Protocol

Study ID: NN8022-4246

In market utilisation of liraglutide used for weight management in the UK: a study in the CPRD primary care database

Redacted protocol
Includes redaction of personal identifiable information only.

Non-interventional study

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PASS information

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Procedure number	
Marketing authorisation holder(s)	Novo Nordisk A/S
Joint Post Authorisation Safety Study (PASS)	No
Research question and objectives	Drug utilisation study to investigate in market utilisation of liraglutide when used for weight management
Country of study	UK
Authors	[redacted], Novo Nordisk [redacted], CPRD

Marketing authorisation holder(s)

Marketing authorisation holder (s) (MAH (s))	Novo Nordisk A/S Novo Allé DK-2880 Bagsværd Denmark
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List of abbreviations

BMI	Body mass index
CPRD	Clinical Practice Research Datalink
DUS	Drug utilisation study
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
GLP-1	Glucagon-like peptide 1
GP	General practitioner
GPP	Good Pharmacoepidemiological Practice
GPRD	General Practice Research Database
ICMJE	The International Committee of Medical Journal Editors
ISAC	Independent Scientific Advisory Committee
NRES	National Research Ethics Service Committee
PASS	Post Authorisation Safety Study
PRAC	Pharmacovigilance Risk Assessment Committee
T2DM	Type 2 diabetes mellitus

1 Responsible parties

Novo Nordisk A/S is the marketing authorisation holder for Saxenda®.

2 Abstract

2.1 Title

In market utilisation of liraglutide used for weight management in the UK: a study in the Clinical Practice Research Datalink (CPRD) primary care database (PASS).

2.2 Rationale and background

As part of the risk management plan for Saxenda®, the aim of this study is to investigate usage of liraglutide for weight management in clinical practice using the CPRD primary care database.

2.3 Research question and objectives

This will be a descriptive drug utilisation study (DUS) to investigate in market utilisation of liraglutide used for weight management, more specifically:

2.3.1 Primary objective

Use of Saxenda® according to 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/m2 (measured less than 6 months before time of first prescription (index date)

- Number of patients with 27 kg/m2<=BMI<30 kg/m2 (measured less than 6 months before time of first prescription (index date) and

    - >=1 relevant comorbidity:
      Dysglycaemia (diabetes mellitus type 2 or prediabetes), hypertension, dyslipidaemia, and/or obstructive sleep apnoea, or

    - none of the above relevant comorbidities

- Number of patients with BMI<27 kg/m2 (measured less than 6 months before time of first prescription (index date)

- Number of patients with BMI not measured within 6 months before index date

Stopping rule :

- Number of patients with at least 5% weight loss (measured 16-24 weeks after index date) and continuing treatment

- Number of patients with less than 5% weight loss (measured 16-24 weeks after index date) and continuing treatment

- Mean weight loss (measured 16-24 weeks after start date of treatment) in patients not treated according to stopping rule.

2.3.2 Secondary objectives

1. Use of Victoza® for weight management

2. Use of Saxenda® according to approved posology

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

Number of patients with Victoza® prescriptions fulfilling at least one of the following criteria:

- at a prescription interval corresponding to a daily dose of 3.0 mg,

- with dose information of 3.0 mg per day, or

- with indication 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 3.0 mg within 4-12 weeks after index date

Concomitant medication with other GLP-1 receptor agonists:

- Number of Saxenda® initiators with other GLP-1 receptor agonists prescribed during continued treatment with Saxenda® (continued treatment is defined as no gaps of more than 30 days between assumed prescription end and the subsequent prescription date).

Concomitant medication with other products for weight management:

- Number of Saxenda® initiators with other products for weight management prescribed during continued treatment with Saxenda (continued treatment is defined as no gaps of more than 30 days between assumed prescription end and the subsequent prescription date).

Duration of treatment with Saxenda® (continued treatment as defined above):

- Number of patients with a treatment duration of:

  0-6, 7-12, 13-18, or 19-24 months, or ongoing (current users).

2.4 Study design

This is a non-interventional descriptive drug utilisation study (PASS) to investigate the use of liraglutide for weight management in patients with newly initiated treatment, using the CPRD primary care database in the United Kingdom (UK). Patients will be treated with commercially available Saxenda® or Victoza® according to routine clinical practice at the discretion of the treating physician.

2.5 Population

Patients in the CPRD primary care database who have been prescribed liraglutide after the UK launch of Saxenda® (and have no liraglutide prescriptions in the previous 12 months).

2.6 Variables

- Patient demographics and other characteristics: year of birth, gender, and for Saxenda® patients also body weight and height (with date of 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: comorbidities (dysglycaemia (diabetes mellitus type 2 or prediabetes), hypertension, dyslipidaemia, and/or obstructive sleep apnoea), dose at 4-12 weeks and 16-24 weeks after first prescription, body weight at 16-24 weeks after first

prescription, concomitant medication with other GLP-1 receptor agonists or with other products for weight management.
- Victoza® patients only: dose throughout the treatment period.

