- DPP-4 inhibitors
- Meglitinides
- SGLT-2 inhibitors
- Sulfonylureas
- Thiazolidinediones

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. In addition the technical complaint should be reported to the Marketing Authorisation Holder via the pharmacy, or similar, where the product was obtained.

Contact details (fax, e-mail and address) for reporting to Novo Nordisk are provided in Attachment I to the protocol.

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

Technical complaints must be reported on a separate technical complaint form. A technical complaint form for each batch or lot number 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 for all Novo Nordisk products and notify the monitor **within 5 calendar days** of obtaining the sample at trial site. The monitor must coordinate the shipment to Customer Complaint Center, Novo Nordisk (the address is provided in Attachment I) and ensure that the sample is sent as soon as possible. A print or copy of the technical complaint form must be sent with the sample.

The investigator must ensure that the technical complaint sample contains the batch or lot number.

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

For non- Novo Nordisk OADs the sample should be returned to the Marketing Authorisation Holder via the pharmacy, or similar, where the product was obtained.

12.5 Pregnancies

12.5.1 Pregnancies in female subjects

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

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

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

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

1) Reporting of pregnancy information

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

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

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

2) Reporting of AE information

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

Forms and timelines for reporting AEs:

Non-serious AEs:

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

SAEs:

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

12.5.2 Pregnancies in female partners of male subjects (Applicable to US only)

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

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

When the pregnancy outcome is **normal** this information is recorded in the subject's medical record only, no further information is collected and reported to Novo Nordisk. When the pregnancy outcome is **abnormal** (i.e. congenital anomalies, foetal death including spontaneous abortion and/or any anomalies of the foetus observed at gross examination or during autopsy), the following must be reported by the investigator to Novo Nordisk electronically (e.g. in PDF format) or by fax:

1) Reporting of pregnancy information

Information from the male subject has to be reported on the Paternal Form. Furthermore, information from the female partner (including information about the pregnancy outcome and health status of the infant until the age of one month) has to be reported on the Maternal Forms 1A, 1B and 2, after an informed consent has been obtained from the female partner.

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

2) Reporting of AE information

The following AEs in the foetus and newborn infant have to be reported:

- Non-serious AEs evaluated as possible/probably related to the father's treatment with the trial product(s).
- SAEs in the foetus and newborn infant - whether or not related to the father's treatment with the trial product(s). This includes an abnormal outcome - such as foetal death (including spontaneous abortion) and congenital anomalies (including those observed at gross examination or during autopsy of the foetus).

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

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

12.6 Precautions and/or overdose

When initiating treatment with Victoza®, 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 have been reported up to 40 times the recommended maintenance dose (72 mg). One case of a [redacted]-fold overdose ([redacted] mg daily) given for [redacted] has been reported. Generally, the patients reported severe nausea, vomiting and diarrhoea, but recovered without complications. None of the patients reported severe hypoglycaemia. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

For non Novo Nordisk marketed products please consult the EU summary of product characteristic and US prescribing information for information on precautions and/or overdose.

12.7 Committees related to safety

12.7.1 Novo Nordisk safety committee

Novo Nordisk will constitute an internal Victoza® safety committee to perform ongoing safety surveillance.

13 Case report forms

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

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.

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

13.1 Corrections to case report forms

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

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

13.2 Case report form flow

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

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

14 Monitoring procedures

During the course of the trial, the monitor will visit the trial site to ensure that the protocol is adhered to, that all issues have been recorded, to perform source data verification and to monitor drug accountability. The first monitoring visit will be performed as soon as possible after FSFV at the trial site and no later than 4 weeks after. The monitoring visit intervals will depend on the outcome of the remote monitoring of the eCRFs, the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP, but will not exceed 8 weeks during recruitment and 12 weeks after end of recruitment for sites with subjects between Visit 1 and Visit 13.

The monitor must be given direct access to source documents (original documents, data and records) including documentation for pre-trial HbA_{1c} (see section 6.7). 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.

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.

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 returned diaries must be filed with source documents.

The monitor will ensure that the CRFs are completed.

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

- Date for obtaining informed consent

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 eCRF. If discrepancies are found, the investigator must be questioned about these.

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

15 Data management

Data management is always the responsibility of Novo Nordisk. Appropriate measures, including encryption of data files containing person identifiable data, will be used to ensure confidentiality of subject data, when they are transmitted over open networks.

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

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

16 Computerised systems

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

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

17 Statistical considerations

Results from the statistical analyses will generally be presented by two-sided confidence intervals with a confidence level of 95%.

The full analysis set (FAS) will be used in the analysis of the efficacy endpoints. For the safety endpoints, the safety analysis set (SAS) will be used.

