Protocol

Study ID: NN304-4528

Retrospective Cohort study of all-Cause and Cardiovascular Mortality in type 2 diabetes patients using basal insulin Detemir and Glargine

Redacted protocol
Includes redaction of personal identifiable information only.

Non-interventional (NIS) post authorisation safety study *(PASS)*

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PASS information

Title	Retrospective cohort study of all-cause and cardiovascular mortality in type 2 diabetes patients using basal insulin detemir and glargine
Protocol version identifier	1.0
Date of last version of protocol	07 May 2019
EU PAS Register number	Study not yet registered
Active substance	Insulin Detemir (A10AE05) Insulin Glargine (A10AE04)
Medicinal product	Levemir® Lantus® Toujeo®
Product reference	NA
Procedure number	NA
Marketing authorisation holder(s)	Novo Nordisk A/S
Joint Post Authorisation Safety Study (PASS)	No
Research question and objectives	The overall objective is to estimate the differences in all-cause and cardiovascular mortality rates between new users of basal insulin Glargine and Detemir in a population-based study of type 2 diabetes patients 40 years or older in UK in the years 2004-2018. The hypothesis is that use of insulin Detemir is associated with a lower all-cause and cardiovascular mortality than use of insulin Glargine.
Country(-ies) of study	United Kingdom (UK)

Marketing authorisation holder(s)

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

ACS	Acute Coronary Syndrome
AE	Adverse Event
AESI	Adverse Event of Special Interest
AMI	Acute Myocardial Infarction
AR	Adverse Reaction
BMI	Body Mass Index
CCDS	Company Core Data Sheet
CI	Confidence Interval
CKD	Chronic Kidney Disease
CMS	Contract Management System
CPRD	Clinical Practice Research Datalink
CRF	Case Report Form
CRO	Contract Research Organisation
CV	Curriculum Vitae
CVD	Cardiovascular Disease
EAS	Efficacy Analysis Set
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU PAS	The EU electronic register of post-authorisation studies maintained by the European Medicines Agency
FAS	Full Analysis Set
GPP	Good Pharmacoepidemiological Practice
GVP	Good Pharmacovigilance Practice
HF	Heart Failure
HR	Hazard Ratio
ICMJE	The International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISPE	International Society for Pharmaceutical Engineering

ITT	Intention to treat
LAR	Legally Acceptable Representative
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
NIS	Non-interventional Study
NPH	Neutral Protamine Hagedorn
ONS	Office for National Statistics?
PAD	Peripheral Arterial Disease
PASS	Post Authorisation Safety Study
PH	Proportional Hazard
QPPV	Qualified person responsible for pharmacovigilance
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SAS	Safety Analysis Set
TIA	Transient Ischemic Attack
T2D	Type 2 diabetes
UK	United Kingdom
UTN	Universal Trial Number
UTS	Up to standard
WHO	World Health Organisation
WMA	World Medical Association

3 Responsible parties

Chief investigator of this study is [redacted] at Novo Nordisk). Other investigators involved include [redacted] at Novo Nordisk), [redacted] at Novo Nordisk), [redacted] at Novo Nordisk), and [redacted] at Novo Nordisk).

4 Abstract

The impact of different types of basal insulins in patients with type 2 diabetes on risk of death and death from cardiovascular diseases is unclear. Compared to the traditional insulin Neutral Protamine Hagedorn (NPH), subsequently developed, longer-acting insulin analogues such as insulin Detemir have shown benefits in randomized controlled trials. Whether these advantages translate into lower mortality among users in real life is unknown. Therefore, the aim of this study is to estimate the differences in all-cause and cardiovascular mortality rates between first time users of basal insulins (Detemir vs Glargine) in a population-based study in UK.

Patients with type 2 diabetes aged ≥40 years, who initiated basal insulin therapy (Detemir or Glargine) in 2004-2018 will be identified from Clinical Practice Research Datalink (CPRD), with comprehensive data on mortality, cause of death, and background variables. The estimates will be adjusted for relevant patient characteristics at time of treatment initiation. Follow-up time will be up to 14 years (median 4 years). Exposure variables are defined in two ways: 1) "ITT (Intention to treat)" where patients are allocated to the first used basal insulin throughout follow-up. 2) "On treatment of the first drug used" where patients are followed while they are on the first used drug and until time of first switch to another treatment, where they are censored. A "lag time of one year" for each treatment episode is used.

In the "on treatment of the first drug used" approach, the exposure is time dependent. Patients can stop and start the first used drug throughout follow-up, but are censored at time of first switch in treatment; including a one year "lag time" for each treatment episode. "Switch" in treatment is defined as start of another basal insulin than "the first used drug". Thus, the categories of exposure are "on Detemir", "on Glargine", or "no exposure/unknown".