2.7 Data sources

CPRD primary care database, supplemented with information from GP questionnaires.

2.8 Study size

Formal sample size calculation not applicable (descriptive study), aim is to include 200-300 patients.

2.9 Data analysis

Descriptive statistics will be reported.

2.10 Milestones

See section 4 below.

3 Amendments and updates

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
N/A				

4 Milestones

Estimated timelines (from launch of Saxenda® in the UK):

Milestone	**Planned date**
Interim analysis	June 2018
Final analysis (to allow for accrual of data, questionnaires to be sent post 24 months)	March 2019
Final report of study results	September 2019

This study will be registered prior to first data capture according to Novo Nordisk requirement on non-interventional study disclosure. 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**.**

5 Rationale and background

Victoza® and Saxenda® are both medicinal products containing the active substance liraglutide. Liraglutide is a long-acting glucagon-like peptide 1 (GLP-1) analogue (incretin mimetic) that has been found to have benefits on glucose metabolism and appetite regulation (1). The mechanisms of action for liraglutide include stimulation of insulin secretion and inhibition of glucagon secretion, in a physiological and glucose dependent-manner. Furthermore, liraglutide has been found to induce reduced sensation of hunger and increased satiety, leading to decreased food intake and subsequent weight loss (1).

Victoza® is indicated for the treatment of adults with type 2 diabetes mellitus (T2DM), and received marketing authorisation from the EMA in June 2009. Saxenda® 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 (such as dysglycaemia, hypertension,dyslipidaemia, or obstructive sleep apnoea). The efficacy of Saxenda® was demonstrated in five phase 2 and 3 clinical trials involving around 5,800 obese/overweight patients, which found that more patients administered Saxenda® achieved clinically relevant weight loss than those treated with placebo (1). Saxenda® received marketing authorisation from the EMA in March 2015. A drug utilisation study (DUS) has been requested by the EMA as part of the Saxenda® risk management plan to investigate in market use of Saxenda® and potential use of Victoza® for weight management. The DUS will allow assessment of usage patterns of liraglutide for weight management.

6 Research question and objectives

To investigate in market utilisation of liraglutide used for weight management, more specifically:

6.1 Primary objective

Use of Saxenda® according to 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.

6.2 Secondary objectives

1. Use of Victoza® for weight management

2. Use of Saxenda® according to approved posology

6.3 Endpoints

6.3.1 Primary endpoints

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 time of first prescription (index date)
    - Number of patients with 27 kg/m^2<=BMI<30 kg/m^2 (measured less than 6 months before time of first prescription (index date) and
        - >=1 relevant comorbidity:
            - Dysglycaemia (diabetes mellitus type 2 or prediabetes), hypertension, dyslipidaemia, and/or obstructive sleep apnoea, or
        - none of the above relevant comorbidities
- Number of patients with BMI<27 kg/m^2 (measured less than 6 months before time of first prescription (index date)

Number of patients with BMI not measured within 6 months before index date
Stopping rule:

- Number of patients with at least 5% weight loss (measured 16-24 weeks after index date) and continuing treatment

- Number of patients with less than 5% weight loss (measured 16-24 weeks after index date) and continuing treatment

- Mean weight loss (measured 16-24 weeks after start date of treatment) in patients not treated according to stopping rule.

6.3.2 Secondary endpoints

The following endpoints 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:

- at a prescription interval corresponding to a daily dose of 3.0 mg,
- with dose information of 3.0 mg per day, or
- with indication 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 3.0 mg within 4-12 weeks after index date

Concomitant medication with other GLP-1 receptor agonists:

- Number of Saxenda® initiators with other GLP-1 receptor agonists prescribed during continued treatment with Saxenda (continued treatment is defined as no gaps of more than 30 days between assumed prescription end and the subsequent prescription date).

Concomitant medication with other products for weight management:

- Number of Saxenda® initiators with other products for weight management prescribed during continued treatment with Saxenda (continued treatment is defined as no gaps of more than 30 days between assumed prescription end and the subsequent prescription date).

Duration of treatment with Saxenda® (continued treatment as defined above):

Number of patients with a treatment duration of:
0-6, 7-12, 13-18, or 19-24 months, or ongoing (current users)

7 Research methods

7.1 Study design

7.1.1 Type of study

This is a PASS, or more specifically a drug utilisation study (DUS) to characterise patients who are newly initiating treatment with Saxenda® or Victoza® (i.e., liraglutide) using the CPRD primary care

database in the United Kingdom . The primary objective is to investigate how Saxenda® is prescribed in clinical practice with respect to the approved indication (including off-label use), dosage and duration of treatment. Secondary objective is to investigate if Victoza® is prescribed for weight management. New initiators of liraglutide post UK launch of Saxenda® will be identified, and the index date (i.e., the initiation of treatment) will be defined as the date of the first prescription for either product. The duration of the study is 24 months from the launch date of Saxenda® in the UK.