The main statistical analyses and summaries will be based on assessments taken while the subject is on treatment. With exception for AEs (see Section 17.4.1.2), the period in which a subject will be considered to be on treatment extends to one day after last administration of trial product.

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

17.1 Sample size calculation

The sample size calculation is based on the objective to detect a difference in the time to inadequate glycaemic control between the Victoza® arm and the OAD arm, using a two-sided log rank test at a 5% significance level. The power is set to 90%.

The distributions of event time for the two treatment arms are derived from a model of the continuous HbA_{1c} measurements. In this model, the post-baseline measurements for each subject are assumed to be normally distributed and, conditional on a random subject effect, independent between assessment times. Based on data from another Novo Nordisk trial (NN2211-1860), the mean HbA_{1c} in the Victoza® arm is anticipated to be at a constant post-baseline level of 6.9% and the standard deviation of the within-subject error is anticipated to be 0.85%. The latter is in reality an estimate of the standard deviation of the total error and is therefore a conservative estimate of the within-subject standard deviation.

A mean treatment difference in HbA_{1c} of 0.3% is considered clinically relevant and is therefore used as the assumption in the model[18]. The HbA_{1c} levels in the two treatment arms are assumed to diverge after the visit at 65 weeks, when the mean in the OAD arm is assumed to increase in one step from 6.9% to 7.2%. Otherwise, the means are assumed to be constant during the observation period between 26 and 104 weeks.

Based on previous trials, the anticipated percentage of subjects who discontinue treatment prematurely (are withdrawn from the trial) without having inadequate glycaemic control is 20% in both treatment arms. As a conservative assumption, these subjects are assumed to discontinue before the week 26 visit and thus not give any contribution to the statistical analysis.

Based on the assumptions above, the required sample size is found to be 1994 subjects. The anticipated percentage of subjects who have had inadequate glycaemic control after 104 weeks is 66% in the Victoza® arm and 76% in the OAD arm. The number of subjects who complete the trial

without premature treatment discontinuation (for any reason including inadequate glycaemic control) is expected to be 462.

In order to investigate the influence of the values of the model parameters on the calculation, sample sizes have been calculated for different alternative scenarios, assuming the mean post-baseline HbA_{1c} level in the Victoza® arm to be 6.8%, 6.9% or 7.0%, the standard deviation to be 0.7% or 0.85%, the treatment difference to be 0.2% or 0.3% and the divergence time to be 52 or 65 weeks. The results are presented in Table 17–1 with the adopted sample size marked in bold.

Table 17–1 Sample size calculations for different scenarios – total number of randomised subjects

		Divergence time			
		52 weeks		65 weeks	
		Standard deviation		Standard deviation	
Mean HbA_{1c} in Victoza® arm	Treatment difference	0.7%	0.85%	0.7%	0.85%
6.8%	0.2%	1138	1782	2394	3840
	0.3%	492	776	1010	1636
6.9%	0.2%	1332	2042	2948	4608
	0.3%	588	902	1272	**1994**
7.0%	0.2%	1668	2456	3948	5868
	0.3%	752	1098	1736	2566

17.2 Definition of analysis sets

The following analysis sets are defined in accordance with the ICH-E9 guideline.

FAS: includes all randomised subjects who have received at least one dose and have any post randomisation data. The statistical evaluation of the FAS will follow the intention-to treat principle and subjects will contribute to the evaluation “as randomised”.

SAS: includes all subjects exposed to at least one dose of trial product. Subjects in the SAS will contribute to the evaluation “as treated”.

Before data are locked for statistical analysis, a review of all data will take place. Any decision to exclude a subject or single observations from the statistical analysis is the joint responsibility of the trial statistician, the international trial manager and the medical specialist. Exclusion of data from analyses will be used restrictively and normally no data should be excluded from the FAS. 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 time to inadequate glycaemic control defined as HbA_{1c} > 7.0% (53 mmol/mol) at two scheduled consecutive visits after the first 26 weeks of treatment and up to 104 weeks. First possible occurrence is at week 38.

The time to inadequate glycaemic control will be compared between the Victoza® arm and the OAD arm using a two-sided nonparametric test at a 5% significance level. The test will be a generalised log rank test for interval censored failure time data[19]. The analysis will not be based on any model assumptions such as proportional hazards. The possible event times will be considered as a discrete set of time points corresponding to the scheduled visits. An alternative but technically equivalent model would be to view the event time as a continuous variable which can only be observed to lie in the interval between the visit when inadequate glycaemic control is established and the previous scheduled visit. Subjects who complete the trial without an event of inadequate glycaemic control will be censored after the last visit at 104 weeks, which means that the event time is only observed to be greater than 104 weeks. Subjects who discontinue treatment before 104 weeks without having an event of inadequate glycaemic control will be censored immediately after the last visit which they attended while on treatment. In particular, subjects changing antidiabetic drug after randomisation will be discontinued from the trial and in relation to the primary endpoint be considered as censored and not having had an event of inadequate glycaemic control.

