Risk of cardiac valve disorders associated with the use of biphosphonates (Cardiac valve disorders and biphosphonate use)

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Study | Finalised

Administrative details

Contact details

Study institution contact
Miriam Sturkenboom
Study contact

mcjm.sturkenboom@gmail.com
Primary lead investigator
Miriam Sturkenboom
Primary lead investigator

PURI
https://redirect.ema.europa.eu/resource/20749

EU PAS number
EUPAS2616

Study ID
20749

DARWIN EU® study
No

Study countries
Italy
Netherlands
United Kingdom

Study description
A signal of disproportionate reporting concerning the risk of cardiac valve calcification leading to cardiac valve insufficiency associated with the use of bisphosphonates was found in EudraVigilance. A similar association between bisphosphonate use and valvular and vascular calcification in women has also been previously described in a cohort study conducted in the United States (MESA study).The primary objective of this signal strengthening study is to confirm or refute the presence of a possible risk of cardiac valve disorders (all types of disorders, confirmed by cardiac imaging) in patients treated with bisphosphonates using EU longitudinal healthcare data from the EU-ADR Alliance. This signal strengthening study will determine the need for, and feasibility of conducting a traditional hypothesis testing study.Signal strengthening will be performed using the most recently updated demographic, clinical, and prescription data from six databases in three EU member states (Italy, Netherlands, the United Kingdom), pooled using a distributed network approach by generation of common input data followed by local aggregation through custom-built software, Jerboa©. Potential cases of cardiac valve disorders in the database network will be identified using database-specific coding algorithms. Exposure to bisphosphonates will be assessed with drug prescription/dispensing data using the World Health Organisation's (WHO) Anatomical Therapeutic Chemical (ATC) classification system. Several signal detection/strengthening methods will be employed to assess the association of cardiac valve disorder and use of bisphosphonates

Study status
Finalised

Research institution and networks

Institutions

Erasmus Medical Centre Rotterdam
First published: 01/02/2024
Last updated 01/02/2024
Institution

Primary Care Research Institute Jordi Gol

The PHARMO Institute for Drug Outcomes Research (PHARMO Institute)

Netherlands
First published: 07/01/2022
Last updated
10/01/2022

Institution | ENCePP partner | Laboratory/Research/Testing facility

Networks

EU-ADR Alliance

First published: 01/02/2024
Last updated
01/02/2024

Network

Study timelines

Date when funding contract was signed
Planned:
02/12/2011
Actual:
02/12/2011

Data collection
Planned:
11/06/2012
Actual:
18/06/2012

Start date of data analysis
Planned:
18/06/2012
Actual:
22/06/2012

Date of interim report, if expected
Planned:
02/07/2012
Actual:
16/07/2013

Date of final study report
Planned:
02/08/2012
Actual:
08/01/2014

Sources of funding

- EMA

Study protocol

D1.b. Final Protocol signal strengthening (BI)_23May2012.pdf(1.23 MB)

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 data collection

Main study objective:
The primary objective of this study is to confirm, or refute, the existence of a statistical association of cardiac valve disorders (all types of disorders, confirmed by echocardiography, cardiac catheterisation, or other imaging modality) and use of bisphosphonate (for all indications), and eventua

Study Design

Non-interventional study design
Case-control
Cohort

Study drug and medical condition

Anatomical Therapeutic Chemical (ATC) code
100000097107
Bisphosphonates

Medical condition to be studied
Cardiac valve disease

Population studied

Short description of the study population
Patients treated with bisphosphonates who are registered in the databases participating in the study. All the subjects of any age with at least one year of data available in the database were included in the study.

Age groups
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
27000000

Study design details

Outcomes
Occurrence of any cardiac valve disorder

Data analysis plan
Through data mining techniques any association of individual bisphosphonates and each outcome definition will be explored and quantified. Various statistical methods have previously been evaluated for this purpose and in this study a combination of the best performing methods, enumerated below, will be applied to data pooled from all six databases. a. Incidence Rate Ratio (IRR) is calculated as the ratio between incidence rate during exposure to the drug compared to a background incidence rate. A Mantel-Haenszel test is used to test the differences between the incidence rates, typically correcting for age and sex. b. Longitudinal Gamma Poisson Shrinker (LGPS) is an adaptation of the GPS method, developed for use in spontaneous reporting databases, to longitudinal data. It applies Bayesian shrinkage to the IRR.c. Automated Matched Case Control Method. For every potential case identified, a predefined number of controls will be matched to the same age, sex, index date.

Documents

Results tables
Executive Summary.pdf(369.17 KB)

Data management

ENCePP Seal

This study has been awarded the ENCePP seal

Conflicts of interest of investigators
ENCePPDoIForms_merged.pdf(427.67 KB)

Composition of steering group and observers
Participants_Cardiac valve disorders and biphosphonate use.pdf(188.04 KB)

Signed code of conduct
CoC Declaration 2616.pdf(375.52 KB)

Signed code of conduct checklist
CoC Checklist 2616.pdf(150.28 KB)

Signed checklist for study protocols
Study Protocols Checklist 2616.pdf(241.69 KB)

Data sources

Data source(s)
THIN® (The Health Improvement Network®)
Drug claims information system
Health Search/IQVIA Health Longitudinal Patient Database
IPCI

Data sources (types)
Administrative data (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
Unknown