The CPRD primary care database, or CPRD GOLD (previously known as GPRD), is the world's largest validated computerised database of anonymised longitudinal medical records for primary care. The CPRD primary care database covers approximately 8.9% of the UK population, including practices in England, Northern Ireland, Scotland and Wales. As of March 2015 there are 685 general practitioner (GP) practices and 13.7 million acceptable (research quality) patients. Data has been collected from GP practices since 1987.

The CPRD primary care database contains patient registration information and all care events that general practice staff record in order to support the ongoing clinical care and management of their patients. This includes demographic information (age, sex, BMI, registration date, transfer out date etc.), records of clinical events (medical diagnoses), referrals to specialists and secondary care settings, prescriptions issued in primary care, diagnostic testing, lifestyle information (e.g. smoking and alcohol status), and all other types of care administered as part of routine GP practice.

The DUS will be conducted combining the strengths of the CPRD primary care diagnostic and prescribing data, complemented with additional information obtained from GP questionnaires.

The GP questionnaires (annex 1) will be used to request additional information where the data recorded within the CPRD primary care database are inadequate or likely to be missing. This is particularly relevant for the prescribed indication, daily dose and for differentiation between usage of Saxenda® and Victoza®, as both are prescribed as pre-filled injectable pens with similar posology. In addition, in the UK GPs are encouraged to prescribe generically, and therefore the trade name is not necessarily captured within the primary care database. Furthermore, the date of initiation of treatment and the BMI at initiation of treatment will be unavailable in the primary care database if an initial prescription was issued by a specialist.

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) checklist can be found in annex 2.

7.1.2 Rationale for study design

The study design is in accordance with the study objectives. The retrospective observational DUS design will involve no intervention and have no impact on usual medical care and will therefore reflect the use of Saxenda® and Victoza® in real-world clinical practice.

7.1.3 Treatment of patients

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

7.1.4 Rationale for treatment

Not applicable.

7.1.5 Study supplies

Study product(s):

Not applicable.

Packaging and labelling of study product(s):

Not applicable.

Auxiliary supply:

Not applicable.

7.2 Setting

7.2.1 Inclusion criteria

New initiators of liraglutide (unbranded, or branded prescription, i.e. Saxenda® or Victoza®), who have no liraglutide prescriptions in the twelve months prior to index date. Patients must be research standard (registered as "acceptable" in the database) with at least one year of up-to-standard registration prior to their index date.

7.2.2 Exclusion criteria

Not applicable.

7.2.3 Withdrawal criteria

Not applicable.

7.2.4 Rationale for selection criteria

The inclusion criteria have been selected to attempt to identify a broad population of new initiators of liraglutide, in routine clinical practice and in keeping with CPRD data quality guidance. This will allow for generalization of results to the broad population of subjects being prescribed Saxenda® or Victoza® in the UK primary care setting.

7.2.5 Flowchart

Table 1and Table 2show the data to be collected respectively for Saxenda® and Victoza® initiators at different time points in relation to initiation of treatment.

Table 1: Saxenda® initiators[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			
Estimated 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
Concomitant medication with other products for weight management *(Brand name and start date)*					X

1) Inclusion criteria must be fulfilled before data extraction is performed
2) Censoring at 24 months after launch
3) Gender, age
4) Diagnosis of or treatment of pre-diabetes, type 2 diabetes mellitus, hypertension, dyslipidaemia and/or obstructive sleep apnoea
5) Latest recording within 6 months before initiation of Saxenda® treatment
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® initiators[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	
Prescription pattern corresponding to Victoza® 3.0 mg/day[4]		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 before data extraction is performed
2) Censoring at 24 months after launch
3) Gender, age
4) According to table 3.

7.3 Variables

Patient demographics and other characteristics:

- Year of birth
- Sex
- Body weight and height, BMI (calculated); date of anthropometric measurements

Drug utilisation:

Saxenda® or Victoza® patients:

- Brand name
- Indication prescribed at index date
- Target dose prescribed at index date
- Repeat prescription dates

Saxenda® patients only:

- Treatment start date and estimated end date
- Duration of treatment (or ongoing users)
- Comorbidities:
    - In the CPRD primary care database, 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, or on read coded clinical and referral events. 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%

In the CPRD primary care database, diagnosis of obstructive sleep apnoea may be based on treatment with continuous positive airway pressure (CPAP) device , or on read coded clinical and referral events.
For the final report, diagnosis of comorbidities will be confirmed by the replies to question 3 in the questionnaires.

