Safety Evaluation of Adverse Reactions in Diabetes - Comparative studies (SAFEGUARD)

First published: 17/09/2012

Last updated: 02/07/2024

Study Finalised

Administrative details

EU PAS number

EUPAS2895

Study ID

20765

DARWIN EU® study

No

Study countries

- [ ] Germany
- [ ] Italy
- [ ] Netherlands
- [ ] Spain

- [ ] United Kingdom
- [ ] United States

Study description

Safety issues associated with blood glucose lowering drugs are not new, the safety of these treatments has been questioned and highly publicized. It has been reported that some of them increase the risk or modify the prognosis of cancer, cardiovascular (CVD) or pancreatic diseases.The primary objective of the comparative studies in SAFEGUARD is to estimate the risk of myocardial infarction (MI), heart failure (HF), ventricular arrhythmia (VA)/sudden cardiac death (SCD), ischemic stroke (IS), hemorrhagic stroke (HS), acute pancreatitis (AP), pancreatic cancer (PC), bladder cancer (BC) and total mortality (TM) associated with the use of non-insulin blood glucose lowering drugs (NIBGLD), insulins and insulin analogs in subjects with T2DM.Data collected in 9 different electronic health databases from 5 different European countries the USA will be used. Nested case control studies in a cohort of T2DM patients will be conducted to assess the association of NIBGLD, insulins, and insulin analogs with MI, HF, VA/SCD, IS, HS, AP, BC and PC and a dynamic retrospective cohort study to estimate the association with TM.For the estimation of the risk, in the case control studies, cases will be compared with matched controls and adjusted for potential confounders. Conditional logistic regression will be used to calculate the unadjusted and adjusted odds ratios (ORs) with their 95% confidence intervals (CIs) with reference to another active compound.For the cohort studies, hazard ratios and incidence rates (IR) and the relative risk for TM with their 95% CIs will be estimated using Cox-regression. Time varying analyses will be conducted for estimation of the effect of duration of treatment. All analyses will be performed for each database separately and the heterogeneity among databases will be examined (e.g., I2). Advanced methodologies, subanalyses and sensitivity analyses will be carried out to deal with methodological issues.(i.e propensity scores, etc).

Study status

Finalised

Research institutions and networks

Institutions

Erasmus Medical Centre Rotterdam

First published: 01/02/2024

Last updated: 01/02/2024

Institution

Novo Nordisk

Consorzio Mario Negri Sud (CMNS)

Italy

First published: 17/01/2011

Last updated: 20/08/2024

Institution Not-for-profit

Health Search, Italian College of General Practicioners

Italy

First published: 02/03/2010

Last updated: 20/08/2024

Institution | Educational Institution | Other

Leibniz Institute for Prevention Research and Epidemiology - BIPS

Germany

First published: 29/03/2010

Last updated: 30/03/2026

Institution | Not-for-profit | ENCePP partner

Pharmacy & Pharmacology, University of Bath

United Kingdom

First published: 30/04/2010

Last updated: 08/04/2019

Institution | Outdated | Educational Institution | Hospital/Clinic/Other health care facility | ENCePP partner

The PHARMO Institute for Drug Outcomes Research (PHARMO Institute)

- [ ] Netherlands

First published: 07/01/2022

Last updated: 19/12/2025

Institution | Non-Pharmaceutical company | ENCePP partner

RTI Health Solutions (RTI-HS)

- [ ] France
- [ ] Spain
- [ ] Sweden
- [ ] United Kingdom
- [ ] United Kingdom (Northern Ireland)
- [ ] United States

First published: 21/04/2010

Last updated: 13/03/2025

Institution | Not-for-profit | ENCePP partner

Department of Medical Informatics - Health Data Science, Erasmus Medical Center (ErasmusMC)

- [ ] Netherlands

First published: 03/11/2022

Last updated: 02/05/2024

Institution | Educational Institution | ENCePP partner

AEMPS Spain, UNIMIB Italy, BWH United States of America

Contact details

Study institution contact

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Study contact

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Primary lead investigator

Miriam Sturkenboom

Primary lead investigator

Study timelines

Date when funding contract was signed

Planned: 23/08/2011

Actual: 23/08/2011

Study start date
Planned: 20/09/2012

Actual: 20/09/2012

Date of final study report
Planned: 30/09/2015

Actual: 30/09/2015

Sources of funding

- EU institutional research programme

More details on funding

Health Area of the European Commission under the VII Framework Programme

Study protocol

ENCEPP_SDPP_2895_Finalprotocol.pdf (968.53 KB)

Regulatory

Was the study required by a regulatory body?