The fully adjusted Cox's Proportional Hazard (PH) model will include the exposures of interest and adjustment variables such as age, calendar year, sex, diabetes duration, Body Mass Index (BMI), history of Cardiovascular Disease (CVD), CVD medication and non-insulin glucose-lowering medications at time of insulin initiation. Time dependent variables are assessed i.e. "non-insulin glucose-lowering medications," bolus insulin" and "smoking status". The study will provide knowledge of comparative mortality among users of insulin Detemir compared to users of insulin Glargine in real clinical practice. Considering the large number of patients who require insulin

therapy, a potential difference in risk of death may have major clinical and public health implications.

4.1 Title

Retrospective cohort study of all-cause and cardiovascular mortality in type 2 diabetes patients using basal insulin Detemir and Glargine (PASS).

4.2 Rationale and background

The study will provide knowledge of mortality among users of insulin Detemir compared to users of insulin Glargine in real clinical practice. Considering the large number of patients who require insulin therapy, new knowledge of a potential difference in risk of death may have major clinical and public health implications.

Insulin Detemir has shown advantages over insulin NPH, such as a lower risk of hypoglycaemia and weight gain, in randomized clinical trials (RCTs) [1,2], as well as in short observational studies [3]; and one long-term observational study conducted in Finland showed survival benefit [4]. However, it is not known whether these potential advantages translate into reduced risk of death in the long term in other populations. RCTs are often of short duration, whereby hard endpoints such as cardiovascular mortality cannot be recognized. Moreover, the patients randomized into clinical trials are not necessarily representative of the general population, because patients with advanced age, co-morbidities, or a history of hypoglycaemias may have been excluded. Overall, the mortality risk associated with insulin use has not been extensively examined in real-life, and well-designed studies assessing Detemir vs Glargine use and risk of death are needed.

4.3 Research question and objectives

The aim of this UK register-based cohort study is to investigate the potential differences in risk of death in users of insulin Glargine and Detemir in terms of all-cause and cardiovascular mortality among patients with type 2 diabetes in real-life clinical practice.

The overall objective is to estimate the differences in all-cause and cardiovascular mortality rates between new users of basal insulin Glargine and Detemir in a population-based study of type 2 diabetes patients 40 years or older in UK in the years 2004-2018.

The hypothesis is that use of insulin Detemir is associated with a lower all-cause and cardiovascular mortality than use of insulin Glargine.

The specific aims are to assess 1) Rates of all-cause mortality, and 2) Rates of cardiovascular mortality

4.4 Study design

This is a PASS.

The study is a retrospective cohort study comparing all-cause and cardiovascular mortality rates (hazard rates) in new users (T2D, ≥ 40 years at initiation) of basal insulins Glargine and Detemir. The study period is defined as 2004 to 2018, as both insulins were available for prescription from 2004 (where both drugs were approved in UK).

4.5 Population

The patients included in the present study have type 2 diabetes, and are aged 40 years or above at time of initiating basal insulin therapy in January 2004- December 2018. The study will include patients for whom the information is of acceptable quality, which is defined by standard checks conducted by the data owners (CPRD).

4.6 Variables

The exposure variables are usage of either insulin Glargine or insulin Detemir. The exposure variables will be defined in two different ways: 1) "ITT (Intention to treat)", or 2) "On treatment of the first drug used" (see section 9.3 for more details).

The outcome variables are all-cause mortality (from CPRD GOLD and linkage to ONS death registration data), and CVD mortality (linkage ONS death registration data).

Covariates to be included are: calendar year of index date, age (years), sex (male/female), socioeconomic status, diabetes duration (years), smoking status (ever , never), non-insulin glucose-lowering medications, bolus insulins, CVD medications, prior hypoglycaemia (Y/N), history of CVD, BMI (continuous), HbA1c (continuous), dyslipidemia (Y/N), elevated blood pressure (Y/N), history of cancer (Y/N), serum creatinine (eGFR, continuous), and history of nephropathy (Y/N), retinopathy (Y/N), neuropathy (Y/N), and CKD (Y/N).

4.7 Data sources

Patients to be included in the study will be identified through registers, i.e. the Clinical Practice Research Datalink (CPRD). Further information can be found here: https://www.cprd.com/

The analysis on cardiovascular mortality will be undertaken based on practices, which have consented linkage. Linkage to ONS death registration data is necessary to retrieve information on cause of death. Linkage to Area Level Data is necessary to obtain data on socioeconomic status, which is considered a potential confounder.