The result of the log rank test will be presented as the asymptotic p-value obtained from a chi-square distribution. If the asymptotic p-value is not considered a valid approximation based on the Mantel-Fleiss criterion[20], then the exact p-value will be calculated.

17.4 Secondary endpoints

17.4.1 Supportive secondary endpoints

17.4.1.1 Efficacy endpoints

Time to premature treatment discontinuation (for any reason including inadequate glycaemic control)

The time to premature treatment discontinuation will be analysed using the same type of generalised log rank test as for the primary endpoint with the difference that subjects who discontinue treatment before 104 weeks without having an event of inadequate glycaemic control will not be considered as censored but as meeting the endpoint. For these discontinued subjects, the event will be considered to have occurred in the interval between the last attended visit on treatment and the next planned visit.

Change from baseline in HbA_{1c} at 104 weeks or at premature treatment discontinuation

The change from baseline in HbA_{1c} will be evaluated using an analysis of covariance (ANCOVA) model where the last post-baseline measurement taken on treatment will enter as the dependent variable, treatment arm and country as factors and baseline HbA_{1c} as a covariate. The estimated differences between Victoza® and OAD will be presented together with the corresponding 95% confidence intervals and two-sided p-values.

To further describe the effects of Victoza® compared to OAD with respect to the change from baseline in HbA_{1c}, supportive analyses will be performed using a mixed model for repeated measurements (MMRM) where all post-baseline measurements taken on treatment will enter as the dependent variable, treatment arm as a factor and baseline HbA_{1c} as a covariate. The factor and the covariate will be nested within visit. An unstructured covariance matrix for the measurements within subject will be employed. From this analysis, the differences between Victoza® and OAD at different visits will be estimated.

The purpose of the MMRM analysis is to estimate the treatment effects that would have been observed if all subjects had remained on treatment and completed all visits, instead of dropping out. The analysis relies on the assumption that data are missing at random (MAR), which means that given the observed data, the events that lead to data being missing are independent of the unobserved data. This is a reasonable assumption also for subjects discontinuing treatment due to inadequate glycaemic control since it can be explained by the observed data obtained prior to discontinuation.

Categorical endpoints related to HbA_{1c}

Secondary categorical efficacy endpoints are subjects who at 104 weeks or at premature treatment discontinuation achieve (Yes/No):

- $HbA_{1c} \leq 6.5\%$
- $HbA_{1c} \leq 7.0\%$ without weight gain
- $HbA_{1c} \leq 7.0\%$ without treatment emergent severe hypoglycaemic episodes or BG confirmed symptomatic hypoglycaemic episodes
- $HbA_{1c} \leq 7.0\%$ without weight gain and no treatment emergent severe hypoglycaemic episodes or BG confirmed symptomatic hypoglycaemic episodes

These endpoints will be analysed separately using the same type of logistic regression model. In the calculation of the responses, the last post-baseline measurements of HbA_{1c} and body weight which were taken on treatment will be used. The model will include treatment arm as a factor and baseline HbA_{1c} as a covariate. The results will be described by the odds ratio for the comparison of Victoza® versus OAD and the associated 95% confidence interval and two-sided p-value.

Other efficacy endpoints

The change from baseline at 104 weeks or at premature treatment discontinuation will be evaluated for:

- FPG
- Body weight
- BMI
- Systolic and diastolic blood pressure

These endpoints will be analysed using the same type of ANCOVA as for HbA_{1c} but with the baseline measurement of the corresponding endpoint as covariate instead of baseline HbA_{1c}. The corresponding supportive analyses to estimate treatment differences at different visits will also be performed.

BMI will be derived at each visit with a body weight measurement by using the body weight from the corresponding visit and the height measured at screening.

17.4.1.2 Safety endpoints

The following secondary endpoints are used to support the safety objectives:

- Number of severe hypoglycaemic episodes
- Number of severe or blood glucose confirmed symptomatic hypoglycaemic episodes
- Number of documented symptomatic hypoglycaemic episodes (ADA)
- Number of SAEs
- Number of AEs leading to permanent discontinuation of trial product
- Change from baseline at 104 weeks or at premature treatment discontinuation:
    - Lipids
    - Biochemistry
    - Haematology
    - Pulse

Adverse events

The collected AEs will be coded using the most recent version of the Medical Dictionary for regulatory Activities (MedDRA) coding. A treatment emergent adverse event (TEAE) is defined as an event that has onset date (or increase in severity) on or after the first day of trial product administration and no later than seven days after the last day of trial product administration.

