Protocol

Study ID: NN8022-4241

In-market utilisation of liraglutide used for weight management in Europe: a retrospective medical record review study

Redacted protocol
Includes redaction of personal identifiable information only.

Non-interventional study

Protocol originator:-
[redacted]

(1) Novo Nordisk – Epidemiology; [redacted]

PASS information

Title	In-market utilisation of liraglutide used for weight management in Europe: a retrospective medical record review study
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Date of last version of protocol	23 November 2015
EU PAS Register number	Study to be registered
Active substance	Liraglutide (ATC code: A10BX07)
Medicinal product	Saxenda® Victoza®
Product reference	
Procedure number	
Marketing authorisation holder(s)	Novo Nordisk
Joint Post Authorisation Safety Study (PASS)	No
Research question and objectives	To investigate in-market utilisation of liraglutide used for weight management: • Use of Saxenda® according to approved indication. • Use of Victoza® for weight management. • Use of Saxenda® according to approved posology.
Country(-ies) of study	Two European Union (EU) countries
Author	[redacted]

Marketing authorisation holder(s)

Marketing authorisation holder (s) (MAH (s))	Novo Nordisk Novo Allé DK-2880 Bagsværd Denmark
MAH contact person	[redacted]

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1 List of abbreviations

ADA	*American Diabetes Association*
BMI	*Body Mass Index*
CPAP	*Continuous Positive Airway Pressure*
CRA	*Clinical Research Associate*
CRF	*Case Report Form*
CRO	*Contract Research Organisation*
CV	*Curriculum Vitae*
DMP	*Data Management Plan*
DUS	*Drug Utilisation Study*
EAS	*Efficacy Analysis Set*
EDC	*Electronic Data Capture*
EMA	*European Medicines Agency*
ENCePP	*European Network of Centres for Pharmacoepidemiology and Pharmacovigilance*
EU	*European Union*
FAS	*Full Analysis Set*
FPG	*Fasting Plasma Glucose*
GLP-1	*Glucagon-Like Peptide-1*
GPP	*Good Pharmacoepidemiological Practice*
GVP	*Good Pharmacovigilance Practice*
HbA1c	*Glycated haemoglobin*
ICMJE	*The International Committee of Medical Journal Editors*
IEC	*Independent Ethics Committee*
IRB	*Institutional Review Board*
ISPE	*International Society for Pharmacoepidemiology*
MAH	*Marketing Authorisation Holder*
OGTT	*Oral Glucose Tolerance Test*
PASS	*Post Authorisation Safety Study*

RMP	*Risk Management Plan*
SAP	*Statistical Analysis Plan*
SmPC	*Summary of Product Characteristics*
T2DM	*Type 2 Diabetes Mellitus*
TLF	*Table, Listing and Figure*
WHO	*World Health Organisation*

2 Responsible parties

Sponsor

The Marketing Authorisation Holder (MAH) will serve as the sponsor of this study. It is the responsibility of the MAH to ensure proper monitoring of the study and compliance with all applicable regulatory guidelines and laws.

Novo Nordisk
Novo Allé
DK-2880 Bagsværd
Denmark

Study Coordination

The MAH has engaged a contract research organisation (CRO) specialising in post-market studies, to provide scientific leadership and to conduct the study. The CRO designed and will conduct the study with review and input from the MAH.

3 Abstract

3.1 Title

In-market utilisation of liraglutide used for weight management in Europe: a retrospective medical record review study (PASS)

Main Authors:
[redacted] Novo Nordisk – Epidemiology
[redacted] – [redacted]

3.2 Rationale and background

As part of the risk management plan (RMP) for Saxenda®, the aim of this study is to investigate usage of liraglutide for weight management in clinical practice.

3.3 Research question and objectives

The aim of this study is to investigate in-market utilisation of liraglutide used for weight management. Specifically, the primary and secondary objectives are to investigate the following:

Primary objective:

To assess the use of Saxenda® according to the approved indication:

Saxenda is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adult patients with an initial Body Mass Index (BMI) of

- ≥ 30 kg/m² (obese), or
- ≥ 27 kg/m² to < 30 kg/m² (overweight) in the presence of at least one weight-related comorbidity such as dysglycaemia (pre-diabetes or type 2 diabetes mellitus), hypertension, dyslipidaemia or obstructive sleep apnoea.

Treatment with Saxenda should be discontinued after 12 weeks on the 3.0 mg/day dose if patients have not lost at least 5% of their initial body weight.

The following endpoints will address the primary objective:

BMI and comorbidities:

- Number of patients with BMI≥30 kg/m^2 (measured less than 6 months before date of first prescription).

- Number of patients with 27 kg/m^2≤BMI<30 kg/m^2 (measured less than 6 months before date of first prescription) and
  - ≥1 relevant comorbidity registered:
    - Dysglycaemia (Type 2 Diabetes Mellitus [T2DM] or prediabetes), hypertension, dyslipidaemia, and/or obstructive sleep apnoea.
  - No relevant comorbidities (described above) registered.
- Number of patients with BMI<27 kg/m^2 (measured less than 6 months before date of first prescription).
- Number of patients with BMI not measured within 6 months before date of first prescription.

Stopping rule:

- Number of patients with at least 5% weight loss (measured 16-24 weeks after first prescription date) and continuing treatment.
- Number of patients with less than 5% weight loss (measured 16-24 weeks after first prescription date) and continuing treatment.
- Mean weight loss (measured 16-24 weeks after first prescription date) in patients not treated according to stopping rule.

Secondary objectives:

1. To assess the use of Victoza® for weight management.
2. To assess the use of Saxenda® according to the approved posology.

The following endpoint will be used to address the first secondary objective:

- Number of patients with Victoza® prescriptions fulfilling at least one of the following criteria:
  - Dose information of 3.0 mg per day, or
  - Indication of weight management.

The following endpoints will be used to address the second secondary objective:

- Adherence to dose escalation according to label:
  - Number of patients who have reached a dose of 3.0 mg within 4-12 weeks after first prescription date.
- Concomitant medication with other GLP-1 receptor agonists:
  - Number of Saxenda® patients with other GLP-1 receptor agonists prescribed during continued treatment with Saxenda® (continued treatment is defined as no gaps between prescriptions of more than 90 days, identified by examining repeat prescription dates).
- Duration of treatment with Saxenda®:
  - Number of patients with a treatment duration of:
    - 0-6, 7-12, 13-18, or 19-24 months, or ongoing (current patients), with continued treatment defined as no gaps between prescriptions of more than 90 days, identified by examining repeat prescription dates.

3.4 Study design

This drug utilisation study (DUS) is a non-interventional, multi-centre post-authorisation safety study (PASS) to investigate the use of Saxenda® and Victoza® in clinical practice in patients who have initiated either treatment in the Saxenda® postmarketing period. The DUS involves retrospective review of patients' medical records in two selected European Union (EU) countries, 24 months after launch of Saxenda® in each of the countries. Physician sites will be selected using several tools, including intelligence databases, e.g., IMS LifeLink™, to obtain a representative sample of prescriptions. A pilot study, which is embedded in the full study, will be conducted 6 months after launch of Saxenda® in each of the two countries, prior to the full DUS. Patients will be treated according to routine clinical practice at the discretion of the treating physician. The study will gather data over the course of routine treatment for Saxenda® and Victoza® treated patients.