4.8 Study size

The total study population fulfilling all inclusion criteria comprise 12884 patients (Glargine: 9850; Detemir: 3034) of which 6898 can be linked to the ONS mortality register.

4.9 Data analysis

Kaplan-Meier curves for survival will be estimated for the cohort, and Cox's proportional hazards (PH) models will be used to calculate adjusted hazard ratios (HRs) with 95% confidence intervals (CI) for mortality associated with insulin use. Age will be used as the underlying time-scale in the model. P-values of less than 0.05 will be considered statistically significant. The Cox's PH model will be adjusted for selected potential confounders as well as for the time dependent variables. The PH assumption for basal insulin and gender will be examined by plotting the stratified Kaplan-Meier curves and by residual plots. Continuous variables will be tested for linearity by including a squared term in the model. For both the ITT analysis and the current use analyses, sensitivity analyses will be performed where missing data will be imputed by multiple imputation.

4.10 Milestones

Planned start of data collection: 01 April 2019

Planned end of data collection: 01 April 2019

Final Report of study results: 30 September 2019

5 Amendments and updates

None.

6 Milestones

Milestone	**Planned date**
Start of data collection	Date 01 April 2019
End of data collection	Date 01 April 2019
Registration in the EU PAS Register	*Date*
Final report of study results	Date 30 September 2019

7 Rationale and background

Considering the large number of patients who require insulin therapy, a potential survival benefit of a particular type of insulin would have major clinical and public health implications. Compared to the traditional NPH insulin, the newer insulins, such as insulin Detemir, have shown lower risk of hypoglycaemia and less weight gain. It is unknown whether these advantages also translate into an improved survival when used in real life. This study will examine the influence of the basal insulins

Detemir and Glargine on risk of cardiovascular death and death from all causes in patients treated by their general practitioner in United Kingdom (UK).

Insulin Detemir has previously shown advantages over insulin NPH, in randomized clinical trials (RCTs) [1,2], as well as in short observational studies [3]; and one long-term observational study conducted in Finland showed survival benefit [4]. However, it is not known whether these potential advantages translate into reduced risk of death in the long term in other populations. RCTs are often of short duration, whereby hard endpoints such as cardiovascular mortality cannot be recognized. Moreover, the patients randomized into clinical trials are not necessarily representative of the general population, because patients with advanced age, co-morbidities, or history of hypoglycaemias may have been excluded. Overall, the mortality risk associated with insulin use has not been extensively examined in real-life, and well-designed studies assessing Detemir vs Glargine use and risk of death are needed.

8 Research question and objectives

The aim of this UK register-based cohort study is to investigate the potential differences in risk of death in users of insulin Glargine and Detemir in terms of all-cause and cardiovascular mortality among patients with type 2 diabetes in real-life clinical practice.

8.1 Primary objective

The overall objective is to estimate the differences in all-cause and cardiovascular mortality rates between new users of basal insulin Glargine and Detemir in a population-based study of type 2 diabetes patients 40 years or older in UK in the years 2004-2018.

The hypothesis is that use of insulin Detemir is associated with a lower all-cause and cardiovascular mortality than use of insulin Glargine.

In this cohort of new users of basal insulins, the specific aims are to asses:

- Rates of all-cause mortality
- Rates of cardiovascular mortality

8.2 *Secondary objective(s)*

NA.

9 Research methods

9.1 Study design

This is a PASS.

The study is a retrospective cohort study comparing all-cause and cardiovascular mortality rates (hazard rates) in new users (T2D, ≥ 40 years at initiation) of basal insulins Glargine and Detemir identified through registers (i.e. CPRD).

9.1.1 Primary endpoint

Title:	Time frame:	Units:
"Age at all cause death or censoring"	Follow-up period "0-14 years"	"days, death: Y/N"
"Age at death of cardiovascular disease"	Follow-up period "0-14 years"	"days, death: Y/N"

9.1.2 Secondary endpoint(s)

None

9.1.3 Treatment of patients

No treatment will be given to the patients in relation to this study. Patients have been included in this study because they have been treated with insulin Glargine or Detemir prior to study initiation; and according to routine clinical practice at that time

9.2 Setting

9.2.1 Study Population

Planned number of patients to be included: 12884 patients (Glargine: 9850; Detemir: 3034) of which 6898 can be linked to the ONS mortality register (all 12884 patients are not linkable to the register with cause specific death information).

Planned number of patients to complete the study: NA

Anticipated number of patients to be included in each country: NA

Time period for the study: 24-JUN-2004 to 31-DEC-2018.

Both insulins (Glargine and Detemir) were available for prescription from 2004 (where both drugs were approved in UK). The study starts at the time where both insulin products were first recorded in the database (identified as 24th of June 2004) to reduce confounding by indication, and to ensure equal treatment and preventive strategies for CVD across the insulin treatments.