- Dose of Saxenda® at 4-12 weeks and 16-24 weeks after index date
- Body weight at 16-24 weeks after index date
- Concomitant medication with other GLP-1 receptor agonists or with other products for weight management (name and time of first prescription)

Victoza® patients only:

- Dose-escalation from 1.2 mg/1.8mg to 3.0 mg throughout the treatment period.

Definition of prescription outside label

Prescription outside label will be categorised as follows:

Saxenda® patients only:

- BMI<27 kg/m^2 within 6 months prior to index date

- 27 kg/m^2<=BMI<30 kg/m^2 (within 6 months prior to index date) and no relevant comorbidities registered (dysglycaemia (diabetes mellitus type 2 or prediabetes), hypertension, dyslipidaemia, and/or obstructive sleep apnoea)
- BMI not measured within 6 months prior to index date
- Non-adherence to dose escalation according to approved label (i.e., daily dose of 3.0 mg not reached within 4-12 weeks after index date)
- Non-adherence to stopping rule (i.e., less than 5% weight loss 16-24 weeks after index date and continued treatment)
- Concomitant medication with other GLP-1 receptor agonists.

Victoza® patients only:

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

7.3.1 Assessments for safety and effectiveness

Not applicable.

7.3.2 Other assessments

Not applicable.

7.4 Data sources

Data will be obtained from the CPRD primary care database, with information supplemented by use of GP questionnaires. Comorbidities will be identified using Read codes in the Clinical and Referral files, product codes from the Therapy file, and laboratory results when relevant.

7.4.1 Visit procedures

Not applicable.

7.5 Study size

This is a descriptive study designed to examine in-market utilisation of Victoza®/Saxenda®, thus no hypothesis testing is planned, and power calculations are not applicable.

Planned number of patients to be included: 200-300 patients.

The estimated response rate based on previous GP questionnaire studies in CPRD is 70%, and the aim is to collect data for at least 200 patients (minimum 100 each group). Therefore, in view of the expected response rate, the aim will be to send approximately 150 questionnaires for patients treated with Saxenda® and approximately 150 questionnaires for patients treated with Victoza® (as available at the time of sending out the questionnaires). If more than 150 patients are available in

the database for either product these will be included in descriptive analyses based on the CPRD GOLD database alone, but questionnaires will be sent out for the 150 patients who first started the treatment only.

7.6 Data management

7.6.1 Data management

Data management will be the responsibility of the organisation performing the research (i.e. CPRD). Data analyses will be performed using Stata v13.1 or later.

7.6.2 Case report forms and rules for completing

Not applicable.

7.6.3 Corrections to CRFs

Not applicable.

7.6.4 CRF flow

Not applicable.

7.7 Data analysis

All data analysis will be performed by CPRD.

Patients will be divided into the following cohorts based on their initial prescription:

Cohort 1 (Saxenda® initiators)

- Saxenda® (by brand)
- Liraglutide 3.0 mg

Cohort 2 (Victoza® initiators)

- Victoza® (by brand)
- Liraglutide 1.2 or 1.8 mg

For liraglutide prescriptions with no recording of brand or when the dose cannot be estimated, this information will be collected through questionnaires. Given that it might not be possible to get this information for all patients, it is possible there will be a cohort where the brand or initial dose is unknown.

Information from the CPRD primary care database and from the questionnaires will be used to present descriptive statistics of the proportion of patients with the endpoints of interest.

Dosage information recorded by the GP will be explored and described in order to estimate daily dose. As prescriptions will not have dosage recorded in this level of detail, time between prescriptions will be used to estimate dosage based on assumptions (see table 3 below), in addition to information obtained from GP questionnaires.

Table 3 demonstrates a hypothetical dosage use for a patient initiating Victoza® (assuming administration of 1.8mg per day) or Saxenda® over a 26 week period, and 6-monthly (26 weeks) intervals thereafter. This includes the minimum number of pre-filled pens used (based on 18mg in 3mls). The estimates assume that patients are able to tolerate weekly increases in dosage according to approved labels and are fully compliant with prescribed treatment.