3.5 Population

Inclusion criteria:

To be eligible for the study, patients will be required to meet both of the following inclusion criteria:

1. Initiation of Saxenda® or Victoza® (initiation is defined as no prescription of the same brand within the previous 12 months).

2. Informed consent obtained before any study-related activities. Study-related activities are any procedures that are carried out as part of the study, including activities to determine suitability of the study.

Exclusion criteria:

The following exclusion criteria will be applied:

1. Patients or physicians who previously participated in interventional studies for Saxenda® or Victoza® will not be eligible to participate in the study.

2. For the full study, sites and patients included in the pilot will be excluded.

Withdrawal criteria:

The patient may withdraw at will at any time.

3.6 Variables

- **Site characteristics:** geographic location, specialty or area of primary practice, practice type, practice size and patient volume.

- **Patient demographics, medical history and other characteristics:** date of birth, sex, and for Saxenda® patients also body weight and height (and date of anthropometric measurements).

- **Drug utilisation:**

    - Saxenda® or Victoza® patients: brand name, indication prescribed at first prescription, target dose prescribed at first prescription, repeat prescription dates

    - Saxenda® patients only: treatment start and end dates, comorbidities (dysglycaemia i.e. T2DM or prediabetes; hypertension, dyslipidaemia, and/or obstructive sleep apnoea), concomitant medication with other glucagon-like peptide-1 (GLP-1) receptor agonist, dose at 4-12 weeks and 16-24 weeks post initiation of treatment, body weight at 16-24 weeks post initiation of treatment.

    - Victoza® patients only: dose throughout the treatment period.

3.7 Study size

This is a descriptive study designed to examine in-market utilisation of liraglutide; thus there will be no hypothesis testing and a power calculation is not applicable. 100 patients will be enrolled for the pilot study (50 in each country, with 25 patients using Saxenda® and 25 patients using Victoza®) and additionally 300 patients will be enrolled for the full study (150 in each country, with 75 patients using Saxenda® and 75 patients using Victoza®).

3.8 Data analysis

This is a descriptive study that will investigate in-market utilisation of liraglutide. No formal statistical testing will be carried out.

4 Amendments and updates

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason

5 Milestones

Milestone	**Planned date**
Registration in the EU PAS Register	Q4 2016
Start of data collection (pilot)	November 2016
End of data collection (pilot)	August 2017
Pilot study report	November 2017
Start of data collection (full study)	April 2018
End of data collection (full study)	February 2019
Database lock	March 2019
End (or completion) of study	June 2019
Final report of study results	August 2019

This study will be registered prior to first data capture according to Novo Nordisk requirement on non-interventional study disclosure. Only the main study site per country will be disclosed via facility name, city and country on the study registration.

For PASS studies in Europe, the study information should be available in the EU Electronic Register of Post-Authorisation Studies (EU PAS Register) maintained by the European Medicines Agency and accessible through the European medicines web portal.

Note: Study registration is regarded as the publication of an internationally-agreed set of information (which can be found at the World Health Organisation [WHO] homepage) about the design, conduct and administration of clinical trials. These details are published on a publicly-accessible website managed by a registry conforming to WHO standards (also found at the WHO homepage), eg www.clinicaltrials.gov.

6 Rationale and background

Saxenda® and Victoza® are both medicinal products containing the active substance liraglutide. Liraglutide is a long-acting glucagon-like peptide-1 (GLP-1) analogue (incretin mimetic), which has

been shown to reduce hyperglycaemia in patients with type 2 diabetes mellitus (T2DM). The mechanisms of action for liraglutide include stimulation of insulin secretion and decrease of glucagon secretion, both in a physiological and glucose dependent-manner. The effects of liraglutide also include reduced sensation of hunger and increased satiety, leading to decreased food intake and subsequent weight loss.

Victoza® is indicated for the treatment of adults with T2DM at doses of 1.2 mg and 1.8 mg, and received marketing authorisation from the European Medicines Agency (EMA) in June 2009. Saxenda® (liraglutide 3.0 mg) is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adults who are obese, or adults who are overweight with at least one weight-related comorbidity. The efficacy of Saxenda® was demonstrated in five phase 2 and 3 clinical trials involving around 5,800 obese/overweight patients, which showed that more patients administered Saxenda® achieved clinically relevant weight loss than those treated with placebo. Saxenda® received marketing authorisation from the EMA in March 2015.

As defined in the Risk Management Plan (RMP) for Saxenda®, a retrospective drug utilisation study (DUS) to investigate patterns of use of Saxenda® and Victoza® in routine clinical practice has been requested by the EMA as a post marketing requirement. As is the case with any medicinal product, real-world use of Saxenda® or Victoza® may differ from the approved indication or recommendations outlined in the Summary of Product Characteristics (SmPC) (1, 2). Considering that these two liraglutide products with the same strength and formulation will be available for different indications with different doses, there is the potential for inadvertent use of one or the other product for either indication. The DUS will allow assessment of usage patterns of liraglutide for weight management, and thereby could refine pharmacovigilance planning and risk management.

7 Research question and objectives

The aim of this study is to investigate in-market utilisation of liraglutide for weight management. Specifically, the primary and secondary objectives are the following:

7.1 Primary objective

To assess the use of Saxenda® according to the approved indication:

Saxenda is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adult patients with an initial Body Mass Index (BMI) of

- ≥ 30 kg/m² (obese), or

- ≥ 27 kg/m² to < 30 kg/m² (overweight) in the presence of at least one weight-related comorbidity such as dysglycaemia (pre-diabetes or type 2 diabetes mellitus), hypertension, dyslipidaemia or obstructive sleep apnoea.

Treatment with Saxenda should be discontinued after 12 weeks on the 3.0 mg/day dose if patients have not lost at least 5% of their initial body weight.

7.2 Secondary objective(s)

1. To assess the use of Victoza® for weight management.

2. To assess the use of Saxenda® according to the approved posology.

7.3 Endpoints

Primary endpoint:

The following endpoints will address the primary objective (concerning Saxenda® only):

BMI and comorbidities:

- Number of patients with Body Mass Index (BMI)≥30 kg/m^2 (measured less than 6 months before date of first prescription).
- Number of patients with 27 kg/m^2≤BMI<30 kg/m^2 (measured less than 6 months before date of first prescription) and
  - ≥1 relevant comorbidity registered:
    - Dysglycaemia (T2DM or prediabetes), hypertension, dyslipidaemia, and/or obstructive sleep apnoea.
  - No relevant comorbidities (described above) registered.
- Number of patients with BMI<27 kg/m^2 (measured less than 6 months before date of first prescription).
- Number of patients with BMI not measured within 6 months before date of first prescription.

Stopping rule :

- Number of patients with at least 5% weight loss (measured 16-24 weeks after first prescription date) and continuing treatment.
- Number of patients with less than 5% weight loss (measured 16-24 weeks after first prescription date) and continuing treatment.
- Mean weight loss (measured 16-24 weeks after first prescription date) in patients not treated according to stopping rule.

Secondary endpoint:

The following endpoint will be used to address the first secondary objective (concerning Victoza® only):

- Number of patients with Victoza® prescriptions fulfilling at least one of the following criteria:
    1. Dose information of 3.0 mg per day, or
    2. Indication of weight management.