For the analyses of all-cause mortality, the mean follow-up time has been estimated to be 4.3 years (range: 0.0 to 14.2 years), during which a total of 3164 deaths occurred (out of the 12884 patients followed).

9.2.2 Inclusion criteria

The data extract was defined very broadly to be all patients with any form of insulin-related prescription. The study will include patients for whom the information is of acceptable quality, which is defined by standard checks conducted by the data owners (CPRD). Moreover, additional data processing criteria (age ≥ 40 at index date, study start at 01-JAN-2004, prior *up-to-standard* (UTS) registration at index date of 1 year, male or female, index date is within UTS period and code should be first ever in study period) was applied prior to extraction. The extracted population has been further processed and refined as described in the following table.

	N
Extracted from CPRD Gold (October 2018)	46114
Diagnosis (ever) of T2D, but not T1D	40406
Prescription (ever) of basal insulins Glargine or Detemir	17126
Index date at 24-Jun-2004 or later (i.e. the date both drugs were on the market.)	16617
Insulin-naïve	12894
1year observation time prior to index date	12884
Aged 40 years or older at index date	12884
Linkable to ONS mortality dataset (set_16_Source)	6898

1. The decision to initiate treatment with commercially available insulin detemir and glargine has been made by the patient/*Legally Acceptable Representative (LAR)* and the treating physician before and independently from the decision to include the patient in this study.

9.2.3 Exclusion criteria

See above.

9.2.4 Rationale for selection criteria

New users of the basal insulin of interest with T2D diabetes above 40 years have been included in the study. Patient below 40 years of age at index date have been excluded as these could potentially be T1D patients. Also, patients with a T1D diagnosis have been excluded. Otherwise, only patients for whom the information is of acceptable quality (which is defined by standard checks conducted by the data owners (CPRD)) have been included. The CPRD are generally representative of the UK population with respect to age, sex, ethnicity, and BMI in most subgroups.

9.2.5 Withdrawal criteria

NA

9.2.6 Visit procedures

NA

9.2.7 Assessments for safety and effectiveness

NA

9.2.8 Other assessments

NA

9.3 Variables

Exposures

The exposure variables will be defined in two different ways: 1) ("Intention-to-treat (ITT)", and 2) "on treatment of the first drug used") as follows:

1) "ITT (Intention to treat)": Patients will be assigned to either insulin Glargine or Detemir according to their first prescription. Drug exposure period starts at the date of the first prescribed prescription and is assumed continued until end of follow-up.

   Duration of use under the "ITT-like" definition: The following categories will be defined: < 1 year, ≥1-2 years, ≥2-3 years, >3 years. If more than 5 events/deaths are available with longer duration of use than 3 years, categories will be generated allowing for longer durations. The "duration of use" is equivalent to "the time in the study" for each patient and is calculated as: current time – index date.

2) "On treatment of the first drug used": Patients will be assigned to either "the first used drug", or "no use/unknown" to every given time during follow-up (all patients start on either Glargine or Detemir). Drug exposure is time-varying. Drug exposure periods starts at the date of the prescriptions. A maximal time between prescription renewals will be used to determine when

patients have stopped treatment (i.e. the given exposure period ends). The maximal time will be set as the 80% quantile of distribution of the prescription renewal times for prevalent users in the database. The prescription renewal distribution will be obtained using the maximum likelihood algorithm proposed in [5], where the backwards recurrence density is studied based on a fixed index date. For this purpose, three different fixed index dates will be used, that span the study period. A one year "lag time" will be added to all exposure periods.

Duration of "on treatment of the first drug used": Patients will be assigned to the same duration categories as described above. However, the duration of "on treatment of the first drug used" will be the cumulative duration of use to every given time (i.e. summarised exposed periods of use for each patient until that given time). Duration of use for a given episode is calculated as: current time – start of current use.

Outcomes

All-cause mortality (CPRD GOLD): Information from the Patient file (death date). Death from any cause (Y/N) will be based on death date – derived using a CPRD algorithm. This outcome definition will be used in analyses including patients from UK practises.

All-cause mortality (ONS): Information from ONS. Death from any cause (Y/N) will be defined as a record in ONS during follow-up. Patients will be considered alive, if they are available for linkage, but do not have a record in ONS. This outcome definition will be used in analyses including patients from English practises who are participating.

CVD mortality: Death from CVD (Y/N) will be defined as a record of selected ICD-10 codes (from ONS) occurring during the follow-up period. The variable "cause", which provides the underlying cause of death, will be used. Death from CVD will be defined as ICD-10 codes I00-I99. Patients with will be considered alive, if they are available for linkage, but do not have a record in ONS.

