PASS Information

Title	Utilisation of dulaglutide in European countries: A cross-sectional, multi-country and multi-source drug utilisation study using electronic health record databases.
Version identifier	Version 1.0
Date of last version	01 May 2016
EU PAS Register No:	Study not registered
Active substance	Dulaglutide (ATC code: A10BX)
Medicinal product(s):	Trulicity 0.75 mg solution for injection Trulicity 1.5 mg solution for injection
Product reference:	EU/1/14/956
Procedure number:	EMEA/H/C/002825
Marketing authorisation holder(s)	Eli Lilly Nederland B.V.
Joint PASS	No
Research question and objectives	The purpose of this study is to describe how dulaglutide is used among different patient groups in European countries. Primary objective: To describe the frequency of dulaglutide use in the population and characterise by age, gender, main co-morbidities and main co-prescriptions overall and in the following subgroups of interest: o Populations of interest: • Patients with severe renal failure • Patients with hepatic disease • Patients with heart failure • Patients with severe gastrointestinal disease • Children and adolescents <18 years of age • Elderly patients ≥75 years • Pregnant and breastfeeding women o Medication use : • Medication errors • Off-label use Secondary objective: To describe the off-label use among each of the above populations of interest.
Country(-ies) of study	Several countries will be selected from the databases under consideration (France, Germany, Spain, Sweden and the United-Kingdom) based on the criteria described in the feasibility analysis (see Section 9.5.2).
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Approval Date: 07-Jun-2016 GMT

Marketing Authorisation Holder

Marketing authorisation holder (MAH)	Eli Lilly Nederland B.V.
MAH contact person	Dr Ayad Ali, Pharmacoepidemiologist Eli Lilly and Company

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2. List of Abbreviations

Term	Definition
ADMs	anti-diabetes medications
ALT	alanine amino transferase
AST	aspartate amino transferase
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AR	adverse reaction
Beta hCG	Beta subunit of human chorionic gonadotrophin
BMI	body mass index
CI	confidence interval
CHMP	Committee for Medicinal Products for Human Use
CPRD	Clinical Practice Research Datalink
CRF	case report form
DA	Disease Analyzer
DPP-4 inh.	dipeptidyl peptidase-4 inhibitors
EHR	electronic health record
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ERB	Ethical review board
GFR	glomerular filtration rate
GLP-1 RAs	Glucagon-like peptide-1 receptor agonists
GVP	good pharmacovigilance practices
HbA1c	haemoglobin A1c (glycated haemoglobin)
HDL-C	high density lipoprotein cholesterol
ICD	International classification of disease
ICD-10	International classification of disease, 10^{th} version
ICH	International Conference of Harmonisation

ISAC	Independent Scientific Advisory Committee
ISPE	International Society for Pharmacoepidemiology
LDL-C	low density lipoprotein cholesterol
MAH	marketing authorisation holder
NPR	National Prescription Registry
PASS	post-authorization safety study
PBRER	periodic benefit-risk evaluation report
PSUR	periodic safety update report
RMP	risk minimization plan
SAE	serious adverse event
SAP	statistical analysis plan
SAR	serious adverse reaction
SIDIAP	Sistema de Información para el Desarrollo de la Investigación en Atención Primària (The Information System for the Development of Research in Primary Care)
SmPC	summary of products characteristics
SOP	standard operating procedure
SPDR	the Swedish prescribed drug register
STROBE	strengthening the reporting of observational studies in epidemiology
T2DM	type 2 diabetes mellitus
UK	United Kingdom

3. Responsible Parties

Project team:

Sponsor: Eli Lilly and Company

Sponsor's EU Qualified Person for Pharmacovigilance (QPPV):

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4. Abstract

Title: Utilisation of dulaglutide in European countries: A cross-sectional, multi-country and multi-source drug utilisation study using electronic health record databases.

Version 1.0 Date: 01 May 2016

Rationale and background:

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are incretin mimetics; they stimulate insulin secretion in a glucose-dependent manner (1,2), and are widely used as glucose-lowering drugs in the treatment of patients with type 2 diabetes mellitus (T2DM) (3).

Dulaglutide is a long-acting GLP-1 RA. Its structure protects it from inactivation by dipeptidyl peptidase-4 (DPP-4) and confers a half-life up to ~4.7 days in humans (4). As a result of this relatively long half-life, dulaglutide can be administered once weekly.

Dulaglutide was approved in the European Union (EU) for the treatment of T2DM in November 2014 (5).

To better understand the utilisation of dulaglutide in real world conditions in the EU, this drug utilisation study (DUS) aims to describe the use of dulaglutide with regard to off-label use and medication errors, as well as the use in subpopulations of patients for which little data exist, including patients with severe renal failure, heart failure, hepatic disease, or severe gastrointestinal disease; children, adolescents, and elderly with T2DM; and pregnant and breastfeeding women.

Research question and objectives:

The purpose of this study is to describe how dulaglutide is used among different patient groups in European countries.

Primary objective:

To describe the frequency of dulaglutide use in the population and characterise by age, gender, main co-morbidities and main co-prescriptions overall and within the following subgroups of interest:

- Populations of interest:
  - Patients with severe renal failure
  - Patients with hepatic disease
  - Patients with heart failure
  - Patients with severe gastrointestinal disease
  - Children and adolescents <18 years of age
  - Elderly patients ≥75 years
  - Pregnant and breastfeeding women
- Medication use:
  - Medication errors
  - Off-label use

Secondary objective:

- To describe the off-label use among each subgroup of the populations of interest.

Study design:

A multi-country, multi-source, cross-sectional, descriptive study using longitudinal data collected from European electronic health record (EHR) databases.

Several countries will be selected from the databases under consideration (France, Germany, Spain, Sweden, and the United-Kingdom [UK]). The justification of the selected countries will be based on the feasibility assessment results and will depend on the market uptake and volume of dulaglutide in each country.

The study will describe the utilisation of dulaglutide for at least three years following the launch of dulaglutide.

Population:

Inclusion criteria:

- Patients for whom a treatment with dulaglutide is initiated during the observation period.
- Patients having at least 6 months of available continuous history prior to the date of the first dulaglutide prescription.

No exclusion criteria will be applied.

Subgroups of interest:

- Populations of interest:
  - Patients with severe renal failure
  - Patients with hepatic disease
  - Patients with heart failure
  - Patients with severe gastrointestinal disease
  - Children and adolescents <18 years of age
  - Elderly patients ≥75 years
  - Pregnant and breastfeeding women
- Medication use:
  - Medication errors
  - Off-label use

Variables:

The following variables will be extracted from databases, whenever available, which will be analysed at the baseline (6-month period prior to dulaglutide initiation) and/or index date (dulaglutide initiation):

- Patients' demographics (age and gender) at baseline
- Relevant comorbidities
- Medical history: disease diagnoses

- Concomitant anti-diabetes medications (ADMs) and other drug exposures
- Average daily dosage of prescriptions
- Prescriptions in combination with other ADMs

Data sources:

The following European EHR databases will be used for the feasibility. A subset of these databases will be then selected for the actual study:

- France: IMS Disease Analyzer (French DA)
- Germany: IMS Disease Analyzer (German DA)
- Spain: The Information System for the Development of Research in Primary Care (SIDIAP)
- Sweden: National Patient Register (NPR) and Swedish Prescribed Drug Register (SPDR)
- United Kingdom: Clinical Practice Research Datalink (CPRD)

Study size:

The first analysis and report will commence once at least 1000 patients initiated with dulaglutide become available in the EHR databases with at least 100 patients in the smallest country. All eligible patients of each selected database will be included in the study. Such a sample size would provide a precision of 3% for the entire sample and a minimum precision of 10% for the country with the smallest sample around an estimated proportion of 50% with 95% confidence intervals.