Table 3: Hypothetical dosage use for a Victoza® (1.8mg) and Saxenda® initiator during the first 2 years of treatment

	Victoza (1.8mg)®				**Saxenda®**			
Week	**Daily dose**	**Weekly dose**	**Cumulative dose**	**Min. number of pre-filled pens**	**Daily dose**	**Weekly dose**	**Cumulative dose**	**Min. number of pre-filled pens**
1	0.6	4.2	4.2	1	0.6	4.2	4.2	1
2	1.2	8.4	12.6	1	1.2	8.4	12.6	1
3	1.8	12.6	25.2	2	1.8	12.6	25.2	2
4	1.8	12.6	37.8	3	3.0	21.0	46.2	3
5	1.8	12.6	50.4	3	3.0	21.0	67.2	4
6	1.8	12.6	63	4	3.0	21.0	88.2	5
7	1.8	12.6	75.6	5	3.0	21.0	109.2	7
8	1.8	12.6	88.2	5	3.0	21.0	130.2	8
9	1.8	12.6	100.8	6	3.0	21.0	151.2	9
10	1.8	12.6	113.4	7	3.0	21.0	172.2	10
11	1.8	12.6	126	7	3.0	21.0	193.2	11
12	1.8	12.6	138.6	8	3.0	21.0	214.2	12
13	1.8	12.6	151.2	9	3.0	21.0	235.2	14
14	1.8	12.6	163.8	10	3.0	21.0	256.2	15
15	1.8	12.6	176.4	10	3.0	21.0	277.2	16
16	1.8	12.6	189	11	3.0	21.0	298.2	17
17	1.8	12.6	201.6	12	3.0	21.0	319.2	18
18	1.8	12.6	214.2	12	3.0	21.0	340.2	19
19	1.8	12.6	226.8	13	3.0	21.0	361.2	21
20	1.8	12.6	239.4	14	3.0	21.0	382.2	22
21	1.8	12.6	252	14	3.0	21.0	403.2	23
22	1.8	12.6	264.6	15	3.0	21.0	424.2	24
23	1.8	12.6	277.2	16	3.0	21.0	445.2	25
24	1.8	12.6	289.8	17	3.0	21.0	466.2	26
25	1.8	12.6	302.4	17	3.0	21.0	487.2	28
26	1.8	12.6	315	18	3.0	21.0	508.2	29
Month	**Daily dose**	**Monthly dose**	**Cumulative dose**	**Min. number of pre-filled pens**	**Daily dose**	**Monthly dose**	**Cumulative dose**	**Min. number of pre-filled pens**
6	1.8	54	315	18	3.0	90	508.2	29
12	1.8	54	642.6	36	3.0	90	1054.2	59
18	1.8	54	970.2	54	3.0	90	1600.2	89
24	1.8	54	1297.8	73	3.0	90	2146.2	120

7.7.1 Evaluability of patients for analysis

Not applicable.

7.7.2 Statistical methods

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

All endpoints will be summarised by descriptive statistics for all eligible patients. No inferential statistical analyses will be conducted.

In brief, the descriptive analyses will present Saxenda® and Victoza® utilisation by indication. The proportion of prescription outside label among users of Saxenda®/Victoza® during the entire study period will be estimated. The proportion of each of the definitions of prescription outside label will be described. Characteristics of patients prescribed Saxenda®/Victoza® according to the respective approved labels will also be evaluated.

For each of the definitions of prescription outside label, the proportions will be calculated as follows:

Saxenda® patients only:

- BMI<27 kg/m^2 within 6 months prior to index date: The proportion of these out of the total number of identified Saxenda® patients will be calculated.
- 27 kg/m^2<=BMI<30 kg/m^2 (within 6 months prior to index date) and no relevant comorbidities registered (dysglycaemia (diabetes mellitus type 2 or prediabetes), hypertension, dyslipidaemia, and/or obstructive sleep apnoea): The proportion of these out of the total number of identified Saxenda® patients will be calculated.
- BMI not measured within 6 months prior to index date: The proportion of these out of the total number of identified Saxenda® patients will be calculated.
- Non-adherence to dose escalation according to approved label (i.e., daily dose of 3.0 mg not reached within 4-12 weeks after index date) : The proportion of these out of the total number of identified Saxenda® patients will be calculated. In addition, the proportion of patients without information on adherence to dose escalation out of the total number of identified Saxenda® patients will be calculated.
- Non-adherence to stopping rule (i.e., less than 5% weight loss 16-24 weeks after index date and continued treatment): The proportion of these out of the total number of identified Saxenda® patients will be calculated. In addition, the proportion of patients without information on adherence to stopping rule out of the total number of identified Saxenda® patients will be calculated.
- Concomitant medication with other GLP-1 receptor agonists: The proportion of these out of the total number of identified Saxenda® patients will be calculated.

Victoza® patients only:
Prescribed dose of 3.0 mg per day and/or prescribed indication of weight management: The proportion of these out of the total number of identified Victoza® patients will be calculated.

Continuous variables will be described by the number of available values, means, standard deviation, median and ranges. Categorical variables will be described as the total number of available values and relative percentage per subgroup of interest. Data not available from the database (or via questionnaires) will be reported as missing.