Time-to-event/censoring: Time at risk will be defined as time from index date to death date (from ONS or GOLD), or at the end-date of follow-up (the earliest of transfer out date (tod) last collection date (lcd) or end of ONS coverage), whichever comes first. For the "on treatment of the first drug used" analyses, an additional censoring criteria will be used: i.e. at the time of first switch to another basal insulin, though if "lag time" has not ended, it is at the time of ended "lag time".

Covariates

Calendar year of index-date: This will be defined as 2004, 2005, …, 2018.

Age (years): Age will be used as the underlying timescale in the Cox's regression model. Age at index date will be defined as date of first record of basal insulins glargine or detemir (from *Therapy* file) minus year of birth (from *Patient* file).

Sex (male/female): Patients will be categorised as male or female according to Information from *Patient* file

Socioeconomic status: Patient Level Index of Multiple Deprivation (IMD2015) from linkage to Area Level Data.

Diabetes duration (years): years from diagnosis of diabetes at the index date. This will be defined as year of first record of a prescription of basal insulin minus year of first record of read code for T2D diagnosis (from *Clinical* file). Diabetes duration will be categorised as ≤1; >1-2; >2-5; >5-10; >10 years.

Smoking status (current, former, never): 1) at time of insulin initiation and 2) a time dependent variable using information from *Test* and *Additional* file (entity type=4). Latest record to every given time will be used.

Non-insulin glucose-lowering medications: 1) at time of insulin initiation defined as a record of selected product codes (from *Therapy* file) within one year before index date of the following medications, which are categorised as: "SGLT2i and/or GLP1" (Y/N), and "other" (biguanides, SU, DPPIV inhibitor, Glinides, Glitazones, and/or alfa-glucosidase inhibitor) (Y/N). 2) Similarly, a time dependent variable will also be defined.

Bolus insulins: Is a time dependent variable indicating prescription of different bolus insulins defined as a record of selected product codes (from *Therapy* file) (Y/N).

CVD medication: Prescription of different kinds of CVD medication will be defined as a record of selected product codes in the Therapy file in the year prior to index date. Types of CVD medication will be defined as: Anti-hypertensive medication (Y/N), Lipid-lowering medication (Y/N), Other CVD preventive medication (Y/N).

Prior hypoglycaemia (Y/N): Defined as a record of a read code ever prior to index date.

History of CVD: will be defined as a record of a read code of acute myocardial infarction (AMI), acute coronary syndrome (ACS), coronary revascularisation and other arterial revascularisation procedures, stroke and transient ischemic attack (TIA), aortic aneurysm, peripheral artery disease (PAD), or heart failure (HF) (from Clinical file) ever prior to index date.

BMI (continuous): Calculated from weight and height from *Test* and *Additional* file (entity type = 13, 14). Latest value prior to treatment initiation will be used for weight. Latest value at any time above age 18 years will be used for height.

For subgroup analyses the following will be used: underweight: BMI <18.5, normal weight: BMI 18.5-25, overweight: BMI ≥25-30, class I obesity: BMI ≥30-35, class II obesity: BMI ≥35-40, class III obesity: BMI ≥40 kg/m2.

HbA1c (continuous): Information from *Test* and *Additional* file (entity type = 275). Latest value prior to the index date will be used.

For subgroup analyses the following categories will be used: below vs above median HbA1c.

Dyslipidemia (Y/N): Information from *Test* and *Additional* file (entity type = 214). Latest values in the year prior to the index date will be used. Dyslipidemia will be defined as total cholesterol >6.2 mmol/l, or LDL cholesterol >6.2 mmol/L, or HDL cholesterol ≤ 1 mmol/L for men, or HDL cholesterol ≤ 1.2 mmol/l for women, or triglyceride ≥ 1.7 mmol/L.

Elevated blood pressure (Y/N): Information from *Test* and *Additional* file (entity type = 1, 392, 475). Latest value prior to index date will be used for systolic and diastolic blood pressure. Elevated blood pressure will be defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥ 90 mmHg.

History of cancer (Y/N): Will be defined as a record of selected read codes ever (from *Clinical* file) before index date.

Serum creatinine (eGFR, continuous): Information from Test and Additional file (entity type = 165). Latest serum creatinine value in the year prior to index date will be used. eGFR will be calculated according to the Cockcroft-Gault formula: eGFR in ml/min = ((140-age in years) * weight in Kg * 1.23 for men,1.03 for women) / serum creatinine in umol/l.

History of diabetes complications (Y/N): Will be defined as a record of selected read codes (see appendix 9) ever (from *Clinical* file) before index date. The following comorbidities/complications will be examined and defined as dichotomous (Y/N) variables: Retinopathy, Nephropathy and Neuropathy.