Data analysis:

The analysis will be performed per country, on the overall data set of eligible patients, 0.75 or 1.5 mg prescription of dulaglutide, and per subgroups.

Data coming from different databases/countries will not be pooled. The analysis will be done per year, and will not be cumulative. Thus data coming from different years will not be pooled either.

The statistical analysis will be descriptive including standard univariate analysis; no inferential statistical analyses will be conducted. Continuous variables will be described by the number of available values: mean, standard deviation, median, Q1, Q3, minimum and maximum. Data not available in the databases will be reported as missing. Categorical variables will be described as the total number of available values and relative percentage per subgroup of interest. Where relevant, 95% confidence intervals will be calculated for the endpoints.

The statistical analysis will be conducted using the SAS® software V9.2 or later on Windows™ (SAS Institute, North Carolina, USA).

Milestones:

The start and end of data collection may change due to the market uptake of dulaglutide and data capture by the databases of respective countries. The dates below are estimates and may need to be updated following feasibility assessment.

Milestones	Planned date
Start of data collection	Estimated Q3 2016 The start of data collection may change due to the market uptake of dulaglutide in the countries and protocol approval from PRAC.
End of data collection	Estimated Q2 2019 The end of data collection may change due to the market uptake of dulaglutide in the countries.
Feasibility assessment report	Estimated Q3 2016
Interim report 1	Estimated Q4 2016
Interim report 2	Estimated Q4 2017
Interim report 3	Estimated Q4 2018
Registration in the EU PAS register [EU PASS Only]	Estimated Q1 2016
Final report of study results	Approximately 5 years from market authorisation (estimated Q4 2019)

5. Amendments and Updates

Not applicable.

6. Milestones

Milestone	Planned date
Start of data collection	Estimated Q3 2016 The start of data collection may change due to the market uptake of dulaglutide in the countries and protocol approval from PRAC.
End of data collection	Estimated Q2 2019 The end of data collection may change due to the market uptake of dulaglutide in the countries.
Feasibility assessment report	Estimated Q3 2016
Interim report 1	Estimated Q4 2016
Interim report 2	Estimated Q4 2017
Interim report 3	Estimated Q4 2018
Registration in the EU PAS register [EU PASS Only]	Estimated Q1 2016
Final report of study results	Approximately 5 years from market authorisation (estimated Q4 2019)

7. Rationale and Background

Glucagon-like peptide-1 receptor agonists (GLP -1 RAs) are incretin mimetics. Similar to endogenous hormone GLP-1 (1), they inhibit glucagon secretion, delay gastric emptying and suppress appetite. They stimulate insulin secretion in a glucose-dependent manner; insulin release stops when the plasma glucose level is low (3 mmol/l) (2). The GLP-1 RAs are widely used as glucose-lowering drugs in the treatment of T2DM (3).

Five GLP-1 RAs are currently approved worldwide for treatment of adults with T2DM: exenatide (2 forms with daily/weekly administration: Byetta® was approved by the EMA in November 2006 / Bydureon® in 2011, Astra Zeneca), liraglutide in July 2009 (Victoza®, Novo Nordisk), lixisenatide in February 2013 (Lyxumia®, Sanofi), albiglutide in March 2014 (Eperzan®, GlaxoSmithKline) and dulaglutide in November 2014 (Trulicity®, Eli Lilly and Company). Currently all are marketed in Europe. Additionally, one formulation which comprises insulin Degludec and liraglutide, IDegLira (Xultophy®, Novo Nordisk) as single-device combination therapy was approved in September 2014.

Dulaglutide is a long-acting GLP-1 RA. Its structure protects it from inactivation by dipeptidyl peptidase-4 (DPP-4) and confers a half-life up to ~4.7 days in humans (4). As a result of this relatively long half-life, dulaglutide can be administered once weekly which may offer an advantage compared to some competitors, such as short acting exenatide which is given twice daily, and liraglutide or lixisenatide which are used once daily. It is to be noticed that as dulaglutide, long-lasting exenatide (Bydureon®), and albiglutide (Eperzan®) are also used once weekly.

The European Union (EU) Commission approved the dulaglutide injectable solution for the treatment of T2DM in November 2014 (5).

As part of the risk management plan (RMP), Eli Lilly, the Marketing Authorisation Holder (MAH) of dulaglutide has agreed to conduct a DUS to describe the use of dulaglutide in particular subgroups of patients in several databases in European countries.

The rationale for this study is the need to gain knowledge about dulaglutide utilisation in real world conditions, as well as information on off-label use, medication errors, and the use in subpopulations of patients for which little data exist (i.e., patients with severe renal failure, heart failure, hepatic disease, or severe gastrointestinal disease; children and adolescents with T2DM < 18 years of age; elderly ≥ 75 years; and pregnant and breastfeeding women).

8. Research Question and Objectives

The purpose of this study is to describe how dulaglutide is used among different patient groups in European countries.

Primary objective:

To describe the frequency of dulaglutide use in the population and characterise by age, gender, main co-morbidities and main co-prescriptions overall and within the following subgroups of interest:

- Populations of interest:
  - Patients with severe renal failure
  - Patients with hepatic disease
  - Patients with heart failure
  - Patients with severe gastrointestinal disease
  - Children and adolescents <18 years of age
  - Elderly patients ≥75 years
  - Pregnant and breastfeeding women
- Medication use:
  - Medication errors
  - Off-label use

Secondary objective:

To describe the off-label use among each subgroup of populations of interest.

9. Research Methods

9.1. Study Design

This is a multi-country, multi-source, cross-sectional, descriptive study using longitudinal data collected from European EHR databases.

Several countries will be selected from the databases under consideration (France, Germany, Spain, Sweden, and the UK). The justification of the selected countries will be based on the feasibility assessment results (Section 9.5.2) and the market uptake and volume of dulaglutide in each country.

Study period

The study will be conducted for at least three years post launch of dulaglutide (January 2015). The analyses and reporting will commence approximately one year after the launch of dulaglutide, as soon as the data on 1000 initiations of dulaglutide are available in the databases with at least 100 cases available in the smallest contributing country.

Three waves of data extraction/collection and analysis will be performed within at least three years, based on launch projections:

- 1st wave: Q3 2016 (covering patients having initiated the drug from Q1 to Q4 2015)
- 2nd wave: Q2 2017 (covering patients having initiated the drug from Q1 to Q4 2016)
- 3rd wave: Q2 2018 (covering patients having initiated the drug from Q1 to Q4 2017)

9.2. Setting and Population

9.2.1. Setting

This study will be conducted using electronic longitudinal databases including data collected in outpatient settings of the target countries.