AE data will be displayed in terms of the number of subjects with at least one event, the percentage of subjects with at least one event, the number of events and the event rate per 1000 patient years of exposure. The main AE summaries will only contain TEAEs. Non-treatment emergent AEs will be included in listings and overview summaries.

Hypoglycaemic episodes

The endpoints involving hypoglycaemic episodes will be analysed separately using a negative binomial regression model with the number of treatment emergent episodes as response, the logarithmic function as link function and the logarithm of the time period in which episodes are considered treatment emergent as offset. The model will include treatment arm as factor and baseline HbA_{1c} as a covariate. The results will be described by the rate ratio for the comparison of Victoza® versus OAD and the associated 95% confidence interval and two-sided p-value.

The hypoglycaemic episodes will also be summarised descriptively in a similar way as the AEs in terms of the number of subjects with at least one event, the percentage of subjects with at least one event, the number of events and the event rate per 1000 patient years of exposure.

Classification of Hypoglycaemia:

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

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

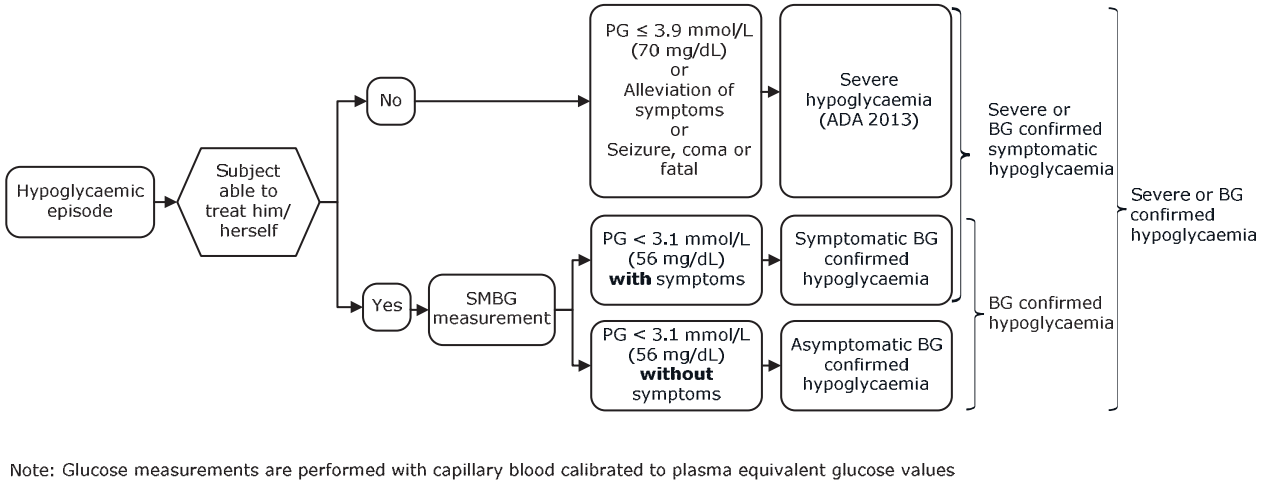
Hypoglycaemic episodes are classified according to the Novo Nordisk classification of hypoglycaemia (see Figure 17–2) and the ADA classification of hypoglycaemia (see Figure 17–3).

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).[21] 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 17–2) in addition to the ADA classification:

- Severe hypoglycaemia according to the ADA classification[22].
- Symptomatic BG confirmed hypoglycaemia: An episode that is BG confirmed by plasma glucose value < 3.1 mmol/L (56 mg/dL) **with** symptoms consistent with hypoglycaemia.
- Asymptomatic BG confirmed hypoglycaemia: An episode that is BG confirmed by plasma glucose value < 3.1 mmol/L (56 mg/dL) **without** symptoms consistent with hypoglycaemia.
- Severe or BG confirmed symptomatic hypoglycaemia: An episode that is severe according to the ADA classification[22] or BG confirmed by a plasma glucose value < 3.1 mmol/L (56 mg/dL) **with** symptoms consistent with hypoglycaemia.
- BG confirmed hypoglycaemia: An episode that is BG confirmed by a plasma glucose value < 3.1 mmol/L (56 mg/dL) **with** or **without** symptoms consistent with hypoglycaemia.
- Severe or BG confirmed hypoglycaemia: An episode that is severe according to the ADA classification[22] or BG confirmed by a plasma glucose value < 3.1 mmol/L (56 mg/dL) **with** or **without** symptoms consistent with hypoglycaemia.