9.4 Data sources

Patients to be included in the study will be identified through registers, i.e. the Clinical Practice Research Datalink (CPRD) (https://www.cprd.com/).

The analysis on cardiovascular mortality will be undertaken based on practices, which have consented linkage. Linkage to ONS death registration data is necessary to retrieve information on cause of death. Linkage to Area Level Data is necessary to obtain data on socioeconomic status, which is considered a potential confounder. Linkage is performed based on a unique identifier.

9.5 Study size

The total study population fulfilling all inclusion criteria comprise 12884 patients (Glargine: 9850; Detemir: 3034) of which 6898 can be linked to the ONS mortality register. For the analyses of all-cause mortality, the mean follow-up time has been estimated to be 4.3 years (range: 0.0 to 14.2 years), during which a total of 3164 deaths occurred. Number of cardiovascular deaths is not known as these will be identified through linkage to the ONS mortality register.

A recent study by Strandberg et al using a cohort of patients in Finland [4] used a similar study design and definitions of study population as we suggest for the current study. This study followed 10467 new users of insulin Glargine and 4749 patients initiating insulin Detemir. Median follow-up time was 1.7 years in the study and 705 deaths were identified among insulin Glargine users and insulin Detemir users during this time. The reported hazard ratio (HR) for all-cause mortality was 0.71 (95%CI, 0.54-0.93) for insulin Detemir users compared with users of insulin glargine.

In the suggested cohort study, we have identified 9850 new users of insulin Glargine and 3034 new users treated with insulin Detemir. The mean follow-up time is estimated to be 4.3 years, which is more than two times longer time of follow-up of the patients than what was available in the study by Strandberg et al. [4] Consequently, more deaths (n=3164) are also observed among insulin Glargine and Detemir users included in the current study. Therefore, we also expect a better precision in the risk estimates.

9.6 Data management

Data are extracted from CPRD GOLD and will be linked to ONS death registration data and area level

9.7 Data analysis

9.7.1 Definition of analysis sets

All patients will be included in the main analyses.

Furthermore, the following subgroups analyses will be performed:

- Analyses including only obese patients (BMI ≥30 kg/m2).
- Analyses including only patients with duration of diabetes ≥5 years.
- Analyses including only patients treated with CVD medication and/or with prior CVD at index date.
- Analyses including only patients with HbA1c above median at index date.

9.7.2 Statistical methods

Kaplan-Meier curves for survival will be estimated for the cohort, and Cox's proportional hazards (PH) models will be used to calculate adjusted hazard ratios (HRs) with 95% confidence intervals (CI) for mortality associated with insulin use. Age will be used as the underlying time-scale in the model. P-values of less than 0.05 will be considered statistically significant. The Cox's PH model will be adjusted for selected potential confounders as well as for the time dependent variables as described in section "P". The PH assumption for basal insulin and gender will be examined by plotting the stratified Kaplan-Meier curves and by residual plots. Continuous variables will be tested for linearity by including a squared term in the model.

Sensitivity analyses

For both the ITT analysis and the current use analyses, sensitivity analyses will be performed where missing data will be imputed by multiple imputation. No further sensitivity analyses are planned for the ITT analysis.

The "on treatment of the first drug used" analysis depends on the classification of exposed periods, and the biases induced by this classification will be evaluated by the following sensitivity analyses:

1) The estimated length of the exposed periods is tested in sensitivity analyses by changing the maximal renewal time used. We will both apply an assumed longer duration of the exposed periods and an assumed shorter duration of the exposed periods, by using the 90% and 70% quantile in the renewal distribution, and by fitting the renewal distribution based on different index dates (early, middle and late in the study period).

2) The robustness of the results will be tested by including no lag time and a lag time of e.g. 2 years for each treatment episode.

We will also perform sensitivity analyses such as the below suggested; whenever found relevant:

1) "Current use" where patients are allocated to currently used product throughout follow-up. In the "current use" approach the exposure is time dependent: "current use of glargine", "current use of detemir", "current use of other basal insulins" or "no exposure/unknown". In case of a switch between the basal insulins the patient is allocated to the most recent insulin in use. A lag time of each exposed period of one 1 year is used.

Addressing confounders

The risk estimates will be adjusted for *a priori* selected potential confounders as follows:

1) The crude model will include age and calendar year

2) All adjusted models will include the following covariates measures at time of treatment initiation i.e. age (as the underlying timescale in Cox's regression model) calendar year, sex, diabetes duration, BMI, history of CVD, CVD medication, and non-insulin glucose-lowering medications.