9.2.2. Inclusion Criteria

The eligible patients are those who meet the following criteria:

- Patients for whom a treatment with dulaglutide is initiated during the observation period.
- Patients having at least 6 months of available continuous history prior to the date of the first dulaglutide prescription.

No exclusion criteria will be applied to the study.

9.2.3. Population of Interest

The population of interest includes all patients receiving an initiation of dulaglutide during the observation period for each wave of the study. The use of dulaglutide will be analysed overall and within the following subgroups of patients.

- Populations of interest:

- Patients with severe renal failure
- Patients with hepatic disease
- Patients with heart failure
- Patients with severe gastrointestinal disease
- Children and adolescents <18 years of age
- Elderly patients ≥75 years
- Pregnant and breastfeeding women

o Medication use:

- Medication errors
- Off-label use

9.3. Variables

Regardless of the coding system used in the database, different populations and subgroups of interest are defined as follows:

Treatment initiation with dulaglutide:

- any record of prescription of dulaglutide during the observation period without prior record of prescription of the same product in the available patient's history
- if no prior history is available to check the above criteria, the prescription is not considered as an initiation

Patients presenting with T2DM:

- with any recorded diagnosis code for T2DM
- or with any recorded treatment code for an ADM other than insulin
- or, with any recorded treatment code for insulin initiated at age >30 (defined as no record of insulin therapy during 6 months prior to first record of insulin treatment)
- or with any record of unspecified diabetes mellitus diagnosis at age >30 and without history of insulin therapy (defined as no record of insulin therapy during 6 months prior to first record of diabetes diagnosis),
- a sensitivity analysis will be conducted to determine the age threshold mentioned above (see section 9.7.3 Sensitivity analysis).

Patients with severe renal failure:

- with a recorded diagnosis of severe renal failure
- or with a recorded glomerular filtration rate (eGFR) value <30 ml/min/1.73 m²

Patients with hepatic disease:

- with a recorded diagnosis of any hepatic disorder

Patients with heart failure:

- with a recorded diagnosis of heart failure

Patients with severe gastrointestinal disease:

- with a recorded diagnosis of any of the following conditions:
  - cancer of the gastrointestinal tract,
  - diseases of the oesophagus,
  - active ulcer at the time of drug initiation (gastric, duodenal, gastro-jejunal, peptic ulcer of unspecified site),
  - active haemorrhagic gastritis, chronic atrophic gastritis, adult hypertrophic pyloric stenosis, obstruction of duodenum, and other motility disorders,
  - digestive fistula,
  - Crohn's disease, ulcerative colitis,
  - diverticular disease of the intestine,
  - severe vomiting, severe diarrhoea and severe constipation
  - motility disorders, including ileus, gastroparesis, et cetera,
  - infectious and inflammatory situations (appendicitis, cholecystitis, cholangitis).

Children and adolescents:

- Age < 18 at the time of treatment initiation
  (subgroups of analysis: 0-4, 5-9, 10-14, and 15-17 years old).

Elderly:

- Age ≥ 75 at the time of treatment initiation.

Pregnant and breastfeeding women:

- Any record of pregnancy or breast feeding at the time of treatment initiation.

Patients with medication errors:

- Prescribed and/or administered > 1 dose per week of dulaglutide (6).
- The number of doses/week will be calculated by measuring the time span between the current prescription and the next one (in weeks) and dividing the number of injections prescribed in the current prescription by this time span. This number of doses/week will be used in the cross sectional study as an attribute of the prescription to assess the occurrence of medication errors as described above.

Patients with off-label use:

- Prescribed dulaglutide with no diagnosis of T2DM as defined above, at the beginning of this list of subgroups of populations.
- Prescribed dulaglutide with a diagnosis of T2DM as defined above and without a record of other ADMs during the 6-month baseline period, i.e. dulaglutide was prescribed as first-line therapy.

9.3.1. Outcomes/Measurements of Interest

The following variables will be analysed in each subgroup of interest and among patients initiated with dulaglutide (Table 9.3.2-1):

- Patients' demographics (age and gender) at baseline
- Relevant comorbidities
- Medical history: disease diagnoses (using appropriate disease classification)
- Concomitant ADMs
- Other drug exposures (main therapeutic classes)
- Average daily dosage of prescriptions
- Prescriptions in combination with other ADMs

9.3.2. Collected variables

To assess the above subgroups and measurements of interest, several variables will be extracted from each database whenever available: demographics, medical history, treatment, clinical and clinical laboratory data on patients. These variables along with their corresponding International Classification of Disease, 10th version (ICD-10) codes are presented in this protocol (Table 9.3.2-1). For CPRD database, the corresponding Read codes will be specified in the statistical analysis plan (SAP).

Table 9.3.2-1. Variables, Subgroups and Measurements of Interest in Dulaglutide Initiators

Variable, subgroup or outcome/measurement	Definition and categories*
Patients demographics at initiation of dulaglutide use:	
Age	< 18, 18-44, 45-64, 65-74, ≥75 years
Gender	Male or Female
BMI categories,	Weight (kg) / Height (cm)^2
	< 18.5, 18.5-25, 26-30, > 30 kg/m^2
Countries	UK, Germany, Sweden (or Spain and France)
Co-morbidities, at initiation of treatment to identify the subgroups of interest:	
• History of severe renal failure	ICD-10 code N18.5, N18.5
• Heart failure	ICD-10 codes I50, I11, I13
• Hepatic disease	ICD-10 codes B18, K70-K77, C22
• Severe gastrointestinal disease	ICD-10 codes C15-C26 K22.0, K22.1, K22.2 -K22.6, K23-K28, K29.0, K29.4 K50, K51, K55, K57
• Children and adolescents	Age < 18 (subgroups: 0-4, 5-9, 10-14, 15-17 years)
• Elderly	Age ≥ 75
• Pregnant women	ICD-10 codes: A34, E23.0, F53, M83,O00-O99, O24.1,
• Breastfeeding women	O24.3, O24.9, Z32-Z36, Z39 Z39.1
Lab tests values (if available):	Abnormal values:
• Haemoglobin A1c (HbA1c)	< 6.5%, >=6.5%
• e-GFR	eGFR value < 30 ml/min/1.73 m²
• Serum Creatinine	< 120, ≥120 µmol/L or mg/dL (male) < 100, ≥100 µmol/L or mg/dL (female)
Urine albumin/creatinine ratio (UACR)	UACR >30 mg/g: albuminuria present:
• LDL-C (LDL-cholesterol)	< 1.6, ≥ 1.6 g/L
• HDL-C (HDL-cholesterol)	< 0.35 g/L, ≥0.35 g/L
• AST/ALT	≤ 2 or > 2 times upper limit of the normal range
• Bilirubin	< 2, >7mg/L
• Beta hCG	Positive