Analyses on the following will be conducted:

Patient demographics and other characteristics:

Descriptive statistics will be provided for the following variables:
- Age
- Sex

Drug utilisation:

Descriptive statistics will be provided for the following variables:

Saxenda® or Victoza® patients:

- Brand name
- Indication prescribed at treatment initiation
- Target dose prescribed at treatment initiation

Saxenda® patients:

- Comorbidities:
  - Dysglycaemia (diabetes mellitus type 2 or prediabetes), hypertension, dyslipidaemia, and/or obstructive sleep apnoea.
- Concomitant medication with other products for weight management (brand name and start date)
- Dose at 4-12 weeks and 16-24 weeks post initiation of treatment
- Duration of treatment (or ongoing users)

Victoza® patients:
- 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
- 27 kg/m^2<=BMI<30 kg/m^2 within 6 months before start date of treatment and no relevant comorbidities registered (dysglycaemia (diabetes mellitus type 2 or prediabetes), hypertension, dyslipidaemia, and/or obstructive sleep apnoea)
- BMI not measured within 6 months before start date of treatment
- Non-adherence to dose escalation according to label (i.e.,3.0 mg not reached within 8 weeks, plus or minus 4 weeks)
  Non-adherence to stopping rule (i.e., less than 5% weight loss after 12 weeks [plus or minus 4 weeks] on Saxenda 3.0 mg and continued treatment)
- Concomitant medication with other GLP-1 receptor agonists

Victoza® patients:

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

7.7.3 Interim analysis

An interim analysis is planned at 15 months post UK launch of Saxenda®. This will be used to gain a better understanding of liraglutide prescribing data in the CPRD primary care database, and if necessary could lead to refinement of the questionnaire (questionnaires are to be sent after the interim report). All possible planned analyses will be conducted in the interim analysis (only using the data in the CPRD primary care database).

7.7.4 Sequential safety analysis/safety monitoring

Not applicable.

7.7.5 Health economics and/or patients reported outcome

Not applicable.

7.8 Quality control

Not applicable.

7.8.1 Monitoring procedures

Not applicable.

7.8.2 Critical documents

Not applicable.

7.8.3 Retention of study documentation

Not applicable.

7.9 Limitations of the research methods

There are a number of potential limitations.

If treatment with Saxenda® or Victoza® has been commenced by a specialist, the index date, BMI and prescribed indication at initiation may not be captured in the database. Additionally, as liraglutide is administered via a pre-filled pen, it could be challenging to determine the prescribed daily target dose. Use of GP questionnaires should provide additional information to supplement the data in the database and reduce the risk of misclassification bias.

The response rate will depend on the proportion of questionnaires that are completed and returned. Based on previous CPRD studies involving questionnaires, a response rate of 70% or over is expected, this will be used to estimate the number of questionnaires to be sent out in order to achieve a sample size of at least 200 patients.

It is not possible to assess compliance with a prescribed treatment, only whether a treatment has been prescribed.

To limit the amount of missing data as much as possible, data collection by use of questionnaires sent to GPs will be added to the information collected from the CPRD database. For the same reason, time windows for visits to the GPs are allowed for assessment of BMI and body weight. A missing data category will be formed for each variable to illustrate the extent of the problem. GPs will be contacted by phone 4 and 8 weeks after receiving the questionnaire if they have not yet responded.

As only descriptive statistics will be provided, no imputation for missing data will be applied.

8 Protection of human subjects

The study will be conducted in accordance with GPP, reference 3.

8.1 Informed consent form for study patients

Not applicable.

8.2 Data handling

Data will be collected and handled in accordance with CPRD governance rules.

8.3 Institutional Review Boards/Independent Ethics Committee

CPRD has obtained ethical approval from a National Research Ethics Service Committee (NRES) for all purely observational research using anonymised CPRD data; namely, studies which do not include patient involvement (e.g. use of GP questionnaires for collection of supplementary pseudonymised data).

Ethical approval will also be sought from the ISAC (Independent Scientific Advisory Committee). The ISAC is a non-statutory expert advisory body established in 2006 by the Secretary of State to provide advice on research related requests to access data provided by Clinical Practice Research Datalink (CPRD).

8.4 Regulatory authorities

Approval of the protocol will also be sought from the EMA. Regulatory authorities will receive the original protocol, amendments to the protocol, and the non-interventional study report according to national requirements.

8.5 Premature termination of the study

The sponsor 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.

8.6 Responsibilities

The medical care given to, and medical decisions made on behalf of, patients are the responsibility of a qualified physician.

8.7 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.

9 Reporting of safety information

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

9.1 Safety information to be collected

Not applicable.

9.2 Safety definitions

Not applicable.

9.3 Collection and reporting of safety information

Not applicable.

9.4 Follow-up of safety information

Not applicable.

10 Plans for disseminating and communicating study results

An interim report and a final study report will be generated. Both reports will be prepared by CPRD.

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.