The following endpoints will be used to address the second secondary objective (concerning Saxenda® only):

- Adherence to dose escalation according to label:
    - Number of patients who have reached a dose of 3.0 mg within 4-12 weeks after first prescription date.
- Concomitant medication with of other GLP-1 receptor agonists:
    - Number of Saxenda® patients with other GLP-1 receptor agonists prescribed during continued treatment with Saxenda® (continued treatment is defined as no gaps between prescriptions of more than 90 days, identified by examining repeat prescription dates).
- Duration of treatment with Saxenda®:
    - Number of patients with a treatment duration of:

- 0-6, 7-12, 13-18, or 19-24 months, or ongoing (current patients), with continued treatment defined as no gaps between prescriptions of more than 90 days, identified by examining repeat prescription dates.

8 Research methods

In this document physician refers to the individual overall responsible for the conduct of the non-interventional study at a study site.

8.1 Study design

8.1.1 Type of study

This DUS is a non-interventional, multi-centre Post Authorisation Safety Study (PASS) to investigate the use of Saxenda® and Victoza® in clinical practice in patients who have initiated treatment in the Saxenda® postmarketing period. The DUS involves retrospective review of patients' medical records in two selected European Union (EU) countries 24 months after launch of Saxenda® in each of the countries. Physician sampling will be built using several tools, including intelligence databases, e.g., IMS LifeLink™, in order to obtain a representative sample of Saxenda®/Victoza® prescriptions according to physician specialty and geography. This data source will be complementary to the full study and will be obtained on a quarterly basis, during the study period. It will provide, on a national level for the two targeted countries, the distribution of sites and prescribers' specialty. It will not identify individual prescribers, but rather guide the site selection for the study performed by [redacted]. Therefore, IMS LifeLink™ will be used a priori to refine the sampling strategy (using regional and specialty distribution of prescribers), and a posteriori to assess the representativeness of prescribers and patients, for both the pilot and full study.

A case report form (CRF), including all the desired data elements, will be available to the selected sites; one CRF is to be completed per patient prescribed Saxenda® or Victoza®. The CRF may be completed by a trained healthcare professional at the site, or by a trained external medical record abstractor. The data will be entered pseudonymised into the CRFs.

A pilot study, to be embedded in the full study, will be conducted 6 months after launch of Saxenda® in each of the two countries, i.e., prior to the full DUS. The objective of the pilot study is to evaluate the feasibility of the full DUS. The feasibility will be evaluated on three main parameters:

1. Possibility of identifying physicians prescribing Saxenda®/Victoza® and participating sites

2. Possibility of identifying patients treated with Saxenda® or Victoza®

3. Availability and quality of the variables used to determine the specified endpoints (see section 7.3)

Based on the data obtained in the pilot study, full study refinements may be necessary before the full retrospective medical record review is implemented in the two countries.

The index date, defined as the start date of data abstraction, will be 6 months after the launch of Saxenda® for the pilot, and 24 months after launch for the full study (see Figure 1 for an overview of the study design). The launch date may be different in the two countries. The data will be collected only after informed consent has been obtained from the patients. All study prescribers within a country will be assigned the same index date and will not be contacted prior to it. Initiation of prescriber-specific activities for selection of patient records meeting study selection criteria will commence on or following the index date. Data on drug utilisation will be censored on the index date. This approach will ensure that study procedures do not influence prescribing practices.

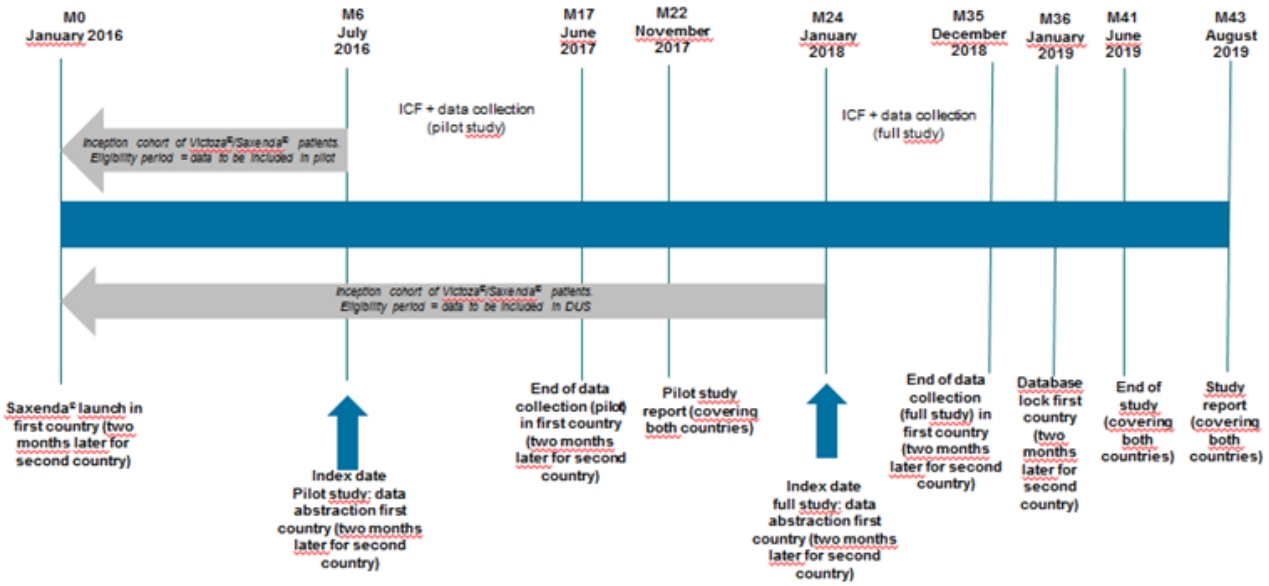

Figure 1 - DUS overview

Notes: The index date (start date of data abstraction) for the pilot study will be 6 months following the launch of Saxenda® in the participating countries; data will be collected on patients from their start date of Saxenda®/Victoza® until the index date for the pilot study. The index date for the full study will be 24 months after the launch of Saxenda®; data will be collected on patients from their start date of Saxenda®/Victoza® until the index date for the full study.
ICF: Informed Consent Form; M: month

8.1.2 Rationale for study design

The study design is in accordance with the study objectives. Being retrospective in design, this study will involve no intervention, and so will not impact usual medical care or affect the treatment of patients. Thus, the study will reflect real-world medical practice without the potential for prescriber response bias which may occur in prospective studies (i.e., the Hawthorne Effect [3]). The full study will not use the same sites and patients as the pilot study in order to account for potential bias, e.g., prescriber response bias, which may be associated with awareness of study objectives following the pilot study. Furthermore, data collection will be initiated following the study-defined abstraction index date. Initiation of selection of patient records meeting study selection criteria will commence on or following this date. Data on drug utilisation will be censored from then and not considered in the analyses. This approach will ensure that study procedures do not influence prescribing practices.

8.1.3 Treatment of patients

Patients will be treated with commercially available Saxenda® or Victoza® according to routine clinical practice at the discretion of the treating physician. Saxenda® and Victoza® both contain the

active substance liraglutide - a long-acting GLP-1 analogue, and are both administered subcutaneously by injection. The approved posology for Saxenda® is a starting dose of 0.6 mg daily, which should be increased to 3.0 mg daily in increments of 0.6 mg with at least one week intervals to improve gastrointestinal tolerability. For Victoza®, the approved posology is a starting dose of 0.6 mg daily, which should be increased to 1.2 mg after at least one week; based on glycaemic response, the daily dose can be increased from 1.2 mg to 1.8 mg after at least one week.