Variables, Subgroups and Measurements of Interest

Variable, subgroup or outcome/measurement	**Definition and categories***
Other comorbidities frequent in T2DM patients:	
Dyslipidemia	ICD-10 codes E78 or lipid modifying agents (ATC C10)
Hypertension	ICD-10 codes I10-I15 or antihypertensives (ATC C02, C03, C04, C07, C08, C09) with no angina pectoris (I20, I25)
Macrovascular complications:	
Ischaemic heart disease	ICD-10 codes I20-I25 or antiangina agents (ACT C01D, C07, C08, C09)
Stroke	I61-I64
Peripheral arterial obstructive disease	I70.2
Microvascular complications:	
Diabetic neuropathy	G62.9
Diabetic retinopathy	H36.0
Diabetic nephropathy	N08.3
Solid tumours (Cancer)	
• liver	ICD-10 codes C220-C229
• pancreas	ICD-10 codes C250-C259
• endometrium	ICD-10 code C541
• colon	ICD-10 codes C182-C189
• rectum	ICD-10 code C20
• breast	ICD-10 codes C500-C509
• bladder	ICD-10 codes C670-C679
Dulaglutide dose: per 0.5 ml	Dose: 0.75 mg / week 1.5 mg / week >1.5 mg / week

Variables, Subgroups and Measurements of Interest

Variable, subgroup or outcome/measurement	Definition and categories*
Concomitant medications for T2DM, at index date of dulaglutide initiation	• Molecule: INN/brand name • ATC code or associated medcode for AMD A10A Insulins and analogues o A10AB Insulins and analogues for injection, fast-acting o A10AC Insulins and analogues for injection, intermediate-acting o A10AD Insulins and analogues for injection, intermediate- or long-acting combined with fast-acting o A10AE Insulins and analogues for injection, long-acting o A10AF Insulins and analogues for inhalation A10B Blood glucose lowering drugs, excluding insulins o A10BA Biguanides o A10BB Sulfonylureas o A10BD Combinations of oral blood glucose lowering drugs o A10BF Alpha glucosidase inhibitors o A10BG Thiazolidinediones o A10BH Dipeptidyl peptidase 4 (DPP-4) inhibitors o A10BX Other blood glucose lowering drugs (exenatide, liraglutide, lixisenatide, albiglutide), excluding insulins A10P SGLT2 Inhibitors
Other concomitant medications, at index date of dulaglutide initiation	• ATC codes or associated medcode for main pharmacological classes.
History of medications for T2DM, during 6-month baseline period	• ATC code or associated medcode for anti-diabetes medications (see above)
History of other medications, during 6-month baseline period	• ATC code or associated medcode for main pharmacological classes.
Off-Label Use	• Patients without T2DM • Patients with T2DM for whom dulaglutide was prescribed as first-line therapy

Variable, subgroup or outcome/measurement	Definition and categories*
T2DM	Any of the below conditions: • ICD-10 code E11 • ATC codes A10P or A10X • ATC codes A10A initiated at age>30 • ICD-10 codes E14 first recorded at age>30 without ATC code A10A in the previous 6 months

Abbreviations: ALT= alanine amino transferase; AST= aspartate amino transferase; Beta hCG=Beta subunit of human chorionic gonadotrophin; BMI= body mass index; eGFR= estimated glomular filtration rate; HDL-C= high density lipoprotein cholesterol; ICD-10= International classification of disease, 10th version; LDL-C= low density lipoprotein cholesterol; T2DM= type 2 diabetes mellitus; UK= United Kingdom.

* continuous variables will be also presented by means, SD, et cetera.

9.4. Data Sources

Several European EHR databases will be used to evaluate dulaglutide uptake, volume and data availability. The following databases have been selected for further consideration based on data availability and completeness:

- France: IMS Disease Analyzer (French DA),
- Germany: IMS Disease Analyzer (German DA),
- Spain: The Information System for the Development of Research in Primary Care (SIDIAP),
- Sweden: National Health registers that is, National patient register (NPR) and the Swedish prescribed drug register (SPDR),
- United Kingdom: Clinical Practice Research Datalink (CPRD).

9.4.1. Disease Analyzer in France and Germany

The IMS Disease Analyzer (DA) is a longitudinal patient database providing information from continuing physician and patient interactions on consultations, diagnoses and treatments. This database is available in France and Germany. Anonymous data are collected continuously through the medical software, allowing longitudinal follow-up of all the different visits of the same patient consulting the same general practitioner (GP) in the panel. The collected data include administrative (for example, insurance scheme, socioeconomic status), demographic (for example, age, gender, region), anthropometric (for example, height, weight, body mass index [BMI]), clinical (signs, symptoms and diagnoses according to ICD-10 classification), laboratory (lab results reported by the physicians) and therapeutic (EPHMRA/ATC class, molecule / brand name, dosage, route of administration) information. An update of the database is done monthly with a lag time of 6 weeks.

Comparisons with external data sources (for example, data from statutory health insurances) underline the validity and representativeness of the German DA in pharmacoepidemiological and pharmacoeconomic studies (7).

The DA is currently used by the European Medicines Agency (EMA) as one of its resources for answering research questions.

DA in France:
The data collection is based on five different EHR applications used by 1200 GPs. The French database is representative in terms of GP distribution, patient profile, age group, and sex. It allows for a longitudinal follow-up of all the different visits of the same patient consulting the same GP in the panel. Due to the role of GPs as the first point of care in France, the loyalty of patients to GPs is very high and each GP provides a continuous follow-up of patients.

DA in Germany:
The German DA is based on patient records continuously collected from 2400 computerised practices (including 1400 GPs and 1000 specialists), using three different EHR application. The sample is designed to be representative of Germany (7).

9.4.2. SIDIAP in Spain

The SIDIAP database contains information from 274 primary care centres in Catalonia, Spain, with a source population of 5.5 million patients which encompasses 80% of the total Catalan population. The SIDIAP aims to register all health information with research value in an anonymised database for every patient.

The Primary Care e-records (eCAP) database which contains information on primary care since 2000 is the basis of the source population in SIDIAP. Various external data sources can be linked to eCAP as required to provide a more complete picture of the cohort profile. In this study, it is proposed to use eCAP, Catalan Health Service Database (SIAP), Pharmacy Official Invoice Database, Primary Care Lab Database, and CMBD-AH to capture the parameters required in this study.

Table 9.4.2-1. Collectable Data in the Databases Linkable to SIDIAP

Variables	Source	Years available
Clinical (GP visits, referrals, vaccines, smoking, drinking, body mass index, blood pressure, spirometry, ICD-10 codes, etc.)	eCAP (Primary Care e-records)	>2000
Sociodemographics (date of birth, gender, country of origin)	SIAP (Catalan Health Service Database)	>2000
Drugs dispensed in community pharmacies	Pharmacy Official Invoice Database (subsidised drugs)	>2005
Lab tests (creatinine, HbA1c, et cetera.)	Primary Care Lab Database	>2006

Abbreviations: GP= general practitioner; HbA1c= haemoglobin A1c; ICD-10= International classification of disease, 10th version.

9.4.3. NPR and SPDR in Sweden

Swedish data combine data from the NPR, covering all specialist and hospital care in Sweden, and the SPDR, covering all drugs dispensed at pharmacies in Sweden. The national registers are

updated at least quarterly. These longitudinal data enable to find out comorbidities and historical clinical information on the subjects treated for their T2DM in a hospital, as well as drug prescription details (both primary and secondary care). Prescriptions are not formally linked to an ICD-10 code, but clinical input could provide rationale for linking prescriptions and diagnosis made in secondary care. However, information on patient anthropometric data (height, weight, BMI) are not available through the databases, nor are lab results and clinical measurements such as HbA1c, blood pressure and blood lipid levels.