Reporting of the findings of CPRD research are subject to a number of governance requirements. One of these is the CPRD small cell governance. The standard line on this can be found at: http://www.cprd.com/ISAC/otherinfo.asp, under 'Reporting of the findings': "It is essential that consideration is given to preserving confidentiality at the reporting stage. The possibility of unintentional (deductive) disclosure arises when cells with small numbers of patients are quoted. Applicants should note that, when reporting the data, CPRD policy is that no cell should contain <5 events."

10.1 Communication and publication

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.

10.2 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), reference 5.

10.3 Publications

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.

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 CPRD and Novo Nordisk's opinions must be fairly and sufficiently represented in the publication.

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

Not applicable.

10.4 Physician access to data and review of results

Not applicable.

11 References

1. Saxenda EMA Public Assessment Report: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003780/WC500185788.pdf
2. EMA/330405/2012 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)
3. International Society for Pharmacoepidemiology (ISPE). Guidelines for Good Pharmacoepidemiology Practices (GPP). Initially issued: 1996. Revision 2, April, 2007

4. World Medical Association (WMA) Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. 64th WMA General Assembly, Brazil, October 2013
5. International Committee of Medical Journal Editors (ICMJE). Uniform Requirements for Manuscripts Submitted to Biomedical Journals (current official version available at www.ICMJE.org)

List of Stand-alone Documents

Number	Document reference number	Title
1	Annex 1	GP questionnaire
2	Annex 2	ENCePP Checklist for Study Protocols

ANNEX 1: GP questionnaire

Dear Doctor,

Saxenda® and Victoza® both contain the active substance liraglutide, a long-acting glucagon-like peptide 1 (GLP-1) analogue. Saxenda® 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. Victoza® is approved for management of type 2 diabetes.

A drug utilisation study (DUS) investigating how liraglutide is being prescribed in clinical practice (when used for weight management) has been requested by the European Medicines Agency (EMA), as part of the risk management plan for Saxenda®. The CPRD primary care database is running this study. Using pseudo-anonymised patient data from the CPRD primary care database, we have identified patients in your practice who have been prescribed liraglutide. As some data are not readily available from the CPRD primary care database (such as indication, brand name of prescribed products and prescribed dose of injectable products), we would appreciate your assistance to supplement the relevant data.

We would be grateful if you could review the medical records of these patients and complete the brief questionnaire below for each identified patient. After completing, please return the form in the freepost envelope provided.

We would like to thank you in advance for your help, this information will allow us to characterise how liraglutide is being used in clinical practice.

Kind regards,

Clinical Practice Research Datalink

Initiation of Saxenda® treatment

1. Can you confirm that this patient was prescribed Saxenda®?

   Yes ☐

   No ☐ (*If "no" please skip to question 6)*

If "yes" please provide information on the prescribed dosing schedule, date of initiated treatment, adult height and latest recorded BMI and body weight prior to initiation of Saxenda® treatment:

Date of initiation of treatment (day/month/year):_____

Was the treatment dose of 3.0 mg/day reached 12 weeks after initiation:

Yes ☐

No ☐

BMI (kg/m^2):_____ Date of measurement (day/month/year): _____

or

Body weight (kg):_____Date of measurement (day/month/year): _____

Adult height:_____

2. Was Saxenda® initially prescribed by a specialist?

Yes ☐

No ☐

If "yes" please provide the date of initiation of treatment/first prescription and BMI , body weight and adult height:

Date of initiation of treatment (day/month/year):_____

BMI (kg/m^2):_____Date of measurement (day/month/year): _____

or

Body weight (kg):_____Date of measurement (day/month/year): _____

Adult height:_____

Information on BMI and/or body weight prior to first prescription of Saxenda® is not available ☐

3. Did this patient have any of the following comorbid medical conditions at initiation of treatment with Saxenda® (please tick the relevant boxes)?

Type 2 diabetes mellitus ☐

Prediabetes	☐
Hypertension	☐
Dyslipidaemia	☐
Obstructive sleep apnoea	☐

4. If this patient has stopped treatment with Saxenda®, what was the duration of treatment (please tick the relevant box)?