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

Figure 17–2 Novo Nordisk classification of hypoglycaemia

ADA classification[22] 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).

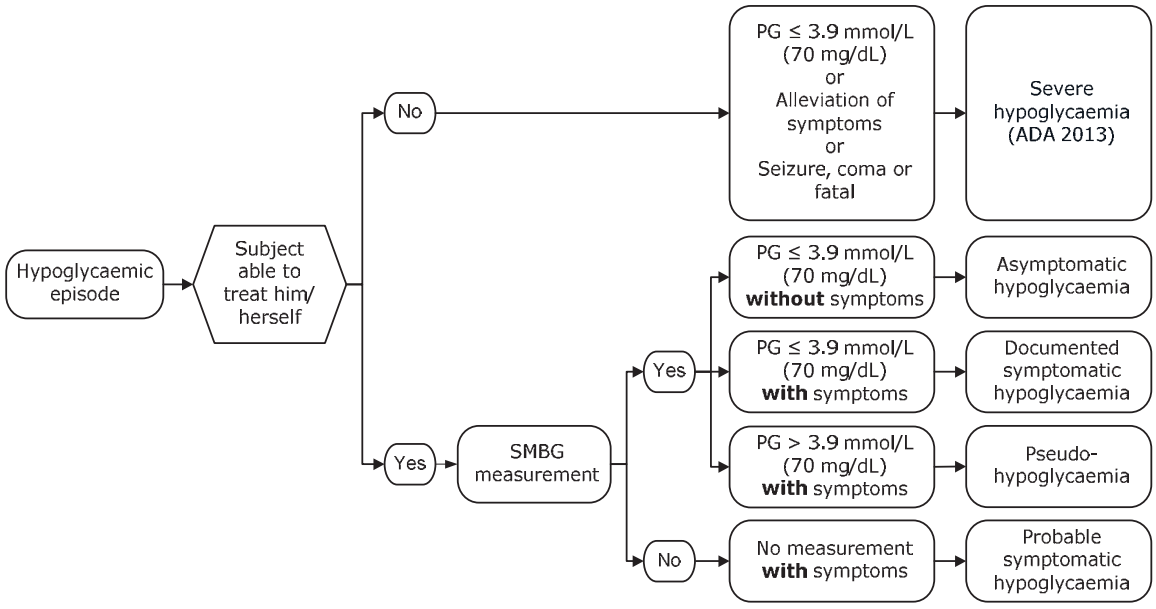


Figure 17–3 ADA classification of hypoglycaemia

Laboratory assessments

Lipids, biochemistry and haematology will be summarised and evaluated by descriptive statistics.

Amylase and lipase will be analysed with the same type of statistical methods as for HbA_{1c} but with the baseline value of the corresponding endpoint as covariate instead of baseline HbA_{1c}. The response as well as the baseline value will be log transformed in the analysis.

eGFR will be derived from serum creatinine using the modification of diet in renal disease (MDRD) formula.

Pulse

Pulse will be summarised descriptively as well as analysed with the same type of statistical methods as for HbA_{1c} but with baseline pulse as covariate instead of baseline HbA_{1c}.

18 Ethics

18.1 Benefit-risk assessment of the trial

The trial will be conducted in compliance with ICH GCP[2] and applicable regulatory requirements, and in accordance with the Declaration of Helsinki[3].

Inclusion and exclusion criteria have been defined in order to ensure that subjects are eligible for trial participation. Furthermore, a withdrawal criterion has been defined to ensure that subjects that in whom glycaemic treatment intensification may be warranted are withdrawn from the trial.

All subjects included in the trial will continue their pre-trial treatment with metformin throughout the trial. During the trial, Victoza® or a marketed OAD will be added. All trial medications have been approved and have shown efficacy in lowering blood glucose levels. It is expected that the majority of subjects entering the trial will achieve an improved glucose control during the trial.

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

Safety information on Victoza® can be found in the approved local label for Victoza®. Safety information of the OADs used in this trial can be found in the approved local label of the individual OAD.

The subjects have the right to withdraw from the trial at any time, without giving a specific reason. Novo Nordisk will be entitled to keep the data collected.

It is concluded that the potential benefits from participating in the trial outweigh the potential risks.

18.2 Informed consent

In seeking and documenting informed consent, the investigator must comply with applicable regulatory requirement(s) and adhere to ICH GCP[2] and the requirements in the Declaration of Helsinki[3].

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. This includes the use of an impartial witness where required according to local requirements.