8.2 Setting

Since the purpose of this study is to investigate real-world, in-market utilisation of liraglutide, patients will be identified based on the prescription rather than on a specific diagnosis. The study will target first-time patients of Saxenda® or Victoza® by identifying a representative sample of physicians who treat diabetic or obese patients for whom Saxenda® or Victoza® can be prescribed. These include general practitioners (GPs), endocrinologists and cardiologists (or other diabetes and obesity specialists) from a variety of settings (e.g., office-based vs. hospital-based, urban vs. rural). Once prescribers of Saxenda® or Victoza® are identified, these will be oversampled to ensure adequate numbers of prescribers (and therefore patients).

8.2.1 Number of patients to be studied

Planned number of patients to be included in the entire study is 400. These will be distributed as follows:

- ***Pilot Study***
  - 100 patients: 50 patients prescribed Saxenda® and 50 patients prescribed Victoza®
- ***Full study***
  - 300 patients: 150 patients prescribed Saxenda® and 150 patients prescribed Victoza®

Anticipated number of patients to be included in each of the two selected EU countries:

- Pilot study: 25 patients prescribed Saxenda® and 25 patients prescribed Victoza®
- Full study: 75 patients prescribed Saxenda® and 75 patients prescribed Victoza®

8.2.2 Inclusion criteria

To be eligible for the study, patients will be required to meet both of the following inclusion criteria:

1. Initiation of Saxenda® or Victoza® (initiation is defined as no prescription of the same brand within the previous 12 months).

2. Informed consent obtained before any study-related activities. Study-related activities (e.g. data collection) are any procedures that are carried out as part of the study, including activities to determine suitability of the study.

8.2.3 Exclusion criteria

1. Patients or physicians who previously participated in interventional programs for Saxenda® or Victoza® will not be eligible to participate in the study.

2. For the full study, sites and patients included in the pilot will be excluded.

8.2.4 Withdrawal criteria:

The patient may withdraw at will at any time.

8.2.5 Rationale for selection criteria

The selection of participating sites as well as the inclusion and exclusion criteria applied in this DUS allow for inclusion of a study population as broad as possible. Furthermore, the sampling strategy will be built so as to obtain a representative sample of physicians. Prescribers will be recruited according to setting characteristics, e.g., size of practice (small, medium, large), location (urban, rural), type (academic, non-academic) and reimbursement systems/patterns. In addition, prescribers who participated in interventional programs for Saxenda® or Victoza® will not be eligible to participate in the study. By applying this approach the representativeness and comprehensiveness of the sample in terms of types of prescribers and study population will ensure generalizability of study results to the broad population of subjects being prescribed Saxenda® or Victoza® in clinical practice. Furthermore, the exclusion criteria will limit potential bias related to awareness of the pilot study objectives and to extended knowledge on prescription of and use of Saxenda® and/or Victoza® (i.e., knowledge that goes beyond that obtained through normal clinical practice).

8.2.6 Flowchart

The data collection period for Saxenda®/Victoza® will be the interval between the launch date of Saxenda® to the index date of the pilot or full study, respectively. Table 1 and Table 2 show the data to be collected respectively for Saxenda® and Victoza® patients at different time points in relation to initiation of treatment. Data collection will encompass the following treatment periods for Saxenda®: (1) a time frame of 6 months prior to treatment initiation, (2) treatment initiation, (3) 4-12 weeks post treatment initiation, (4) 16-24 weeks post treatment initiation, and also (5) throughout the entire treatment period. Data collection will encompass the following treatment periods for Victoza®: (1) treatment initiation, and (2) throughout the entire treatment period.

Table 1 - Saxenda® patients[1]

Weeks in relation to initiation of treatment/time of first prescription	Prior to treatment initiation	0	4 – 12 weeks	16 – 24 weeks	Throughout the treatment period[2]
Visit window			+4 weeks	+4 weeks	
Demography[3]		X			
Co-morbidities[4]	X				
Body Weight		X[5]		X[6]	
Adult height	X				
BMI		X[5]			
Brand name		X			
Indication prescribed		X			
Target dose prescribed		X			
Current dose[7]			X	X	
Treatment start date		X			
Treatment stop date					X
Concomitant medication with GLP-1 receptor agonists *(Brand name and start date)*					X

1) Inclusion criteria must be fulfilled (incl. obtained informed consent) before data extraction is performed
2) Censoring at 24 months after launch
3) Sex, age
4) Diagnosis of or treatment of pre-diabetes, type 2 diabetes mellitus (T2DM), hypertension, dyslipidaemia and/or obstructive sleep apnoea.
5) Latest recording within 6 months before first prescription of Saxenda®
6) If not available the earliest subsequent body weight and date of measurement should be recorded
7) If treatment discontinuation occurs prior to/between the specified time points, the dose of Saxenda® at time of treatment discontinuation should be recorded.

Table 2 - Victoza® patients[1]

Weeks in relation to initiation of treatment/time of first prescription	0	Throughout the treatment period[2]
Demography[3]	X	
Brand name	X	
Indication prescribed	X	
Target dose prescribed	X	
Dose-escalation of Victoza® 1.2 or 1.8 mg/day to Victoza® 3.0 mg/day		X

1) Inclusion criteria must be fulfilled (incl. obtained informed consent) before data extraction is performed
2) Censoring at 24 months after launch
3) Sex, age

8.3 Variables

Site characteristics:
To evaluate the representativeness of sites the following information will be collected for each participating site using a site questionnaire:

- Geographic location of physician site
- Specialty of participating physician (e.g., GPs, cardiologists, endocrinologists [or other diabetes and obesity specialists])
- Practice type (e.g., community hospital, academic/medical centre, office based)
- Practice size (number of physicians who practice at site)
- Patient volume (i.e., number of patients and estimated number of patients prescribed Saxenda® or Victoza®).

Additionally, the number of sites invited to participate within each specialty will be collected along with reason for refusal in order to evaluate the response rate and representativeness of the specialty. Sites and physicians will not be identifiable in the study report.

Patient demographics, medical history, and other characteristics:

- Date of birth
- Sex

Body weight (latest recording within 6 months before date of first prescription of Saxenda®), height, BMI (calculated), and date of anthropometric measurements (for Saxenda® patients only)

Drug utilisation:

Saxenda® or Victoza® patients:

- Brand name
- Indication prescribed at treatment initiation
- Target dose prescribed at treatment initiation
- Repeat prescription dates

Saxenda® patients only:

- Treatment start date and end date
- Comorbidities:
    - Dysglycaemia (T2DM or prediabetes), hypertension, dyslipidaemia, and/or obstructive sleep apnoea, before first prescription date. Diagnosis of dysglycaemia or dyslipidaemia may be based on relevant concomitant glucose lowering therapy (ATC code A10) or lipid lowering therapy (ATC code C10), respectively. In addition, diagnosis of dysglycaemia may be in the form of a relevant glycated haemoglobin (HbA1c), Oral Glucose Tolerance Test (OGTT) or fasting plasma glucose (FPG) measurement. According to the American Diabetes Association (ADA), prediabetes and diabetes may be defined based on the following laboratory cut-off values (4):
      Prediabetes:
        - FPG ≥ 100 mg/dL (5.6 mmol/L) and ≤ 125 mg/dL (6.9 mmol/L) and/or
        - 2 hour post-challenge (OGTT) plasma glucose ≥ 140 mg/dL (7.8 mmol/L) and ≤ 199 mg/dL (11.0 mmol/L) and/or
        - HbA1c 5.7-6.4% (both inclusive)