9.4.4. CPRD in the UK

The CPRD is a well-validated database with high-quality information on medications, laboratory data, specialist referral and diagnoses assigned by primary care clinicians. It is jointly funded by the NHS National Institute for Health Research (NIHR) and the Medicines and Healthcare products Regulatory Agency (MHRA).

The CPRD has one of the world's largest computerised databases of anonymised longitudinal medical records from primary care that is linked with other healthcare data in the UK. Currently, data are being collected on approximately 5 million active patients from around 683 primary care practices throughout the UK (about 8% of the universe).

9.4.5. Summary of Data Sources

The following table (Table 9.4.5-1) presents the expected data which could be provided from local databases.

Table 9.4.5-1. Data Availability per Database / Country

Data availability per country (local database)	France (FR-DA)	Germany (DE-DA)	Spain (SIDIAP)	Sweden (NPR and SPDR)	The UK (CPRD)
Demographics (age, gender)	Yes	Yes	Yes	Yes	Yes
Clinical parameters (height, weight, BMI,)	Yes	Yes	Yes	No	Yes
Physiological status: pregnancy breastfeeding women	Very limited	Very limited	Very limited	Very limited	Very limited
Date of consultation	Yes	Yes	Yes	Yes	Yes
Diagnosis	Yes ICD-10 codes	Yes ICD-10 codes	Yes ICD-10 codes	Yes ICD-10 codes	Yes READ codes
Prescribed drug characteristics (name, form, package, classification code)	Yes (ATC/EphMRA codes)	Yes (ATC/EphMRA codes)	Yes (ATC codes)	Yes (ATC codes)	Yes (associated medcodes)
Dosage	Yes	Yes	Yes	Yes	Yes
Duration exposure	Yes	Yes	Yes	Yes	Yes

Co-prescriptions	Yes	Yes	Yes	Yes	Yes
Treatment history	Yes	Yes	Yes	Yes	Yes
Biological test (HbA1c, cholesterol level, creatinine, ..)	Yes	Yes	Yes	No	Yes

Abbreviations: CPRD= Clinical Practice Research Datalink; DE-DA= Deutschland Disease Analyzer; FR-DA= France Disease Analyzer; HbA1c= haemoglobin A1c; ICD-10= International classification of disease, 10th version; NPR= National Prescription Registry; SIDIAP= The Information System for the Development of Research in Primary Care; SPDR= Swedish prescribed drug register.

9.5. Study Size

9.5.1. Sampling

The real number of eligible patients included in the dulaglutide group will depend on the uptake and volume of the drug in each country.

The sample size formula, based on the normal approximation to the binomial distribution, for calculation of the number of subjects *n* required to determine a proportion *p* with a precision *e* with a two-sided α first-type error is the following:

$$\boldsymbol{n} = \frac{\boldsymbol{p}\times(\boldsymbol{1}-\boldsymbol{p})\times \boldsymbol{z}_{\boldsymbol{1}-\boldsymbol{\alpha}/\boldsymbol{2}}{}^{\boldsymbol{2}}}{\boldsymbol{e}^{\boldsymbol{2}}} \quad (1)$$

Based on this sample, and considering a confidence interval of 95%, in order to be able to determine any percentage with a precision of at least ±5%, 384 subjects will be necessary. This corresponds to a hypothetical proportion of 50% which is generally considered acceptable as it yields to the largest sample size for each precision level. Respectively, a precision of at least ±3% or ±10% would necessitate a sample size of 1066 or 97 dulaglutide initiated patients.

In this study, assuming that we would like to be able to describe any proportion with a precision of at least 10% in each country, a minimum sample size of 100 cases is required for any of the countries. Assuming we want that the smallest country to represent at least 10% of the whole sample, it was pragmatically decided to start the study when data on 1,000 initiations of dulaglutide are available in the considered databases with at least 100 cases available in the smallest contributing country.

9.5.2. Feasibility Assessment

Some other characteristics of candidate databases along with current counts of physicians diabetic patients, as well as those treated with GLP-1 receptor agonists is presented below (Table 9.5.2-1).

Table 9.5.2-1. Database Characteristics and Patient Numbers

Database description	France (DA)	Germany (DA)	Spain (SIDIAP)	Sweden (NPR and SPDR)	The UK (CPRD)
Size of the panel (number of physicians or practices)	1,100 GPs	1,409 PCPs	274 practices	All patients according to inclusion criteria	683 PCPs
Data available since	1997	1992	2000 – 2006§	2005 (1997)	1994
Data lag time	1 month	6 weeks	1 year (data provided in May)	6 months	
Pharmacy information	not available	not available	available	available	not available
Number of patients treated with an anti-diabetic treatment / with diabetes	61,591	96,947 in 2013 / 159,014 last 5 years	23,000 treated for T2DM in 2013	Ca. 400,000	16,479 newly-diagnosed patients in 2014
Number of patients treated with GLP-1 RAs	2,462	2,873 in 2013 / 5,457 last 5 years	About 3,500 in 2013	Ca. 12,000	1,877 new users in 2014; total: 8,010 patients

Abbreviations: CPRD= Clinical Practice Research Datalink ; DA= Disease Analyzer; GLP-1 RA= glucagon-like peptide-1 receptor agonists; GP= general practitioner; NPR= National Prescription Registry; PCP= SIDIAP= The Information System for the Development of Research in Primary Care; SPDR= Swedish prescribed drug register; T2DM= type 2 diabetes mellitus.

* information available for reimbursed drugs
§ depending on the source

More specific feasibility analyses will be conducted to determine whether the data sources capture sufficient exposure to dulaglutide, allowing the DUS to start. Each database being considered will be checked on the following aspects:

- The number of eligible patients (treated with dulaglutide with 6 months baseline data prior to the first observed/recorded prescription)
- The availability and validity of each variable of interest.

The feasibility assessment will help to choose the three countries to be involved in the study, and it will also provide information for the start of data collection.

The timing and frequency of the feasibility analyses will be determined by IMS and Lilly, with the anticipation that it will take place at a maximum of twice every 12 months, in each country.

9.6. Data Management

The processes for database management will differ per country. In general, data are stored at the database level and analysed locally. The SAS Software will be used to access the raw data, manage the analytic datasets and compute data analysis.

Each database complies with local regulations in terms of data protection and record retention. The study will follow relevant chapters of European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) and International Conference of Harmonisation ICH guidelines for data management.

Data will be checked in terms of consistency before data analysis. This is mainly due to the fact that the record of information in EHR databases is not controlled (unlike case report forms). Thus the data needs to be checked for consistency in terms of range of values, units of measurement, relevance of clinical information (for example, pregnancy for men). Some data providers, such as IMS Health, have already integrated these checks in their data production workflow, so that the checks are conducted systematically on all incoming patient records before allowing them to be integrated into the database.