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.

18.3 Data handling

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

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

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

18.4 Information to subject during trial

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

18.5 Premature termination of the trial and/or trial site

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

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

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

19 Protocol compliance

Deviations from the protocol should be avoided.

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

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

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

20 Audits and inspections

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

21 Critical documents

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

- Regulatory approval and/or acknowledgement of notification as required
- Approval/favourable opinion from IRBs/IECs clearly identifying the documents reviewed as follows: protocol, any protocol amendments, subject information/informed consent form, any other written information to be provided to the subject and subject recruitment materials
- List of IRB/IEC members and/or constitution (or a general assurance number/statement of compliance)
- Curricula vitae of investigator and sub-investigator(s) (current, dated and signed - must include documented GCP training or a certificate)
- Signed receipt of Investigator's brochure (if applicable), signed receipt of Victoza® SmPC or similar labelling (according to local regulations)
- Signed and dated Agreement on Protocol
- Signed and dated agreement on protocol amendment, if applicable
- Contract, signed by the investigator and/or appropriate parties on behalf of the investigator's site and Novo Nordisk
- Source document agreement
- Central laboratory certification and normal ranges
- Insurance statement, if applicable
- Financial disclosure form from investigator and sub-investigator(s)

Only applicable for US trial sites:

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

FDA form 1572:
For US sites

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

For sites outside the US:

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

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

By signing the protocol, each investigator agrees to comply fully with ICH GCP[2], applicable regulatory requirements and the Declaration of Helsinki[3].

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[23].

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. 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.

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[13].

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.

Novo Nordisk will analyse and report data from all sites together. In a multi-centre trial, any publication of results in a journal article must acknowledge all trial sites. 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[23] (sometimes referred to as the Vancouver Criteria).

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

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

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

23.2 Investigator access to data and review of results

As owner of the trial database, Novo Nordisk has the discretion to determine who will have access to the database. Individual investigators will have their own research subjects' data, and will be provided with the randomisation code after results are available.

24 Retention of clinical trial documentation

24.1 Retention of clinical trial documentation

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

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

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

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

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

25 Institutional Review Boards/Independent Ethics Committees and regulatory authorities

IRB/IEC:

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

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

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

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

The investigator must maintain an accurate and complete record of all submissions made to the IRB/IEC. The records must be filed in the investigator 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.

Novo Nordisk accepts liability in accordance with:

Russia: Federal Law of 12 April 2010 No. 61-FZ "On Medicinal Drugs' Circulation" and the Civil Code of the Russian Federation.

27 References

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Global and country key Novo Nordisk staff

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

Content: Global key staff and Country key staff

Protocol Amendment

no 1
to Protocol, final version 1
dated 04 September 2015

Trial ID:NN2211-4232

LIRA-PRIME: Efficacy in controlling glycaemia with Victoza® (liraglutide) as add-on to metformin vs. OADs as add-on to metformin after up to 104 weeks of treatment in subjects with type 2 diabetes inadequately controlled with metformin monotherapy and treated in a primary care setting

Trial phase: 4

Applicable to all countries

Amendment originator:

[redacted]

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1 Introduction including rationale for the protocol amendment

The reason for initiating this protocol amendment is that the current protocol text on drug accountability does not allow the subjects to keep unused and partly used trial product during the trial. In this trial the trial products are handed out by pharmacies or similar. Since some subjects may not be able to collect new trial product from the pharmacy on the same day as they attend a site visit and hand in the trial product that were prescribed at the previous site visit, this means that these subjects may risk being without trial product for one or more days unless the current protocol text on drug accountability is changed. Therefore, the protocol text regarding drug accountability has been revised as described below.

This protocol amendment will include new wordings in order to prevent potential cases of patients using trial products that have exceeded the expiry date. In addition this amendment will include clarifications of the randomisation ratio, sample size calculation and specific statistical analyses in line with suggestions from FDA.
Columbia has been included in the trial after the finalisation date of protocol version 1.0 and therefore country specific issues for Columbia has been added.

Finally, this protocol amendment will include updates and clarifications to wordings that may be confusing in their current form. This includes removal of a sentence in protocol section 6.7, rewording of section 8.2.1, updating figure 12.1 describing the initial reporting of AEs to align this with the remaining text in the protocol and other minor changes.

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 Table of Contents

Attachment II – Country list of key staff and relevant departments

2.2 Section 5.1 Type of trial

Subjects will be randomised *in a 1:1 manner* to one of two treatment arms: Victoza® or OAD.

2.3 Section 6.2 Inclusion criteria

4. Stable daily dose of metformin as monotherapy ≥ 1500 mg or maximum tolerated dose ~~within~~ *for* ≥ 60 days prior to the screening visit.