      T2DM:
        - FPG ≥126 mg/dL (7.0 mmol/L) and/or
        - 2 hour post-challenge (during an OGTT) plasma glucose ≥ 200 mg/dL (11.1 mmol/L) and/or
        - HbA1c ≥ 6.5%
    - Diagnosis of obstructive sleep apnoea may be based on treatment with continuous positive airway pressure (CPAP) device.
- Concomitant medication with other GLP-1 receptor agonists (brand name and start date).
- Dose at 4-12 weeks and 16-24 weeks post initiation of treatment
- Body weight at 16-24 weeks post initiation of treatment. If body weight is not available within this interval, the earliest subsequent body weight and date of measurement should be recorded

Victoza® initators only:

- Dose throughout the treatment period

Prescription outside label

Prescription outside label will be categorised as follows:

Saxenda® patients:

- BMI<27 kg/m^2 within 6 months before date of first prescription
- 27 kg/m^2≤BMI<30 kg/m^2 within 6 months before date of first prescription and no relevant comorbidities registered (dysglycaemia [T2DM or prediabetes], hypertension, dyslipidaemia, and/or obstructive sleep apnoea)
- BMI not measured within 6 months before date of first prescription
- Non-adherence to dose escalation according to SmPC (i.e., daily dose of 3.0 mg not reached within 4-12 weeks post initiation of treatment)
- Non-adherence to stopping rule (i.e., less than 5% weight loss after 16-24 weeks on Saxenda® 3.0 mg and still on continued treatment)
- Concomitant medication with other GLP-1 receptor agonists

Victoza® patients:

- Dose of 3.0 mg per day
- Prescribed indication of weight management

8.3.1 Assessments for safety and effectiveness

DUSs are specifically designed to collect information about drug utilisation only. Any relationship between the drug and any adverse events are not within the scientific scope of these studies and therefore will not be collected.

8.3.2 Other assessments

Not Applicable

8.4 Data sources

Retrospective abstraction of data from patient medical records will be performed by trained healthcare professionals or external medical record abstractors. Data for each patient will be recorded in accordance with normal clinical practice and no additional assessments or tests considered as interventional will be required. Data obtained from the pilot study on physician (type of specialty), site (geographic location, practice type, size and patient volume) and patient (using retrospective abstraction of data from patient medical records) representativeness will be the basis for the feasibility assessment of the full DUS.

Concomitant medication with GLP-1 receptor agonists entered into the CRF will be coded using the WHO Drug Reference List.

All data will be entered pseudonymised into the CRF. See section 8.3 for the list of data to be collected; these data will be collected 6 months and 24 months after the launch of Saxenda®, for the pilot and full study, respectively (see Figure 1).

The physician must keep a patient enrolment log and a log of patients evaluated for but not included in the study throughout the enrolment period. The log will include information on the number of patients approached to participate the study, the number of patients who accepted, the number of patients confirmed eligible, the number and reason patients were ineligible, and the number of patients who refused. These data will allow calculation of the participation rate. Each patient signing an informed consent form will be uniquely identified in the study by a patient identification number.

8.5 Study size

This is a descriptive study designed to examine in-market utilisation of Saxenda®/Victoza® and thus no hypothesis testing is planned and power calculations are not applicable. 100 patients will be enrolled for the pilot study, and an additional 300 patients will be enrolled for the full study.

8.6 Data management

A data management plan (DMP) will be created and will describe all functions, processes, and specifications for data collection, cleaning and validation for the DUS. High data quality standards will be maintained and processes and procedures utilized to repeatedly ensure that the data are as clean and accurate as possible when presented for analysis. Data quality will be enhanced through a series of programmed data quality checks that automatically detect out-of-range or anomalous data at the time of data entry.

Data management is the responsibility of [redacted]. Appropriate measures such as encryption or deletion must be enforced to protect the identity of patients in all presentations and publications as required by local/regional/national requirements.

All data captured at sites will be collected and entered directly by a healthcare professional at the site or an external medical record abstractor into the CRFs. Each site will only have access to the patient data entered by the individual site. Appropriate measures such as encryption of data files must be used to assure confidentiality of patient data when it is transmitted over open networks.

8.6.1 Case report forms (CRFs) and rules for completing

All participating sites will have access to the data entered for subjects enrolled at their site. All site staff will be fully trained in CRF completion. Healthcare professionals and/or medical record abstractors will be responsible for entering extracted subject data into a secure web-based EDC database via CRFs. All CRFs should be completed by designated, trained personnel or the study

coordinator or external data abstractor, as appropriate. The CRFs should be reviewed, signed, and dated by the investigator (or designee).

In most cases, the source documents are contained in the subject's medical record and data collected in the CRFs must match the data in the medical records. All original source documentation is expected to be stored at the site for the longest possible time required by local applicable regulations. The site will be instructed to notify the Sponsor before any destruction of medical records of study participants.

By signing the affirmation statement electronically, the physician confirms that the information is complete and correct.

8.6.2 Corrections to CRFs

CRF data can be corrected only by the physician, the physician's authorised staff or an external medical record abstractor. An audit trail will be maintained. If corrections are made by the physician's authorised staff after the date of the physician's signature on the affirmation statement, the statement must be signed again by the physician.

8.6.3 CRF flow

When data is entered, it will be available to Novo Nordisk and/or CRO for data verification activities.

When the final non-interventional study report is available, the data will be archived by Novo Nordisk.

8.7 Data analysis

All data analysis will be performed by [redacted].

As this is a descriptive study that will investigate in-market utilisation of liraglutide, no formal statistical testing will be conducted.

Characteristics of study participants will be reported as mean, standard deviation, median, first and third quartiles and range for continuous variables and as number and proportion of patients with observed (non-missing) data for categorical variables. Study participation will be presented, including number of sites approached for the study and response rate, by specialty, and number of patients approached, response rates, and reasons for refusal. Characteristics of the participating sites and patients will be presented, stratified by country. The data may also be evaluated and presented for other meaningful subgroups of patients (e.g., by sex or age). Comparison between participants and non-participants will be made for sites and patients. Participating and non-participating sites will be compared on geographic location, area of primary practice, practice type, practice size and

patient volume. Comparison of participating patients and the total population of patients treated with Saxenda® or Victoza® will be made, subject to data availability.

8.7.1 Evaluability of patients for analysis

The full analysis set (FAS), including all recruited patients, will be analysed in the study.

8.7.2 Statistical methods

Details of the data analyses, along with table, listing and figure (TLF) templates, will be fully described in a Statistical Analysis Plan (SAP).

In brief, the descriptive analyses will present Saxenda® and Victoza® utilisation by indication. Results will be evaluated by site characteristics, including country and geographic region within country, to ascertain any patterns of prescribing by specific indication. The main analysis will be to estimate the proportion of prescriptions outside label among Saxenda® or Victoza® patients during the entire study period in the countries of interest. The proportion of each of the forms of prescription outside label will be described (see section on prescription outside label). Characteristics of patients prescribed Saxenda® or Victoza® according to the respective approved SmPCs will also be evaluated.