3) The final adjusted model will additionally include the selected covariates that by inclusion in the above specified model will change the risk estimate by 10% or more i.e. potentially the following covariates measured at index date: socioeconomic status, smoking status, HbA1c, prior hypoglycaemia, nephropathy, retinopathy, neuropathy, CKD, dyslipidemia, hypertension, eGFR, history of cancer.

4) Potential time dependent confounding will also be assessed, i.e. "use of non-insulin glucose-lowering medications", "use of bolus medications" and "smoking status"

The following subgroup analyses will be performed:

1) Analyses including only obese patients (BMI ≥30 kg/m2).

2) Analyses including only patients with duration of diabetes ≥5 years.

3) Analyses including only patients treated with CVD medication and/or with prior CVD at index date.

4) Analyses including only patients with HbA1c above median at index date.

9.7.3 Interim analysis

NA.

9.7.4 Sequential safety analysis/safety monitoring

NA.

9.8 Quality control

NA.

9.8.1 Monitoring procedures

NA.

9.8.2 Critical documents

ISAC (Independent Scientific Advisory Committee) approval is required prior release of CPRD data to any third party, so as to ensure that the standard of studies carried out using CPRD data is maintained. Also access to linked data requires approval from ISAC.

9.8.3 Retention of study documentation

Novo Nordisk will comply with Good Pharmacoepidemiological Practice (GPP) and relevant national legislation related to archiving of study documentation.

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

9.9 Limitations of the research methods

The limitations of the study include the following issues:

- Data has been generated for other purposes than the current study
- We may not be able to account completely for confounding by indication
- We might have misclassification due to the assumption that "no information" in the register indicates "no exposure" for some of the variables; which may not always be true.
- The generalisability of the results may be limited to those patients that are included in CPRD
- We cannot exclude unknown confounders i.e. whether the insulin groups are comparable at baseline.
- The validity and completeness of the adjustment variables is uncertain
- If the total exposed time on the specific drugs are too short to have a biological influence we will not be able to detect a potential benefit of the assessed drugs in the current study.

9.10 Other aspects

NA.

10 Protection of human subjects

The study will be conducted in accordance with GPP (6).

10.1 Data handling

NA.

10.2 Institutional Review Boards/Independent Ethics Committee, health authorities and other relevant national institutions/bodies

ISAC (Independent Scientific Advisory Committee) approval is required prior release of CPRD data to any third party, so as to ensure that the standard of studies carried out using CPRD data is maintained. Also access to linked data requires approval from ISAC.

10.3 Premature termination of the study

The sponsor may decide to stop the study or part of the study at any time.

If a study is prematurely terminated or suspended, information must be provided to the relevant national bodies as required by national regulation and procedures.

10.4 Responsibilities

NA.

11 Collection and reporting of safety information

This study is based on secondary use of data and therefore Individual Case Safety Reports (ICSR) will not be performed.

The following information will be collected (MedDRA codes):

SOC Cardiac disorders
HLTTs:
Cardiac arrhythmias
Cardiac disorder signs and symptoms
Cardiac valve disorders
Coronary artery disorders
Endocardial disorders
Heart failures
Myocardial disorders
Pericardial disorders

SOC Vascular disorders
HLTTs:
Arteriosclerosis, stenosis, vascular insufficiency and necrosis
Cerebrovascular embolism and thrombosis
Pulmonary embolism and thrombosis
Vena caval embolism and thrombosis
Vascular disorders NEC

Vascular hypertensive disorders

All-cause mortality:
SOC: General disorders and adm. site conditions
HLGT: Fatal outcomes

11.1 Collection of adverse events

NA

11.2 Reporting of adverse events

NA

11.3 Follow-up on safety information

NA

11.4 Regulatory reporting requirements for adverse events

NA

11.5 Collection and reporting of technical complaints

NA

11.6 Collection, storage and shipment of technical complaint samples

NA

11.7 Collection and reporting of pregnancies in female patients or male patients' female partners and collection of ARs in infants exposed via breastfeeding

NA

11.8 Precautions/Over-dosage

NA

11.9 Novo Nordisk safety committee(s)

Novo Nordisk has an internal insulin detemir safety committee that performs ongoing safety surveillance of the study product(s).

12 Plans for disseminating and communicating study results

12.1 Registration of study information

In accordance with Novo Nordisk commitment to transparency in clinical activities, this study will be registered on www.clinicalTrials.gov and www.novonordisk-trials.com.

This non-interventional PASS, must be registered in the EU Electronic Register of Post-Authorisation Studies (EU PAS Register) maintained by the European Medicines Agency and accessible through the European Medicines Agency's web portal.

12.2 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.