2.4 Section 6.7 Pre-trial HbA_{1c}

~~Informed consent must be obtained prior to performing any trial related HbA_{1c} measurement.~~

2.5 Section 8.2.1 Concomitant illness and medical history

Procedures and assessments performed at visit 1 and/or 2 are considered screening procedures. The results of these procedures ~~should be~~ *are* considered pre-existing conditions and should be reported as medical history or concomitant illness.

Type 2 diabetes mellitus and diabetes complications present at screening must be reported in the diabetes module. All other ~~R~~*r*elevant concomitant illness/medical history *not* related to diabetes should be ~~transcribed to the eCRF.~~ *entered in the concomitant illness/medical history module.*

2.6 Section 9.1 Trial products

It is the responsibility of the investigator that the patient is instructed in the use of trial drug during the trial and the expected adverse events. *The investigator should remind the subject to be aware of trial product expiration.*

2.7 Section 9.2 Labelling

Applicable for Canada, *Columbia,* India, Latvia, Lebanon and US

2.8 Section 9.4 Drug accountability and destruction

Drug accountability will be performed based on prescribed trial product by *the* investigator. At each visit (except for visit number 3) the ~~I~~*i*nvestigator will prescribe trial product and at the next visit the subject will return to the site used~~, *and* partly used and not used~~ trial products *including empty packaging material* dispensed from the pharmacy. *Subjects are allowed to keep partly used and unused trial products.* At the site it will be documented what was prescribed and what the subject returned to the investigator ~~at the next visit~~.

Through this procedure the investigator can verify that correct trial product has been dispensed.

Subjects are instructed to return all used, partly used and unused trial product including empty packaging material at the latest at their final site visit.

Applicable for Canada, *Columbia,* India, Latvia, Lebanon, Russia, Serbia and Turkey

2.9 Section 12.2 Reporting of adverse events

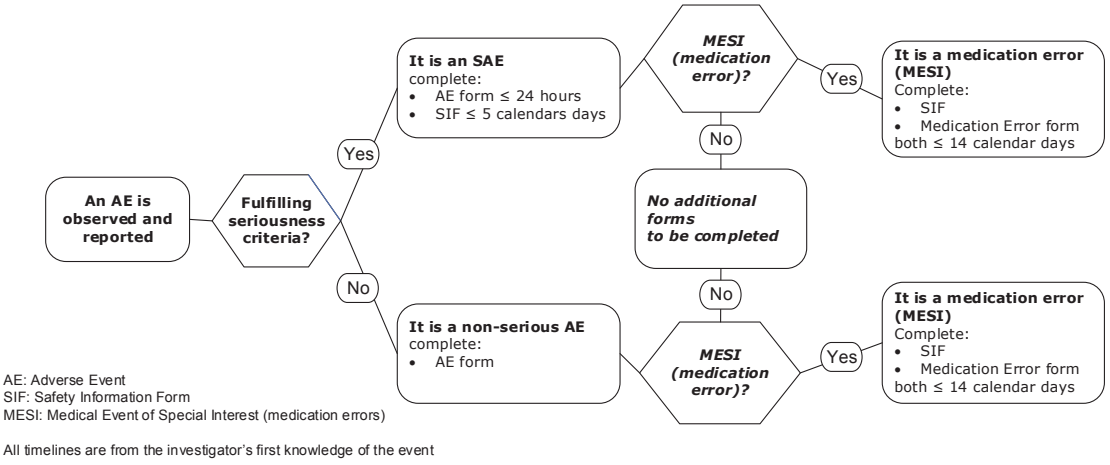
- Company core data sheet (CCDS), Victoza®, 6.0 mg/mL, version 17.0 or any updates thereto
- *Company core data sheet (CCDS) for Novo Nordisk A/S OAD: NovoNorm®/GlucoNorm®, version 13.0 or any updates thereto.*

- Non Novo Nordisk A/S marketed products: European summary of product characteristics or other relevant labelling, current version or any updates thereto.

