DARWIN EU® – Benzodiazepine use during pregnancy: a descriptive study characterising exposure, pregnancy loss, and covariates to inform future safety studies

First published: 02/04/2025

Last updated: 07/08/2026

Study Ongoing

Administrative details

EU PAS number

EUPAS1000000536

Study ID

1000000536

DARWIN EU® study

Yes

Study countries

Norway

Spain

Study description

Benzodiazepines are commonly prescribed for their anxiolytic, hypnotic, and sedative effects. Despite the use of benzodiazepines during pregnancy, there is limited evidence to support their use during this period or to favor their use over alternative treatments that may provide similar symptom relief with differing safety profiles. Understanding the patterns of benzodiazepine use during pregnancy in Europe, together with the rates of pregnancy losses, is essential for evaluating safety and effectiveness.

Despite detailed pregnancy information in many data sources, pregnancy episodes in electronic health record (EHR) data are often inconsistently coded across sources.

As part of the upcoming benzodiazepines periodic safety update report single assessment (PSUSA), the Pharmacovigilance Risk Assessment Committee (PRAC) has requested real-world evidence (RWE) on the utilisation of commonly used benzodiazepines during pregnancy.

Additionally, the background rates of pregnancy losses will be described to help contextualise the assessment of treatment safety during pregnancy.

To date, two data partners within the DARWIN EU® Data Network have pre-processed pregnancy episodes and developed a Pregnancy Extension Table (PET).

While the table has been successfully employed in other contexts, this study marks the first application of this table within the DARWIN EU® Data Network.

Study status

Ongoing

Research institutions and networks

Institutions

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

Networks

Data Analysis and Real World Interrogation Network (DARWIN EU®)

- Belgium
- Croatia
- Denmark
- Estonia
- Finland
- France
- Germany
- Greece
- Hungary
- Italy
- Netherlands
- Norway
- Portugal

Spain

Sweden

United Kingdom

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Network

Contact details

Study institution contact

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Study contact

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Primary lead investigator

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Primary lead investigator

Study timelines

Date when funding contract was signed

Planned: 16/07/2024

Actual: 16/07/2024

Study start date

Planned: 16/07/2024

Actual: 16/07/2024

Date of final study report
Planned: 30/09/2025

Sources of funding

- EMA

Study protocol

DARWIN EU_Protocol_P3-C3-009_Bromazepam_V2.pdf (1015.03 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:

Disease epidemiology

Drug utilisation

Data collection methods:

Secondary use of data

Study design:

Population-level cohort

Drug/s user cohort

Population-level cohort

Cohort analysis

Main study objective:

1. To characterise users of benzodiazepine and alternative treatments (SSRIs, SNRIs, Z-hypnotics, and Melatonin) during pregnancy in terms of demographics, prior medications, history of mental illness and other comorbidities.
2. To characterise treatments with benzodiazepine and alternative treatments during pregnancy in terms of duration, posology, and indication of prescription during pregnancy.
3. To describe the prevalence of benzodiazepine and alternative treatments' use during pregnancy
4. To describe trajectories of prescriptions fills for benzodiazepine and

alternative treatments throughout the year before pregnancy, pregnancy period, and one month following pregnancy end date.
5. To estimate the incidence of pregnancy loss among all pregnancies and in benzodiazepines and alternative treatment users during pregnancy (when numbers allow).
6. To characterise individuals with pregnancy loss in terms of demographics, comorbidities, and treatments of interest.

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

Medicinal product name, other

Commonly used benzodiazepines

Anatomical Therapeutic Chemical (ATC) code

(N05BA) Benzodiazepine derivatives

Benzodiazepine derivatives

(N05CD) Benzodiazepine derivatives

Benzodiazepine derivatives

Population studied

Short description of the study population

Participants in the study will be required to fulfil the following criteria:

Inclusion criteria (Table 5):

1) Observation period within the study period (1st January 2010-31st December 2023, or latest data availability).

2) Female sex at birth.

3) At least one year of prior history recorded before start of pregnancy episode.

4) A pregnancy episode recorded during the study period (defined by the pregnancy start date), with a pregnancy start date on or before December 31, 2022 (to allow sufficient time between index date and last date of database data availability to cover a full-term pregnancy).(29)

5) Pregnancy end date follows pregnancy start date (in time).

6) Pregnancy duration (in days) is greater than 1 but less than 308 days (equivalent to 44 weeks of gestation).

Exclusion criteria (Table 6):

1) Molar and ectopic pregnancies will be excluded (concept ids: 439083 and 437611).

Disease Epidemiology (objective 5): Two approaches will be used:

• No exclusion for prior history of pregnancy

• Excluding anyone with a history of pregnancy in the -365 days.

• Excluding anyone with an unknown pregnancy outcome.

Special population of interest

Pregnant women

Study design details

Setting

This study was conducted using routinely collected data from primary care, specialist care, hospital, and birth registry data sources in the DARWIN EU®

network of data partners from two European countries in one EU member state. All data had been previously mapped to the Observational Medical Outcomes Partnership (OMOP) common data model (CDM) prior to this study.

Outcomes

Objective 1: Characteristics of benzodiazepine and alternative treatment users.

Objective 2: Benzodiazepine and alternative treatment first era's treatment duration, posology (dose), and
indication.

Objective 3: Prevalence of benzodiazepine and alternative treatments use.

Objective 4: Prescription trajectories of benzodiazepine and alternative treatments use, categorised into:

• Restarting the same treatment.

• Switching to a different treatment.

• Restarting the same treatment while also switching to another.

• Discontinuing treatment altogether (neither the original treatment nor any potential switch), relative to the entire period analysed.

Objective 5:

Pregnancy loss: Date of pregnancy end date, comprising any of the following events: miscarriage/abortion
(spontaneous), stillbirth (death of foetus, foetal loss, intrauterine death, dead born), as recorded in the PET.

(20) Additionally, miscarriage and stillbirth were assessed separately.

Objective 6: Characteristics of individuals with pregnancy loss.

Exploratory outcome:

Objective 7: Incidence of potential negative control outcomes among benzodiazepine and alternative treatment users during pregnancy. The outcome was based on the presence of at least one diagnostic code (SNOMED) code to identify the first occurrence of the following conditions:

- Musculoskeletal injuries
- Skin conditions
- Urinary tract infection

Documents

Study report

DARWIN EU_Report_P3-C3-009_Benzodiazepines during pregnancy V6.0.pdf

(7.17 MB)

Shiny App

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.

Data sources

Data source(s)

Norwegian Linked Health registry at University of Oslo

The Information System for Research in Primary Care (SIDIAP)

Norwegian Linked Health registry at University of Oslo, Pregnancy cohort

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Data sources (types)

Electronic healthcare records (EHR)

Use of a Common Data Model (CDM)

CDM mapping

Yes

CDM Mappings

CDM name

OMOP

CDM website

https://www.ohdsi.org/Data-standardization/

CDM version

https://ohdsi.github.io/CommonDataModel/index.html

Data quality specifications

Check conformance

Unknown

Check completeness

Unknown

Check stability

Unknown

Check logical consistency

Unknown

Data characterisation

Data characterisation conducted

Unknown