Yes

Is the study required by a Risk Management Plan (RMP)?

Not applicable

Methodological aspects

Study type

Study type list

Study topic:

Disease /health condition

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Assessment of risk minimisation measure implementation or effectiveness

Data collection methods:

Secondary use of data

Main study objective:

The main objective of these observational studies is to estimate the risk of myocardial infarction (MI), heart failure (HF), ventricular arrhythmia (VA)/sudden cardiac death (SCD), ischemic stroke (IS), hemorrhagic stroke (HS), acute pancreatitis (AP), pancreatic cancer (PC), bladder cancer (BC) and total mortality (TM) associated with the use of NIBGLD and insulins and insulin analogs.

Study Design

Non-interventional study design

Case-control

Cohort

Study drug and medical condition

Anatomical Therapeutic Chemical (ATC) code

(A10) DRUGS USED IN DIABETES

DRUGS USED IN DIABETES

Medical condition to be studied

Type 2 diabetes mellitus

Population studied

Short description of the study population

All patients in the databases during the study period who have at least 365 consecutive days of valid data with at least one prescription/dispensing of a NIBGLD (ATC: A10B – Annex 1) or insulin or insulin analogues (ATC: A10A – Annex 1) in the study period.

Age groups

- Adolescents (12 to < 18 years)
- Children (2 to < 12 years)
- Infants and toddlers (28 days – 23 months)
- Term newborn infants (0 – 27 days)
- Adults (18 to < 46 years)
- Adults (46 to < 65 years)
- Adults (65 to < 75 years)
- Adults (75 to < 85 years)
- Adults (85 years and over)

Special population of interest

Other

Special population of interest, other

Diabetes mellitus patients

Estimated number of subjects

2200000

Study design details

Outcomes

The primary objective of these observational studies is to estimate the risk of myocardial infarction (MI), heart failure (HF), ventricular arrhythmia (VA)/sudden cardiac death (SCD), ischemic stroke (IS), hemorrhagic stroke (HS), acute pancreatitis (AP), pancreatic cancer (PC), bladder cancer (BC) and total mortality (TM) associated with the use of NIBGLD and insulins and insulin analogs. To assess the background rates of the different events of interest in the population of subjects with T2DM

Data analysis plan

The incidence rate (IR) and direct standardized incidence rates (SIRs) with the 95% confidence intercal (95%CI) of each outcome of interest in each database will be estimated at the population level for harmonization purposes. To assess the risk of the outcomes of interest (MI, HF, VA/SCD, HS, IS, AP, PC and BC), associated with the use of NIBGLD and insulins and insulin analogues, Conditional logistic regression will be used to calculate the unadjusted and adjusted odds ratios (ORs) with their 95% confidence intervals (CIs) with reference to another active compound which will be selected based on drug utilization studies. For the cohort studies, hazard ratios and incidence rates (IR) as well as the relative risk for TM with their 95% CIs will be estimated using Cox-regression analysis. All analyses will at first be performed for each database(DB) separately and the heterogeneity among DBs will be examined

through heterogeneity indexes. Different sensitivity analyses will be performed

Documents

Study results

Safety Evaluation of Adverse Reactions in Diabetes_report.pdf (954.98 KB)

Data management

ENCePP Seal

The use of the ENCePP Seal has been discontinued since February 2025. The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

This study has been awarded the ENCePP seal

Conflicts of interest of investigators

DoI_MStukenboom_EMC.pdf (1.46 MB)

Composition of steering group and observers

ENCEPP_SDPP_2895_Scientific Advisory Board.pdf (77.91 KB)

Signed code of conduct

2012-0013_DoC Code of Conduce_SDPP-2895.pdf (33.53 KB)

Signed code of conduct checklist

2012-0013_Checklist of the CoC_SDPP-2895.pdf (1.05 MB)

Signed checklist for study protocols

2012-0013_Checklist Study Protocl_SDPP-2895.pdf (182 KB)

Data sources

Data source(s)

Clinical Practice Research Datalink

Health Search/IQVIA Health Longitudinal Patient Database

Integrated Primary Care Information (IPCI)

Data source(s), other

CPRD, Health Search/CSD LPD, IPCI

Data sources (types)

Administrative healthcare records (e.g., claims)

Drug dispensing/prescription data

Electronic healthcare records (EHR)

Use of a Common Data Model (CDM)

CDM mapping

No

Data quality specifications

Check conformance

Unknown

Check completeness

Unknown

Check stability

Unknown

Check logical consistency

Unknown

Data characterisation

Data characterisation conducted

No