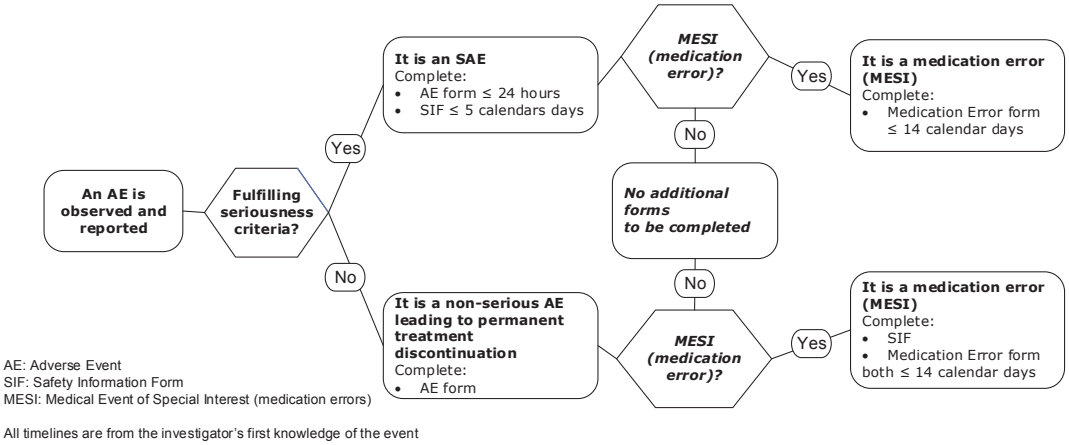
2.10 Section 12.2 Reporting of adverse events

Figure 12.1 Initial reporting of AEs

(Old figure 12.1)



(Updated figure 12.1)



2.11 Section 17.1 Sample size calculation

Based on the assumptions above, the required sample size is found to be 1994 subjects. The anticipated *number* ~~percentage~~ of subjects who have had inadequate glycaemic control after 104 weeks is *526* ~~66%~~ in the Victoza® arm and *606* ~~76%~~ in the OAD arm. *In each arm, 200 subjects are expected to discontinue treatment prematurely without having inadequate glycaemic control*. The number of subjects who complete the trial without premature treatment discontinuation (for any reason including inadequate glycaemic control) is expected to be 462.

2.12 Section 17.2 Definition of analysis sets

FAS: includes all randomised subjects ~~who have received at least one dose and have any post randomisation data~~. The statistical evaluation of the FAS will follow the intention-to-treat principle and subjects will contribute to the evaluation "as randomised".

2.13 Section 17.3 Primary endpoint

The test will be a generalised log rank test for interval censored failure time data[19]. The analysis will not be based on any model assumptions such as proportional hazards *and it will not adjust for any covariates*.

2.14 Section 17.3 Primary endpoint

Subjects who complete the trial without an event of inadequate glycaemic control will be censored after the last visit at 104 weeks, which means that the event time is only observed to be greater than 104 weeks. *If a subject has an HbA_{1c} measurement above 7.0% at the week 26 visit or later but discontinues treatment before the next planned visit, the last observation will be carried forward and the subject will be considered to have had an event of inadequate glycaemic control at the next planned visit. Otherwise, s*~~S~~Subjects who discontinue treatment before 104 weeks without having a~~n~~ *confirmed* event of inadequate glycaemic control will be censored immediately after the last visit which they attended while on treatment. ~~In particular, subjects changing antidiabetic drug after randomisation will be discontinued from the trial and in relation to the primary endpoint be considered as censored and not having had an event of inadequate glycaemic control.~~

Protocol Amendment Local US

no 2
to Protocol, final version 2.0
dated 01 June 2016

Trial ID:NN2211-4232

LIRA-PRIME: Efficacy in controlling glycaemia with Victoza® (liraglutide) as add-on to metformin vs. OADs as add-on to metformin after up to 104 weeks of treatment in subjects with type 2 diabetes inadequately controlled with metformin monotherapy and treated in a primary care setting

Trial phase: 4

Applicable to US only

Amendment originator:

[redacted]

Clinical Trial Management

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1 Introduction including rationale for the protocol amendment

The reason for initiating this protocol amendment is that the current protocol inclusion criteria does not allow for an HbA_{1c} reading to be obtained assessing eligibility prior to screening. Some subjects may not have an HbA_{1c} reading in their charts from within the past 90 days which prevents them from being screened for inclusion into the trial. Therefore, the protocol text regarding timing of HbA_{1c} readings has been revised as described below.

This protocol amendment will include new wordings in order to allow subjects to have an HbA_{1c} reading measured and evaluated prior to screening.

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 6.7 Pre-trial HbA_{1c}

For evaluating whether a subject meets inclusion criterion 5, the requirements for documentation are:

- The most recent available HbA_{1c} obtained by a health care professional and documented in the medical records.
- Only HbA_{1c} measured within the last 90 days prior to the screening visit can be used.

If there is no documented HbA_{1c} value measured within the last 90 days prior to the screening visit available, the investigator may obtain a pre-screening consent from the potential subject and hereafter obtain an HbA_{1c} value, which must be analysed locally. The result must be available and evaluated prior to screening.