At the end of the study, one or more publication(s) may be prepared by physician(s) in collaboration with Novo Nordisk. Novo Nordisk reserves the right to postpone publication and/or communication for up to 60 days to protect intellectual property, and reserves the right not to release interim results or data until a study report is available. 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 Commitment to share information about clinical studies.

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

Novo Nordisk maintains the right to be informed of any physician plans for publication and to review any scientific paper, presentation, communication or other information concerning the investigation described in this protocol. Any such communication must be submitted in writing to the Novo Nordisk study manager prior to submission for comments. Comments will be given within four weeks from receipt of the planned communication.

12.3 Physician access to data and review of results

NA.

13 References

1. Tricco AC, Ashoor HM, Antony J, Beyene J, Veroniki AA, Isaranuwatchai W, et al. Safety, effectiveness, and cost effectiveness of long acting versus intermediate acting insulin for patients with type 1 diabetes: systematic review and network meta-analysis. BMJ 2014;349:g5459 doi: 10.1136/bmj.g5459 [PMC free article] [PubMed]

2. Monami M, Marchionni N, Mannucci E. Long-acting insulin analogues versus NPH human insulin in type 2 diabetes: a meta-analysis. Diabetes Res Clin Pract 2008;81:184–9. doi: 10.1016/j.diabres.2008.04.007 [PubMed]

3. Meneghini LF, Rosenberg KH, Koenen C, Merilainen MJ, Lüddeke HJ. Insulin detemir improves glycaemic control with less hypoglycaemia and no weight gain in patients with type 2 diabetes who were insulin naive or treated with NPH or insulin glargine: clinical practice experience from a German subgroup of the PREDICTIVE study. Diabetes Obes Metab 2007;9:418–27. [PubMed]

4. Strandberg AY, Hoti FJ, Strandberg TE, Christopher S, Haukka J, Korhonen P.All-Cause and Cause-Specific Mortality among Users of Basal Insulins NPH, Detemir, and Glargine. PLoS One. 2016 Mar 31;11(3):e0151910. doi: 10.1371/journal.pone.015191

5. Støvring H, Pottegård A, Hallas J. Determining prescription durations based on the parametric waiting time distribution. Pharmacoepidemiol Drug Saf. 2016 Dec;25(12):1451-1459. doi: 10.1002/pds.4114. Epub 2016 Sep 26.

6. Guidelines for good pharmacoepidemiology practice (GPP).Pharmacoepidemiol Drug Saf. 2016 Jan;25(1):2-10. doi: 10.1002/pds.3891. Epub 2015 Nov 5.

Appendix A Safety definition and evaluation of outcome, severity and causality

NA.

ANNEX 1. List of Stand-alone Documents

List of Stand-alone Documents

None.

ANNEX 2. ENCePP Checklist for Study Protocols

Study title:
Retrospective Cohort study of all-Cause and Cardiovascular Mortality in type 2 diabetes patients using basal insulin Detemir and Glargine

Study reference number:
NN304-4528

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	4.10
1.1.2 End of data collection[2]	☒	☐	☐	4.10
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	4.10

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
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)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8.1
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8
2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	8.1
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**

[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 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.6
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	8.1
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	9.7.2
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	9.2.2
4.2.2 Age and sex?	☒	☐	☐	9.2.2
4.2.3 Country of origin?	☒	☐	☐	9.2.2
4.2.4 Disease/indication?	☒	☐	☐	9.2.2
4.2.5 Duration of follow-up?	☐	☒	☐	9.2.2
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.2

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☒	☐	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	9.3
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.3

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.4
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☒	☐	
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☒	☐	☐	9.7.2
7.1.1. Does the protocol address confounding by indication if applicable?	☒	☐	☐	9.7.2
7.2 Does the protocol address:				
7.2.1. Selection biases (e.g. healthy user bias)	☐	☒	☐	
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.7.2
7.3 Does the protocol address the validity of the study covariates?	☒	☐	☐	9.9

Comments:

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.7.2

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	9.4
9.1.3 Covariates?	☒	☐	☐	9.4
9.2 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)	☒	☐	☐	9.3
8.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	9.3
9.3 Is a coding system described for:				
9.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	9.3
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3
9.3.3 Covariates?	☐	☐	☐	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.4

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7.2
10.2 Are descriptive analyses included?	☐	☒	☐	
10.3 Are stratified analyses included?	☒	☐	☐	9.7.2
10.4 Does the plan describe methods for adjusting for	☒	☐	☐	9.7.2

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
confounding?				
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.2
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.7.2

Comments:

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

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.5

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.3
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.3 Have data protection requirements been described?	☐	☐	☒	

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

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

Date: 07/03/2019

Signature: _____

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