<1 week	☐
1-4 weeks	☐
5-8 weeks	☐
9-12weeks	☐
3-6 months	☐
6-9 months	☐
9-12 months	☐
12-18 months	☐
18-24 months	☐
ongoing	☐

5. If the patient continued on Saxenda®, please provide any body weight (BW) values measured within 16-24 weeks (i.e. 4-6 months) after starting Saxenda® treatment

Body weight (kg)_____Date (day/month/year)_____

Body weight (kg)_____Date (day/month/year)_____

Body weight (kg)_____Date (day/month/year)_____

Body weight (kg)_____Date (day/month/year)_____

Initiation of Victoza® treatment

6. Can you confirm that this patient has been prescribed Victoza® (liraglutide) since "XXXX(date of Saxenda launch)"?

   If "yes", please provide date of initiation of treatment, primary indication and prescribed treatment dose:

   Date of initiation of treatment (day/month/year):_____

   Indication for Victoza® treatment:_____

   Treatment dose prescribed:_____

   _____

ANNEX 2. ENCePP Checklist for Study Protocols

Section 1: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the formulation of the research question clearly explain:				
1.1.1 Why the study is conducted? (eg to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	10
1.1.2 The objectives of the study?	☒	☐	☐	10
1.2 Does the formulation of the research question specify:				
1.2.1 The target population? (ie population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	13
1.2.2 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
1.2.3 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Section 2: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
2.2 Is the planned study population defined in terms of:				
2.2.1 Study time period?	☒	☐	☐	13
2.2.2 Age and sex?	☐	☐	☒	
2.2.3 Country of origin?	☐	☐	☒	
2.2.4 Disease/indication?	☐	☐	☒	
2.2.5 Co-morbidity?	☐	☐	☒	
2.2.6 Seasonality?	☐	☐	☒	
2.3 Does the protocol define how the study population will be sampled from the source population? (eg event or inclusion/exclusion criteria)	☒	☐	☐	14

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	11
3.2 Is the study design described? (eg cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	13
3.3 Does the protocol describe the measure(s) of effect? (eg 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)	☐	☐	☒	
3.4 Is sample size considered?	☐	☐	☒	
3.5 Is statistical power calculated?	☐	☐	☒	

Section 4: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
4.1.1 Exposure? (eg pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc)	☒	☐	☐	13
4.1.2 Endpoints? (eg clinical records, laboratory markers or values, claims data, self report, patient interview including scales and questionnaires, vital statistics, etc)	☒	☐	☐	13
4.1.3 Covariates?	☒	☐	☐	13
4.2 Does the protocol describe the information available from the data source(s) on:				
4.2.1 Exposure? (eg date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	17
4.2.2 Endpoints? (eg date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	17
4.2.3 Covariates? (eg age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc)	☒	☐	☐	17
4.3 Is the coding system described for:				
4.3.1 Diseases? (eg International Classification of Diseases (ICD)-10)	☒	☐	☐	19
4.3.2 Endpoints? (eg Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☐	☐	☒	
4.3.3 Exposure? (eg WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
4.4 Is the linkage method between data sources described?	☐	☐	☒	

Section 4: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
(eg based on a unique identifier or other)				

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? (eg operational details for defining and categorising exposure)	☒	☐	☐	13
5.2 Does the protocol discuss the validity of exposure measurement? (eg 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? (eg current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

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?	☒	☐	☐	11
6.2 Does the protocol discuss the validity of endpoint measurement? (eg precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	

Section 7: Biases and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address:				
7.1.1 Selection biases?	☐	☒	☐	
7.1.2 Information biases? (eg anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	27
7.2 Does the protocol address known confounders? (eg collection of data on known confounders, methods of controlling for known confounders)	☐	☐	☒	
7.3 Does the protocol address known effect modifiers? (eg collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	
7.4 Does the protocol address other limitations?	☒	☐	☐	27

Section 8: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the plan include measurement of absolute effects?	☐	☐	☒	
8.2 Is the choice of statistical techniques described?	☒	☐	☐	24
8.3 Are descriptive analyses included?	☒	☐	☐	24
8.4 Are stratified analyses included?	☐	☐	☒	
8.5 Does the plan describe the methods for identifying:				
8.5.1 Confounders?	☐	☐	☒	
8.5.2 Effect modifiers?	☐	☐	☒	
8.6 Does the plan describe how the analysis will address:				
8.6.1 Confounding?	☐	☐	☒	
8.6.2 Effect modification?	☐	☐	☒	

Section 9: Quality assurance, feasibility and reporting	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Does the protocol provide information on data storage? (eg software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☒	☐	
9.2 Are methods of quality assurance described?	☐	☒	☐	
9.3 Does the protocol describe quality issues related to the data source(s)?	☐	☒	☐	
9.4 Does the protocol discuss study feasibility? (eg sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☐	☒	
9.5 Does the protocol specify timelines for				9
9.5.1 Study start?	☒	☐	☐	
9.5.2 Study progress?	☒	☐	☐	
9.5.3 Study completion?	☒	☐	☐	
9.5.4 Reporting?	☒	☐	☐	
9.6 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	9
9.7 Are communication methods to disseminate results described?	☒	☐	☐	29
9.8 Is there a system in place for independent review of study results?	☐	☒	☐	

Section 10: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**

Section 10: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	28
10.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
10.3 Have data protection requirements been described?	☐	☒	☐	

Name of protocol originator: [redacted]

Date: / /

Signature: _____