Analyses on the following will be conducted:

Site characteristics

Descriptive statistics will be provided for the following variables:

- Geographic location of physician site (number and proportion)
- Specialty or area of primary practice (e.g. GPs, cardiologists, endocrinologists (or other diabetes and obesity specialists), etc.) (number and proportion)
- Practice type (e.g. community hospital, academic/medical centre, office based, etc.) (number and proportion)
- Number of physicians who practice at site (mean, standard deviation, median, first and third quartiles and range)
- Patient volume (i.e. number of patients and estimated number of patients using Victoza® or Saxenda®) (mean, standard deviation, median, first and third quartiles and range)

Patient demographics, medical history, and other characteristics:
Descriptive statistics will be provided for the following variables:

- Age (mean and standard deviation; number and proportion for age categories)
- Sex (number and proportion)

Drug utilisation:

Descriptive statistics will be provided for the following variables:

Saxenda® or Victoza® patients:

- Brand name (number and proportion)
- Indication prescribed at treatment initiation (number and proportion)
- Target dose prescribed at treatment initiation (number and proportion for target dose categories: 3.0 mg/day (for Saxenda® patients) and 1.2 mg/day, 1.8 mg/day or 3.0 mg/day (for Victoza® patients)

Saxenda® patients only:

- Comorbidities:
  - Dysglycaemia (T2DM or prediabetes), hypertension, dyslipidaemia, and/or obstructive sleep apnoea (number and proportion)
- Dose at 4-12 weeks and 16-24 weeks post initiation of treatment (mean, standard deviation)
- Duration of treatment (or ongoing treatment) (mean, standard deviation, median, first and third quartiles and range; number and proportion for treatment completion: completed treatment or ongoing treatment)

Victoza® patients only:

- Increase in Victoza® dose to 3.0 mg/day (number and proportion)
- Prescription of Victoza® for weight management (number and proportion)

Prescription outside label:

Descriptive statistics for the following:

Saxenda® patients:

- BMI<27 kg/m^2 (number and proportion)
- 27 $kg/m^2 \leq$BMI<30 kg/m^2 and no relevant comorbidities registered (dysglycaemia (T2DM or prediabetes), hypertension, dyslipidaemia, and/or obstructive sleep apnoea) (number and proportion)
- BMI not measured within 6 months before date of first prescription (number and proportion)
- Non-adherence to dose escalation according to label (i.e., 3.0 mg not reached within 4-12 weeks after date of first prescription) (number and proportion)
- Non-adherence to stopping rule (i.e., less than 5% weight loss after 16-24 weeks on Saxenda® 3.0 mg and still on continued treatment) (number and proportion)

- Concomitant medication with other GLP-1 receptor agonists (brand name) (number and proportion)

Victoza® patients:

- Dose information of 3.0 mg per day (number and proportion)
- Prescribed indication of weight management (number and proportion)

All analyses will be performed using SAS 9.2 (or higher) statistical software (SAS Institute Inc., Cary, North Carolina, USA). Programs, logs, and output will be reviewed for accuracy according to relevant standard operating procedures.

8.7.3 Interim analysis

At the end of the pilot study a qualitative pilot study report will be provided to assess the feasibility of the full study. This will include assessment of the number of Saxenda® prescriptions identified, taking into account the uptake of Saxenda® in the specific country. The availability and quality of the data collected in the pilot for some of the specified endpoints is likely to be limited, especially for adherence to dose escalation, duration of treatment, and adherence to stopping rule. Based on the feasibility assessment, a recommendation will be made on continuation of the study or, if relevant, alternative approaches.

Data on the following endpoints will be captured in the pilot study:

Primary endpoint:

The following endpoints will address the primary objective (concerning Saxenda® only):

BMI and comorbidities:

- Number of patients with BMI≥30 kg/m^2 (measured less than 6 months before date of first prescription)
- Number of patients with 27 kg/m^2≤BMI<30 kg/m^2 (measured less than 6 months before date of first prescription) and
  - >=1 relevant comorbidity registered:
    - Dysglycaemia (T2DM or prediabetes), hypertension, dyslipidaemia, and/or obstructive sleep apnoea.
  - No relevant comorbidities (described above) registered

- Number of patients with BMI<27 kg/m^2 (measured less than 6 months before date of first prescription)
- Number of patients with BMI not measured within 6 months before date of first prescription.

Stopping rule:

- Number of patients with at least 5% weight loss (measured 16-24 weeks after first prescription date) and continuing treatment
- Number of patients with less than 5% weight loss (measured 16-24 weeks after first prescription date) and continuing treatment
- Mean weight loss (measured 16-24 weeks after first prescription date) in patients not treated according to stopping rule.

Secondary endpoint

The following endpoint will be used to address the first secondary objective (concerning Victoza® only):

- Number of patients with Victoza® prescriptions fulfilling at least one of the following criteria:
    - Dose information of 3.0 mg per day, or
    - Indication of weight management.

The following endpoints will be used to address the second secondary objective (concerning Saxenda® only):

- Adherence to dose escalation according to label:
    - Number of patients who have reached a dose of 3.0 mg within 12 weeks after first prescription date
- Concomitant medication use of other GLP-1 receptor agonists:
    - Number of Saxenda® patients with other GLP-1 receptor agonists prescribed during continued treatment with Saxenda® (continued treatment is defined as no gaps between prescriptions of more than 90 days, identified by examining repeat prescription dates)
- Duration of treatment with Saxenda®:

- Number of patients with a treatment duration of:
    - 0-3, 4-6 months, or ongoing (current patients), with continued treatment defined as no gaps between prescriptions of more than 90 days, identified by examining repeat prescription dates.

8.7.4 Sequential safety analysis/safety monitoring

Not Applicable.

8.7.5 Health economics and/or patients reported outcome

Not Applicable.

8.8 Quality control

This study will be outsourced to a CRO, selected in accordance with Novo Nordisk standard operating procedures (SOPs). The study will be performed by the CRO, with guidance, input, review and approval of Novo Nordisk, including development of materials, recruitment, training and management of sites, site monitoring, EDC and data management and analysis.

8.8.1 Monitoring procedures

During the site initiation visit, the monitor will provide training on the conduct of the study to the physician, and all site staff involved in the study. To ensure the integrity of the data, sites will be monitored by a trained monitor. A risk based monitoring approach will be conducted during the study involving remote data monitoring and ad hoc on site monitoring that will be performed to examine compliance with the protocol and adherence to the data collection procedures, to assess the accuracy and completeness of submitted data, and to verify that records and documents are being properly maintained for the duration of the study. The monitor will perform source data verification by review of original patient records. The physician will allow the monitor to have direct access to appropriate parts of patients' medical records relating to their participation in this study, for the purpose of verifying the data submitted by the site.

The monitor will close out each site after the last patient's data collection is completed, all data have been entered in the CRF and all outstanding monitoring issues have been resolved or addressed.

Representatives of Novo Nordisk and Competent Authorities must be permitted to audit/inspect all study-related documents and other materials at the site, including the Investigator Site File, the completed CRFs and the patients' original medical records. Audits/inspections may be conducted at any time during or after the study to ensure the validity and integrity of the study data.

8.8.2 Critical documents

Before the physician starts the study (i.e., obtains informed consent from the first patient), the following documents must be available at Novo Nordisk:

- Regulatory approval and/or notification as required
- Documentation of the physician's qualifications as medically qualified (for instance a short CV or authorisation), in addition to qualification documentation of other site staff involved in study conduct
- Signed and dated agreement on the final protocol
- Approval/favourable opinion from Independent Ethics Committee (IEC) (or other appropriate bodies if required locally) clearly identifying the documents reviewed: the protocol, any amendments, patient information/informed consent form and any other written information to be provided to the patient, patient enrolment procedures
- Copy of IEC approved patient information/informed consent form/any other written information/advertisement
- Non-interventional study agreement.

