# Large-scale evidence generation and evaluation across a network of databases for type 2 diabetes mellitus (LEGEND-T2DM)

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## Administrative details

EU PAS number
EUPAS43551
Study ID
44530
DARWIN EU® study
No
Study countries
Spain
United Kingdom (Northern Ireland)
United States

#### Study description

Therapeutic options for type 2 diabetes mellitus (T2DM) have expanded over the last decade with the emergence of sodium-glucose co-transporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP1) receptor agonists, which reduced the risk of major cardiovascular events in randomized controlled trials. Cardiovascular evidence for older second-line agents, such as sulfonylureas, and direct head-to-head comparisons, including with dipeptidyl peptidase 4 (DPP4) inhibitors, are lacking, leaving a critical gap in our understanding of the relative effects of T2DM agents on cardiovascular risk and on patient-centered safety outcomes. The Large-Scale Evidence Generations Across a Network of Databases for T2DM (LEGEND-T2DM) initiative is a series of systematic, largescale, multinational, real-world comparative cardiovascular effectiveness and safety studies of all 4 major second-line anti-hyperglycemic agents including SGLT2 inhibitor, GLP1 receptor agonist, DPP4 inhibitor and sulfonylureas and leverages the Observational Health Data Science and Informatics (OHDSI) community that provides access to a global network of administrative claims and electronic health record (EHR) data sources. Across data sources, LEGEND-T2DM will identify all adult, T2DM patients who newly initiate a traditionally second-line T2DM agent, including individuals with and without established cardiovascular disease. Using an active comparator, new-user cohort design, LEGEND-T2DM will execute all pairwise class-vs-class and drug-vs-drug comparisons in each data source that meet a minimum patient count of 1,000 per arm and extensive study diagnostics that assess reliability and generalizability through cohort balance and equipoise to examine the relative risk of cardiovascular and safety outcomes. The primary cardiovascular outcomes include a 3-point and a 4-point composite of major adverse cardiovascular events, and series of safety outcomes.

#### **Study status**

Ongoing

## Research institutions and networks

## **Institutions**

## University of California

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Institution

#### **Networks**

Observational Health Data Sciences and Informatics (OHDSI) Network

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Network

## Contact details

**Study institution contact** 

Marc Suchard msuchard@ucla.edu

 $\Big( \mathsf{Study} \ \mathsf{contact} \, \Big)$ 

msuchard@ucla.edu

**Primary lead investigator** 

#### Marc Suchard

**Primary lead investigator** 

# Study timelines

#### Date when funding contract was signed

Planned: 01/10/2021

#### Study start date

Planned: 01/11/2021

Actual: 01/11/2021

#### **Date of final study report**

Planned: 01/11/2022

## Sources of funding

Other

## More details on funding

US Department of Veterans Affairs, National Institutes of Health

## Study protocol

Protocol\_v1\_0\_0\_EUPAS.pdf (448.23 KB)

## Regulatory

#### Was the study required by a regulatory body?

No

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

Not applicable

## Methodological aspects

# Study type

## Study type list

#### **Study type:**

Non-interventional study

#### Scope of the study:

Drug utilisation

Effectiveness study (incl. comparative)

#### Main study objective:

To determine, through systematic evaluation, the comparative effectiveness and safety of traditionally second-line T2DM agents, SGLT2 inhibitors and GLP1 receptor agonists, with each other and with DPP4 inhibitors and sulfonylureas, for cardiovascular and safety outcomes.

# Study Design

#### Non-interventional study design

## 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

#### Age groups

- 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

Renal impaired

#### **Estimated number of subjects**

1000000

# Study design details

#### **Outcomes**

3- and 4-point major cardiovascular events, Acute myocardial infarction, acute renal failure, glycemic control, hospitalization for heart failure, measured renal dysfunction, stroke, sudden cardiac death, and 22 other patient-centered safety outcomes

#### Data analysis plan

LEGEND-T2DM will execute all pairwise class-vs-class and drug-vs-drug comparisons in each data source that meet a minimum patient count of 1,000 per arm and extensive study diagnostics that assess reliability and generalizability through cohort balance and equipoise to examine the relative risk of cardiovascular and safety outcomes. Our systematic framework will address residual confounding, publication bias and p-hacking using data-driven, large-scale propensity adjustment for measured confounding, a large set of negative control outcome experiments to address unmeasured and systematic bias, prespecification and full disclosure of hypotheses tested and their results. LEGEND-T2DM is dedicated to open science and transparency and will publicly share all our analytic code from reproducible cohort definitions through turn-key software, enabling other research groups to leverage our methods, data, and results in order to verify and extend our findings.

## 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

## Data sources

#### **Data sources (types)**

Administrative healthcare records (e.g., claims)

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