9.7. Data Analysis

9.7.1. General Statistical Considerations

The analysis will be performed per country, on the overall data set of eligible patients and per subpopulations.

Data coming from different databases/countries will not be pooled due to the difference between structure of panels of health care professionals who contribute the data, asynchronicity of databases, heterogeneity in data structure, coding, and prescribing practices. The analysis will be done per year, and will not be cumulative. Thus data coming from different years will not be pooled either.

The statistical analysis will be descriptive including standard univariate analysis; no inferential statistical analyses will be conducted. Continuous variables will be described by the number of available values, mean, standard deviation, median, Q1, Q3, minimum and maximum. Data not available in the databases will be reported as missing. Categorical variables will be described as the total number of available values and relative percentage per subgroup of interest. When relevant, 95% confidence intervals will be calculated for the endpoints.

The statistical analysis will be conducted using the SAS® software V9.2 or later on Windows™ (SAS Institute, North Carolina, USA).

9.7.2. Subgroups and Outcomes/Measurements Analysed to Answer the Endpoints

Analyses will be performed in the 9 subgroups of interest (See Section 9.2.3).

9.7.3. Sensitivity Analyses

A sensitivity analysis will be conducted for the calculation of off-label use. For this variable, the definition of patients with T2DM will be considered based on the criteria from variables sections. However, for the following criteria two ranges of age will be analysed, once at age>30 and <50 and the other at age>50. Both results will be presented in the study and then discussed.

- ATC codes A10A initiated at age>30
- ICD-10 codes E14 first recorded at age>30 without ATC code A10A in the previous 6 months

9.7.4. Data Tabulation

The following outcomes/measurements of interest will be analysed:

- Patients' demographics (age and gender) at baseline
- Relevant comorbidities
- Medical history: disease diagnoses (using appropriate disease classification)
- Concomitant ADMs
- Other drug exposures (main therapeutic classes)
- Average daily dosage of prescriptions
- Prescriptions in combination with other ADMs

These characteristics will be described for overall patients initiated with dulaglutide and in the subgroups of interest corresponding to dulaglutide initiators. Some characteristics of dulaglutide initiators will be described at both the index date and the baseline period, for example, concomitant medications will be defined as those prescriptions recorded at the index date of dulaglutide initiation, while medication history will be defined as those medications which were recorded during the 6-month baseline period prior to dulaglutide initiation.

Note that subgroups will not be mutually exclusive: a patient could be part of more than one subgroup (for example, elderly patients ≥75 years and with hepatic disease). The column 'All' in Table 9.7.4-1 will include the results corresponding to the overall data set and not the sum of the results of each subgroup. It also includes patients who are not categorised in any of the subgroups.

Table 9.7.4-1. Mock Table for the Description of the Use of Dulaglutide - Primary Objective: Description of the Use of Dulaglutide per Subgroups

Dulaglutide **Country: Sweden**	**Subgroups of interest**				
Outcomes/Measurements of interest	**1.Patients with severe renal failure** (N=xx)	**2.Patients with hepatic disease** (N=xx)	**...**	**9.Patients with off-label use** (N=xx)	**10.All** (N=xx)
Age (ranges)					
Missing					
< 18 years	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
0-4	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
5-9	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
10-14	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
15-17	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
18-44 years	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
45-64 years	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
65-74 years	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
≥75 years	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
Mean (SD)					
Min-Max					
Median [Q1- Q3]					
Gender					
Missing	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
Male	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
Female	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
Medical history					
T2DM duration: Time since diagnosis:					
Missing	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
> 1 year	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
[1-5	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
> 5 years	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
Mean (SD)					
Min-Max					
Median [Q1- Q3]					
T2DM treatment duration:					
Missing	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
> 1 year	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
[1-5]	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
> 5 years	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
Mean (SD)					
Min-Max					
Median [Q1- Q3]					

Mock Table for the Description of the Use of Dulaglutide - Primary Objective: Description of the Use of Dulaglutide per Subgroups

Dulaglutide **Country: Sweden**	**Subgroups of interest**				
Outcomes/Measurements of interest	**1.Patients with severe renal failure** (N=xx)	**2.Patients with hepatic disease** (N=xx)	**...**	**9.Patients with off-label use** (N=xx)	**10.All** (N=xx)
Comorbidities	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
Obesity Status (by BMI)					
Missing	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
<18.5 kg/m²	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
Normal: 18.5-25 kg/m²	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
>25-30 kg/m²	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
>30 kg/m²	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
Mean (SD)					
Min-Max					
Median [Q1- Q3]					
Hypertension	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
Dyslipidemia	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
Macrovascular complications:					
Ischaemic heart disease	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
Stroke	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
Peripheral arterial obstructive disease	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
Microvascular complications:					
Diabetic neuropathy	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
Diabetic retinopathy	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
Diabetic nephropathy	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
Solid tumours:	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
Liver	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
Pancreas	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
Endometrium	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
Colon	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
Rectum	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
Breast	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
Bladder	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)

Mock Table for the Description of the Use of Dulaglutide - Primary Objective: Description of the Use of Dulaglutide per Subgroups

Dulaglutide **Country: Sweden**	**Subgroups of interest**				
Outcomes/measurements of interest	**1.Patients with severe renal failure** (N=xx)	**2.Patients with hepatic disease** (N=xx)	**...**	**9.Patients with off-label use** (N=xx)	**10.All** (N=xx)
Dulaglutide exposure Average daily dose Missing Mean (SD) Min-Max Median [Q1- Q3]	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)

Mock Table for the Description of the Use of Dulaglutide - Primary Objective: Description of the Use of Dulaglutide per Subgroups

Dulaglutide **Country: Sweden**	**Subgroups of interest**				
Outcomes/measurements of interest	**1.Patients with severe renal failure** (N=xx)	**2.Patients with hepatic disease** (N=xx)	**...**	**9.Patients with off-label use** (N=xx)	**10.All** (N=xx)
Concomitant medications (at index date) Anti-diabetic treatments:	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
• Insulins and analogues (short- and long-acting, for injection and inhalation) (meal-time, for example, Insulin Lispro; and basal, for example Insulin Glargine).	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
• Biguanides (for example, Metformin)	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
• Sulfonylureas (for example, Glipizide)	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
• Alpha-glucosidase inhibitors (for example, Acarbose)	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
• Thiazolidinediones (for example, Pioglitazone)	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
• Dipeptidyl peptidase-4 inhibitors (for example, Sitagliptin)	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
• Sodium glucose cotransporter-2 (SGLT2) inhibitors (for example, Empagliflozin)	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
• Other GLP-1 RA	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
• Meglitinides (for example, Repaglenide)	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
• Amylin analogues (for example, Pramlintide)	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
And: • Single-pill combinations of oral ADMs • Single-injection combinations of insulin and GLP-1 RA (for example, Insulin Degludec and Liraglutide)	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)

Concomitant medications (at index date) Other treatments (main classes)	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
Dulaglutide off-label use - Patients without T2DM - Patients with T2DM for whom dulaglutide was prescribed as first-line therapy	xx (xx.x%) xx (xx.x%) xx (xx.x%)	xx (xx.x%) xx (xx.x%) xx (xx.x%)		xx (100%) xx (xx.x%) xx (xx.x%)	xx (xx.x%) xx (xx.x%) xx (xx.x%)
Medication history (at baseline period) Anti-diabetic treatments: - specific classes	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)
Medication history (at baseline period) Other treatments: - specific classes	xx (xx.x%)	xx (xx.x%)		xx (xx.x%)	xx (xx.x%)

Abbreviations: ADM= anti-diabetes medications; BMI= body mass index; GLP-1 RA= glucagon-like peptide-1 receptor agonists; T2DM= type 2 diabetes mellitus.