8.8.3 Retention of study documentation

Novo Nordisk will comply with all the requirements of Good Pharmacoepidemiological Practice (GPP) and relevant national legislation related to archiving of study documentation. Records containing patient sensitive data must not be archived by Novo Nordisk, but must be kept with physician and patient and according to local regulations pertaining to personal data protection.

The physician must agree to archive the documentation pertaining to the study in an archive after completion or discontinuation of the study, if not otherwise notified. The physician should not destroy any documents without prior permission from Novo Nordisk.

Novo Nordisk will retain the documentation pertaining to the study according to company procedure and in accordance with national regulations if they require a longer retention period.

8.9 Limitations of the research methods

As this is a non-interventional study, potential bias cannot be ruled out.
Data collection will reflect routine clinical practice rather than mandatory assessments at pre-specified time points, which may have an impact on the amount of data available and its interpretation.

Biases

Selection bias

In order to minimize selection bias, the sampling strategy that was designed for the proposed study, will truly reflect real-life clinical practice since it will capture all possible treatment settings. In addition, selection bias due to sampling and participation will be addressed by comparing selected characteristics of the study patients and prescribers with those recorded in an external national database (IMSLifeLink).

Information bias

At the prescriber (site) level, information bias is mitigated by the retrospective design. This study involves no intervention and treatment of patients considered eligible and their medical records at a site have been completed prior to the country-specific index date. Thus, the knowledge about this study (and its conduct) will not have had impact on the standard medical care and Saxenda® or Victoza® prescription practices at a site and will not have affected the treatment of patients. Data collected from medical records will therefore reflect real world medical practice.

At the patient level, misclassification of drug exposure has to be considered. Medical records provide detailed information on prescribed and/or dispensed medications but may not contain information on the intended duration of use (days of supply) and often do not contain information on the actual use of the medications by the patient. Thus, patients may be classified as exposed to a drug although they actually have not taken the drug. For this reason, great care will be taken to ensure the quality of the information that is abstracted, and prescribers' follow-up by clinical research associates (CRAs) will be enforced.

Missing Data

Some limitations with regard to data completeness may occur in this study, mainly related to the information captured in the patients' medical records. Measures to ensure the completion of the CRF is conducted in a systematic, professional, and unbiased manner include:

- CRF completion guidelines will provide consistent instructions on completion of the CRF.

- All individuals performing data abstraction from medical records will be trained on appropriate data abstraction techniques in order to minimize possible discrepancies between interpretation of the information recorded by the prescriber in the medical records and the individual performing the review and abstraction of the data.

- Missing data will be followed up on during remote monitoring contacts.

It is important to capture information on drug use from the start to end of treatment in order to fully assess drug utilisation. However, given the journey of patients with obesity or diabetes - these patients may be treated by several different specialist physicians - complete information over the 24 months of retrospective follow up may not be accessible by the site. For example, for patients whose treatment was initiated in settings other than the study site, there may be a lack of data on treatment initiation (e.g., brand name, start date, prescribed indication and target dose), which are required to fully evaluate drug utilisation. This is a potential limitation inherent of retrospective study designs. In this DUS, every effort will be made - as far as is possible - to obtain data from all relevant healthcare practices in order to capture the journey of patients as fully as possible.

8.10 Other aspects

None

9 Protection of human subjects

To ensure the quality and integrity of research, this study will be conducted in accordance with the International Society for Pharmacoepidemiology guidelines for GPP (International Society for Pharmacoepidemiology [ISPE] 2007) (5) and in accordance with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (ENCePP 2014) (6). The ENCePP Checklist for Study Protocols (ENCePP 2011), see Annex 2, will be completed, and the study will be registered in the ENCePP study registry (ENCePP 2010).

This PASS study will comply with the definition of the non-interventional (observational) study provided in Directive 2010/84/EU and the 2013 Guideline on (GVP: Module VIII – Post-Authorisation Safety Studies (EMA 2013) (7). The study will comply with the nature of non-interventional (observational) studies referred to in the International Conference on Harmonisation (ICH) harmonised tripartite guideline, Pharmacovigilance Planning - E2E (ICH 2004).

9.1 Informed consent form for study patients

Informed consent from all study participants is required.

In obtaining and documenting informed consent, the physician must comply with the applicable regulatory requirement(s) and adhere to the requirements in the Declaration of Helsinki (8).

Prior to any study-related activity, the physician must give the patient both oral and written information about the study in a form that the patient can read and understand. This includes the use of impartial witness where required.

A voluntary, signed and personally dated, informed consent form will be obtained from the patient prior to any study-related activity. Consent can be obtained both onsite during a visit or remotely. In

that latter, the physician will send two copies of the Informed Consent Form (ICF) to the patient's house who will sign both, keep one and send back the other in a pre-stamped envelope to the physician.

The task of seeking informed consent can only be performed by the physician or another medically qualified person delegated by the physician, if permitted by local regulation, who must sign and date the patient information/informed consent form. If information becomes available that may be relevant to the patient's willingness to continue participating in the study, the physician must inform the patient in a timely manner and a revised written informed consent must be obtained.

9.2 Data handling

If the patient withdraws the previously given informed consent, the patient's data will be handled as follows:

- Data collected will be used as part of the statistical analysis.

9.3 Institutional Review Boards (IRBs)/Independent Ethics Committee (IEC)

Before commencement of the study, the protocol, any amendments, patient information/informed consent form, any other written information to be provided to the patient, patient enrolment procedures, if any, the physician's current CV and/or other documentation evidencing qualifications and other documents as required by the local IRB/IEC should be submitted. The submission letter should clearly identify (by study identification number, including version, title and/or date of the document) which documents have been submitted to the IRB/IEC. Written approval/favourable opinion must be obtained from IRB/IEC before commencement of the study.

During the study, the physician must promptly in accordance with local requirements report the following to the IRB/IEC: amendments to the protocol according to local requirements, annually written summaries of the study status and other documents as required by the local IRB/IEC. Unexpected serious adverse reactions should be reported according to local regulatory requirements and will not be collected in this study.

Amendments must not be implemented before approval/favourable opinion, unless necessary to eliminate immediate hazards to the patients.

The physician must maintain an accurate and complete record of all submissions made to the IRB/IEC. The records should be filed in the physician's study file and copies must be sent to Novo Nordisk or CRO.

9.4 Regulatory authorities

Regulatory authorities will receive the non-interventional study application, amendments to the protocol and the non-interventional study report according to national requirements.

9.5 Premature termination of the study

The sponsor, physician or a pertinent regulatory authority may decide to stop the study or part of the study at any time, but agreement on procedures to be followed must be obtained.

If a study is prematurely terminated or suspended, the physician and/or sponsor should promptly inform the IEC/IRB and provide a detailed written explanation. The pertinent regulatory authorities should be informed according to national regulations.

9.6 Responsibilities

The physician is accountable for the conduct of the study. If any tasks are delegated, the physician should maintain a list of appropriately qualified persons to whom he/she has delegated specified significant study-related duties.

The physician must follow the instructions from Novo Nordisk or the CRO when processing data.

The physician must take all necessary technical and organisational safety measures to prevent accidental or wrongful destruction, loss or deterioration of data. The physician must prevent any unauthorised access to data or any other processing of data against applicable law.

