Use of benzodiazepines and risk of hip/femur fracture. A methodological comparison across data sources and epidemiological design.

First published: 04/09/2012

Last updated: 22/02/2024

Study Ongoing

Administrative details

EU PAS number

EUPAS2385

Study ID

6179

DARWIN EU® study

No

Study countries

- ☐ Denmark
- ☐ Germany
- ☐ Netherlands

☐ Spain

☐ United Kingdom

Study description

The studies described in this protocol are all performed within the framework of PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium) Work Package 2 and Working Group 1. The primary aim of these studies is to develop, test and disseminate methodological standards for the design, conduct and analysis of Pharmacoepidemiological (PE) studies applicable to different safety issues and using different data sources. To achieve this, results from PE studies on 5 key Drug / adverse events (D-AEs) pairs performed in different databases will be evaluated. The use of benzodiazepines associated to the risk of hip/femur fracture is one of the D-AEs pairs of interest. Therefore, emphasis will be on the methodological aspects of the studies in this protocol and not on the clinical consequences of studying the association under investigation.

Study status

Ongoing

Research institutions and networks

Institutions

Agencia Española de Medicamentos y Productos Sanitarios (Spanish Agency for Medicines and Medical Devices, AEMPS)

☐ Spain

First published: 01/02/2024

Last updated: 04/09/2024

Institution | EU Institution/Body/Agency | Not-for-profit | Regulatory Authority | ENCePP partner

Division of Pharmacoepidemiology & Clinical Pharmacology (PECP), Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University

Netherlands

First published: 01/03/2010

Last updated: 23/05/2024

Institution | Educational Institution | ENCePP partner

Agencia Española de Medicamentos y Productos Sanitarios (Spanish Agency for Medicines and Medical Devices, AEMPS)

Spain

First published: 01/02/2024

Last updated: 04/09/2024

Institution | EU Institution/Body/Agency | Not-for-profit | Regulatory Authority | ENCePP partner

European Medicines Agency (EMA)

First published: 01/02/2024

Last updated: 01/02/2024

Institution

Ludwig-Maximilians-University Munich

First published: 01/02/2024

Last updated: 01/02/2024

Institution

Merck Sharp & Dohme LLC

United States

First published: 01/02/2024

Last updated: 08/07/2025

Institution Pharmaceutical company

GlaxoSmithKline (GSK)

First published: 01/02/2024

Last updated: 01/02/2024

Institution

Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) Spain, European Medicines Agency United Kingdom, Lægemiddelstyrelsen (Danish Medicines Agency) (DKMA) Denmark, Ludwig-Maximilians-Universität-München (LMU MUENCHEN) Germany, MerckSerono Switzerland, Glaxo Smith Kline United Kingdom

Networks

PROTECT

- [ ] Belgium
- [ ] Denmark
- [ ] France
- [ ] Germany
- [ ] Italy
- [ ] Netherlands
- [ ] Poland
- [ ] Spain
- [ ] Sweden
- [ ] Switzerland
- [ ] United Kingdom

First published: 26/06/2013

Last updated: 14/01/2025

Network

Contact details

Study institution contact

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Study contact

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Primary lead investigator

Francisco De Abajo

Primary lead investigator

Study timelines

Date when funding contract was signed

Planned: 19/08/2009

Actual: 19/08/2009

Study start date

Planned: 03/10/2011

Actual: 03/10/2011

Date of final study report

Planned: 01/02/2014

Sources of funding

- Pharmaceutical company and other private sector
- EU institutional research programme

More details on funding

Amgen, AstraZeneca, Genzyme, GlaxoSmithKline, MerckSerono, Novartis, Roche, Pfizer, Innovative Medicines Initiative (IMI)

Study protocol

PROTECT_Final Protocol_ BenzoHIPfracture_14Nov2011Amend1_approved29Feb2012.pdf (1.26 MB)

PROTECT_WP2 Final Protocol_ BenzoHIPfracture_14Nov2011_Amend4_Dec2013.pdf (1.84 MB)

Regulatory

Was the study required by a regulatory body?

No

Methodological aspects

Study type

Study type list

Study type:

Non-interventional study

Scope of the study:

Assessment of risk minimisation measure implementation or effectiveness

Disease epidemiology

Other

If ‘other’, further details on the scope of the study

Analysis of discrepancies in results between different databases

Main study objective:

To assess the association between the use of benzodiazepines and the risk of hip/femur fracture with different study designs across different primary care databases and to compare the results between databases, across designs to evaluate the impact of design/database/population differences on the outcome of the studied association.

Study Design

Non-interventional study design

Cohort

Case-control

Other

Non-interventional study design, other

Case-crossover, self-controlled case series, Descriptive study = description of exposure and/or outcome in the whole database during a defined period of time

Study drug and medical condition

Anatomical Therapeutic Chemical (ATC) code

(N05BA) Benzodiazepine derivatives

Benzodiazepine derivatives

(N05CD) Benzodiazepine derivatives

Benzodiazepine derivatives

(N05CF) Benzodiazepine related drugs

Benzodiazepine related drugs

(N05CM) Other hypnotics and sedatives

Other hypnotics and sedatives

Medical condition to be studied

Hip fracture

Femur fracture

Population studied

Age groups

- Preterm newborn infants (0 – 27 days)
- Term newborn infants (0 – 27 days)
- Infants and toddlers (28 days – 23 months)
- Children (2 to < 12 years)
- Adolescents (12 to < 18 years)
- 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)

Estimated number of subjects

55700000

Study design details

Data analysis plan

Descriptive study of use of BZD and incidence/prevalence of hip/femur fractures.Cohort: Incidence rates of hip/femur fractures (IR), Poisson regression analysis will be used to estimate age and gender adjusted Incidence Rate Ratio (IRR) and Time-dependent Cox proportional hazards models.Case-Control: Conditional logistic regression analysis to estimate the odd ratio (OR) and 95% CI of hip/femur fracture associated with the current use of benzodiazepines as compared to past use and adjusting for confounding variables. Case-crossover:Conditional logistic regression. It is analogous to a matched case-control study design, where one compares a ‘case’ person-moment with a series of ‘control’ person-moments from different subjects. Self Control Case Series: IR will be calculated for each risk window and data will be analyzed with conditional Poisson regression adjusted by gender and age to calculate incidence rate ratios

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.

Signed checklist for study protocols

ENCePPChecklistforProtocol- F Abajo & C Huerta signed.pdf (54.85 KB)

Data sources

Data source(s)

THIN® (The Health Improvement Network®)

Clinical Practice Research Datalink

Danish registries (access/analysis)

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