Note: the table structure may be adjusted in the final study report.

9.7.5. Statistical Analysis Plan

The SAP will be based on the study protocol and developed after its finalisation. It will describe in details the methodological approach that will be used to perform the final analyses, explicitly state the objectives, study design, variables of interest and statistical methodology.

Any variation among countries will be described and justified. Table shells and mock figures corresponding with the analyses and variables specified in the study protocol will also be developed. The SAP will be drafted before the feasibility assessment and will be finalised afterwards. The final version will be approved and signed by Lilly and IMS before the beginning of data collection, as recommended by ENCePP guidelines (8), and according to IMS standard operating procedures (SOPs).

9.8. Quality Control

The study will use existing databases being used widely for research, which contain data collected according to local and European law. The study programs for data management or statistical analyses will be dual validated by 2 individuals to ensure data integrity and accuracy.

The project team will follow corporate IMS Health SOPs in line with conducting observational and safety studies as well as Lilly and IMS's Quality agreement.

According to these SOPs, all project documents (that is,, Study Protocol and SAP) will be approved by the client before data extraction. Internal quality review of deliverables is part of corporate SOPs of IMS and all intermediate and final deliverables will be reviewed by one or more subject matter experts.

In addition to the above process, and upon Lilly's request, IMS will document and provide back to Lilly a quality review by a qualified individual external to the writing team of all final

deliverables (for example, interim and final reports, abstracts, posters, manuscripts) to include the following:

1. Confirm that the source of the data and/or results has been documented and that results and data have been checked by comparison to the source.
2. Check the internal consistency of the medical research data presented in the document.
3. Confirm that the conclusions are accurate, objective, balanced, and consistent with other published or released results.
4. Confirm that the format and content of the document are aligned with applicable external requirements.
5. Final annotated version of any disclosures (abstracts, posters and manuscripts).

9.9. Limitations of the Research Methods

9.9.1. Limitations Related to Specific Databases

The main limitations are related to the variables availability in the databases used to answer the study objectives:

- Data reported in the French and German DA are collected through GPs. Nevertheless, a proportion of dulaglutide prescriptions will be initiated by specialists and renewed by the GP. Some patients treated with dulaglutide will probably be followed-up only by a specialist and not be present in DA databases. Consequently, the number of patients initiated could be lower than expected in these databases.
- Some variables will not be reported for all patients by the physicians (it depends on physicians' willingness and the usefulness of the variable for clinical practice).
- The disease diagnosis will be missing for some patients or not correctly reported, especially at primary care level. Codes to identify antidiabetic treatments will be used to compensate for this under reporting of diagnoses for diabetic patients for example.
- The identification of the disease severity is very limited in the databases; it is necessary to define diagnosis via ICD-10 codes (DA, registry data).
- Lab values are not available for all patients in all databases.
- Lab values (for example, HbA1C) and risk factors (for example, BMI, blood pressure, cholesterol level) are not available in the Swedish health registers, but would be available in EHRs.
- Pregnancy (via ICD-10) information is very limited in the French and German DA.
- Data about breastfeeding are very limited in the databases.
- The number of doses administered per week is not known in SIDIAP. The number of doses dispensed in retail pharmacies can be estimated, but it needs to be considered as a proxy measure of administered doses.

- The SIDIAP database does not include information about diabetes history.
- The SIDIAP database includes only data from patients collected in the Catalonia region, and will not be representative of all T2DM patients in Spain.
- Since it will not be possible to distinguish between patients that were appropriately prescribed dulaglutide monotherapy (ie, when diet and exercise alone did not provide adequate glycaemic control and the use of metformin was considered inappropriate due to intolerance or contraindications) and patients who were prescribed monotherapy inappropriately (i.e. did not meet these criteria), the number of patients found to be taking off-label first line dulaglutide will be an overestimate of the number of actual patients taking off label first line dulaglutide.
- Medication errors will be evaluated based on the time span between the first prescription and the next one. In a number of cases the next prescription will not be still captured in the database. These cases will be considered as missing data for the analysis of medication errors. Other sources of bias:
- **Selection bias**: in some databases (for example, French and German DA) the sample of physicians are representative of the physicians in each country in terms of the stratification factors used to select the panel. However, it is not known whether the physicians who belong to the panel have the same prescription behaviour as the physicians who are not part of the panel, especially those who were invited to take part but refused. Similar considerations can be expressed for physicians who belong for a long time and physicians recently included in the panel. To control these biases as much as possible, the distribution of the strata in each data base will be compared to the distribution of strata of the corresponding physicians' population in the country. This limit does not apply to the Swedish cohorts because of their exhaustiveness.
- **Misclassification bias**: Misclassification bias can result if study subjects are not categorised correctly with regards to exposure or selected patient characteristics. Since the data bases are fully anonymised, it is impossible to verify the information with source data. This bias cannot be controlled as there is no possibility to check the information in databases. For example, the definition of severe renal failure is based on eGFR. However, this value may not be recorded relevantly in the database. Consequently, there may be false negatives of severe renal failure, that is, those with this condition who are classified as not having the severe renal failure.
- **Information bias**: Recording bias can result if the information is not systematically recorded, which is the case in EHR databases (as opposed to claims databases). Consequently, the missing information is not missing by random. For example, clinicians tend to register abnormal values more often than normal ones. In this study, we will not impute missing values and report them as such.

9.10. Other Aspects

Not applicable.

10. Protection of Human Subjects

This study will be conducted in accordance with applicable laws and regulations of the region, country or countries where the study is being conducted, as appropriate.

The study will be submitted to ethical review boards (ERBs) for approval whenever required by local law. Regulatory authorities will be notified and approval sought as required by local laws and regulations. Progress reports will be submitted to ERBs and regulatory authorities as required by local laws and regulations.

10.1. Regulatory and Ethics Considerations

There are no specific requirements for this type of study conducted using secondary data for France and Germany.

The study will be submitted to the ethics committees in the corresponding countries from which the databases will be used to follow the regulatory and ethical requirements of each country as described below:

In Spain, the study requires three submissions / approvals:

- All post-authorisation safety study (PASS) studies performed in Spain needs to be classified by the Spanish Agency of Drugs. The agency takes about 3 weeks for classification (required for the next step).
- In a second step, the study protocol will be presented to the Scientific Committee from SIDIAP. The approval of the Scientific Committee is required to perform the study.
- A third and last step is the presentation of the study to the Ethical Committee of the Hospital Germans Trías i Pujol of Badalona.
- IMS will prepare the necessary documents and present the study on behalf of Lilly to the required agencies and committees.