Upon request from Novo Nordisk or the CRO, the physician must provide Novo Nordisk/CRO with the necessary information to enable Novo Nordisk to ensure that such technical and organisational safety measures have been taken.

9.7 Indemnity statement

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

Novo Nordisk assumes no liability in the event of negligence or any other liability by the clinics or doctors conducting experiments or by persons for whom the said clinic or doctors are responsible.

10 Reporting of safety information

DUS are specifically designed to collect information about drug utilisation only. No safety information will be collected or reported.

11 Plans for disseminating and communicating study results

A pilot study report will be generated after data collection is complete for the pilot study. A final study report will be generated after data collection is complete for the full DUS and will be

submitted to the competent authorities within 6 months upon study completion. Both reports will be prepared by [redacted].

The information obtained during the conduct of this study is considered confidential and can be used by Novo Nordisk for regulatory purposes and for the safety surveillance of the study product. All information supplied by Novo Nordisk in connection with this study must remain the sole property of Novo Nordisk and is to be considered confidential information. No confidential information must be disclosed to others without prior written consent from Novo Nordisk. Such information must not be used except in the performance of this study. The information obtained during this study may be made available to other physicians who are conducting other studies with the study product, if deemed necessary by Novo Nordisk.

11.1 Communication and publication

No permission to publish must be granted to any CRO involved in the study described in this protocol.

Novo Nordisk commits to communicating or otherwise making available for public disclosure results of studies 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 by other means.

Novo Nordisk reserves the right not to release data until specified milestones, e.g. a non-interventional study report is available. This includes the right not to release interim results from non-interventional studies, because such results may lead to conclusions that are later shown to be incorrect.

At the end of the study, one or more public disclosures for publication may be prepared collaboratively by physician(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 study will be subject to public disclosure on external web sites according to international regulations, as reflected in the Novo Nordisk Code of Conduct for Clinical Trial Disclosure.

In a multi-centre study based on the collaboration of all study sites, any publication of results in a journal article must acknowledge all study sites. Where required by the journal, the physician from each site will be named in the acknowledgement.

11.2 Authorship

Authorship of publications should be in accordance with guidelines from The International Committee of Medical Journal Editors' Uniform Requirements (sometimes referred to as the Vancouver Criteria) (9).

11.3 Publications

The physician must ensure submission of the results of the study (either abstract or full study report) to IEC (or other appropriate bodies as required locally) if the protocol or protocol abstract was submitted to any of these.

In accordance with Novo Nordisk commitment to transparency on our clinical trial activities this study will be registered by Novo Nordisk at www.clinicaltrials.gov and www.novonordisk-trials.com in accordance with Novo Nordisk Clinical Trials Disclosure Code of Conduct.

For PASS studies in Europe, the study information should be available in the EU PAS Register (see section 5).

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

11.3.1 Site-specific publication(s) by physician(s)

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

Novo Nordisk reserves the right to prior review of such publication and to ask for deferment of publication of individual site results until after the primary manuscript is accepted for publication.

11.4 Physician access to data and review of results

As owners of the study database, Novo Nordisk has discretion to determine who will have access to the database. Generally, study databases are only made available to regulatory authorities.

12 References

1. Novo Nordisk. Victoza® (Summary of Product Characteristics). Denmark, December 2014.
2. Novo Nordisk. Saxenda® (Summary of Product Characteristics). Denmark.
3. Mangione-Smith R, Elliott MN, McDonald L, McGlynn EA. An observational study of antibiotic prescribing behavior and the Hawthorne effect. Health Serv Res 2002;37(6):1603-23.
4. American Diabetes Association. Standards of Medical Care in Diabetes-2015. Diabetes Care 2015;38(1).

5. International Society for Pharmacoepidemiology (ISPE). Guidelines for Good Pharmacoepidemiology Practices (GPP). Initially issued: 1996. Revision 2, April, 2007.
6. EMA/95098/2010 Rev 3, July 2014 - The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Guide on Methodological Standards in Pharmacoepidemiology.
7. EMA/813938/2011 Rev 1, 19 April 2013 - GVP Module VIII: Post-authorization safety studies (together with EMA/395730/2012 Rev 1, 19 April 2013 - Annex: Member States' requirements for transmission of information on non-interventional post authorization safety studies).
8. World Medical Association (WMA) Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. 64th WMA General Assembly, Brazil, October 2013.
9. International Committee of Medical Journal Editors (ICMJE). Uniform Requirements for Manuscripts Submitted to Biomedical Journals (current official version available at www.ICMJE.org).

ANNEX 1. List of Stand-alone Documents

There are no stand-alone documents.

ANNEX 2. ENCePP Checklist for Study Protocols

ENCePP Checklist for Study Protocols

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:

In-market utilisation of liraglutide used for weight management in Europe: a retrospective medical record review study

Study reference number:

[The EU PAS registry number will be added after registration]

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	14
1.1.2 End of data collection[2]	☒	☐	☐	14
1.1.3 Study progress report(s)	☐	☒	☐	
1.1.4 Interim progress report(s)	☒	☐	☐	14
1.1.5 Registration in the EU PAS register	☒	☐	☐	14
1.1.6 Final report of study results.	☒	☐	☐	14

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an				

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	15
2.1.2 The objective(s) of the study?	☒	☐	☐	15-16
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	21
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

2.1.4 and 2.1.5: This is a descriptive drug utilisation study therefore there are no formal hypotheses to be tested.

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	18-21
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	16-18
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	

Comments:

3.3: Not applicable in this descriptive study.

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	21
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	18
4.2.2 Age and sex?	☐	☐	☒	
4.2.3 Country of origin?	☒	☐	☐	18
4.2.4 Disease/indication?	☒	☐	☐	16
4.2.5 Co-morbidity?	☒	☐	☐	16
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	21-22

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	22
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the	☐	☐	☒	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
drug?				
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

5.2, 5.3, 5.4 and 5.5: not applicable for this study design.

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	16-18
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☐	☒	
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	

Comments:

7.1 and 7.2: This analysis is descriptive in nature and therefore confounders and effect modifiers are not explicitly identified or addressed.

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	26-27
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	26-27
8.1.3 Covariates?	☒	☐	☐	26-27
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	24-26
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	24-26
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	24-26
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☒	☐	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities(MedDRA) for adverse events)	☐	☒	☐	
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☐	☐	☒	

Comments:

9.1: Not applicable in this descriptive study.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	29-31
10.3 Are descriptive analyses included?	☒	☐	☐	29-31
10.4 Are stratified analyses included?	☒	☐	☐	28
10.5 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:

10.2: Analyses will only include descriptive measures, in accordance with the study objectives. 10.5 and 10.6: This study is descriptive and therefore there are no plans for adjusting for confounding or effect modification.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	35

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	34
11.3 Are methods of quality assurance described?	☒	☐	☐	33
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	33
11.5 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	35
12.1.2 Information biases?	☒	☐	☐	35
(e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)				
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☒	☐	
12.3 Does the protocol address other limitations?	☒	☐	☐	34-36

Comments:

12.2: A pilot study will be conducted prior to the full study to assess study feasibility.

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	37-38
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	36

Comments:

13.2: The study has not yet been reviewed by an ethical review committee.

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	13

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	39-40
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	39-40

Comments:

Name of the main author of the protocol: [redacted]

Date: 23 November 2015

Signature: [redacted]

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