In Sweden, the study requires two submissions / approvals:

- In order to gain access to the linked register, an approval from the local ethical review board is necessary, whereby the research project and ethical aspects should be explained in a formal application, with attached protocol. The ethics approval is dependent on the data being made publicly available in some form.
- Then, a standard application will be submitted to the National Board of Health with attached approval from Ethical Committee.

The ethical approvals process takes approximately 10-11 weeks.

In the UK, the study requires one submissions / approvals:

- The study protocol must be submitted to the Independent Scientific Advisory Committee (ISAC) using the CPRD ISAC Application form. This was developed by the CPRD

Group in consultation with ISAC. Protocol requirements are broadly based on the International Society for Pharmacoepidemiology (ISPE), Good Pharmacoepidemiology Practices, and have been implemented to ensure that the issues considered essential for ISAC evaluation are covered in the protocol.

The ethical approvals process takes up to one month and a half, including the submission of the modifications or additional request.

11. Management and Reporting of Adverse Events/Adverse Reactions

Adverse Event Collection for Observational Studies

During the course of observational research using existing secondary databases, the proposed study will not involve chart review or validation to obtain additional information on the adverse events. Thus, Lilly is not expecting to report any adverse events or reactions.

Researchers will report all adverse reactions with attribution explicitly stated in the individual patient records to the appropriate party (for example, regulators or marketing authorisation holder) as they would in normal practice as required by applicable laws, regulations, and practices.

12. Plans for Disseminating and Communicating Study Results

The study will be registered in ENCePP e-register of studies by Lilly.

An interim analysis and a report will be prepared once a year for three years post data collection.

A final study report will be written in MS Word format using Lilly's template and following strengthening the reporting of observational studies in epidemiology (STROBE) and good pharmacovigilance practices (GVP) recommendations (9,10). The final study report will be submitted to Committee for Medicinal Products for Human Use (CHMP)/EMA within one year after study conclusion.

Study findings may be presented at a congress to be specified later.

Publications may result from this study and be submitted to a peer-reviewed journal.

13. References

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Annex 1. List of Stand-Alone Documents

Not applicable.

Annex 2. ENCePP Checklist for Study Protocols

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

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 & does not replace the format of the protocol for PASS as recommended in the Guidance & Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
Utilisation of dulaglutide in European countries: A cross-sectional, multi-country and multi-source drug utilisation study using electronic health record databases.

Study reference number:
EMEA/H/C/002825

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]	☒	☐	☐	13,15
1.1.2 End of data collection[2]	☒	☐	☐	13,15
1.1.3 Study progress report(s)	☒	☐	☐	13,15
1.1.4 Interim progress report(s)	☒	☐	☐	13,15
1.1.5 Registration in the EU PAS register	☒	☐	☐	1,15
1.1.6 Final report of study results.	☒	☐	☐	13,15

Comments:
The study milestones may change according to the dates of drug launch in the participating countries (see p13 and §6: Milestones p15).

[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)
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 important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	10,16,17
2.1.2 The objective(s) of the study?	☒	☐	☐	10,17
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	18,19
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:

For 2.1.3, see §9.2.2: Inclusion criteria p.18 and § 9.2.3: subgroups of interests p.19 of the protocol. For 2.1.4, there is no formal hypothesis.

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)	☒	☐	☐	11,18
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	
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:

For 3.2, the objectives will be answered by descriptive analysis. The endpoints are defined as in §9.3.1: Outcomes/Measurements of interests p20.

Section 4: Source and study populations	Yes	No	N/A	Page Number(s)
4.1 Is the source population described?	☒	☐	☐	18,19
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	13,15
4.2.2 Age and sex?	☒	☐	☐	11,19,22
4.2.3 Country of origin?	☒	☐	☐	12,24,25
4.2.4 Disease/indication?	☒	☐	☐	16,19,24
4.2.5 Co-morbidity?	☒	☐	☐	22
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)	☒	☐	☐	27

Comments:

For 4.2.6, there is no seasonality for diabetes disease.

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

Section 5: Exposure definition and measurement	Yes	No	N/A	Page Number(s)
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)	☒	☐	☐	22
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	22
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	22
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☒	☐	☐	

Comments:

The exposure to GLP-1 receptors agonists will be assessed.

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?	☐	☐	☒	
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:

For 6.1, the survey is descriptive. No specific endpoints are defined, see §9.3.1: Outcomes/Measurements of interest p20 thal will be analysed.

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:

N/A

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.)	☒	☐	☐	24-27
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.)	☒	☐	☐	20,22
8.1.3 Covariates?	☐	☐	☒	
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)	☒	☐	☐	24-27
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	20,22

Section 8: Data sources	Yes	No	N/A	Page Number(s)
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☐	☐	☒	
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	22
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	22
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	22
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

For Endpoints: see § 9.3.1 outcomes/measurements p 20. For 8.1, see §9.4: Data sources p24-27. For 8.3, see §9.3.2: Table of subgroups, variables, outcomes/measurements p22.

Section 9: Study size and power	Yes	No	N/A	Page Number(s)
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	12,27

Comments:

For 9.1, see §9.5: Study size, §9.5.1: Sampling p27 and §9.5.2: Feasibility assessment.

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?	☒	☐	☐	12,29
10.3 Are descriptive analyses included?	☒	☐	☐	12,22,29
10.4 Are stratified analyses included?	☒	☐	☐	12,22,29
10.5 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:

For 10.1,2,3, see §9.3.2: Table of subgroups and variables p22 and §9.7: Data analysis p29.

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?	☒	☐	☐	29
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	25
11.3 Are methods of quality assurance described?	☒	☐	☐	35
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	36
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	29

Comments:

For 11, see § 9.6: Data management p29 and § 9.8 Quality control p35.
For 11.4 see § 9.9.1 Limitations related to specific databases p36.

Section 12: Limitations	Yes	No	N/A	Page Number(s)
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	37
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	37
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	28
12.3 Does the protocol address other limitations?	☒	☐	☐	36,37

Comments:

For 12, see § 9.9 Limitations of the research methods p36,37.

Section 13: Ethical issues	Yes	No	N/A	Page Number(s)
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	38,39
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	38,39

Comments:

For 13.1, see § 10 Protection of human subjetcs, § 10.1.1 Regulatory and Ethics considerations p.38.

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?	☒	☐	☐	14

Comments:

For 14.1, see §5: Amendments and updates p14.

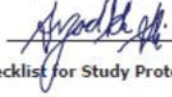
Section 15: Plans for communication of study results	Yes	No	N/A	Page Number(s)
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	41
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	41

Comments:

For 15.1, see §12 p41, the final study report including the results of all countries will be submited to EMA, and study findings may be presented in congresses.

Name of the main author of the protocol: Ayad Ali, PhD

Date: 28 April 2015

Signature: 

Annex 3. Additional Information

None.

Leo Document ID = 7143d46b-91de-456b-a038-8287c70adee0

Approver: David Bradley Woodward (AM\A515116)
Approval Date & Time: 30-May-2016 12:50:50 GMT
Signature meaning: Approved

Approver: Valerie Elizabeth Simmons (EMA\YE74498)
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Signature meaning: Approved

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Approval Date & Time: 07-Jun-2016 13:44:17 GMT
Signature meaning: Approved