Post-Authorization Safety Program—Validation of the Clinical Practice Research Datalink for the Study of Cardiovascular and Neoplasm Events in Users of Treatments for Overactive Bladder

First published: 09/01/2014

Last updated: 02/07/2024

Study | Finalised

Administrative details

EU PAS number

EUPAS5529

Study ID

38910

DARWIN EU® study

No

Study countries

United Kingdom

Study description

Mirabegron is a first in class therapeutic agent, with a mechanism of action distinct from that of antimuscarinic agents indicated for the treatment of overactive bladder (OAB). This is a retrospective cohort study of new users of individual antimuscarinic drugs: oxybutynin, tolterodine, darifenacin, solifenacin, trospium, and fesoterodine. The objectives are: to describe drug-use patterns, to calculate background rates of cardiovascular (CV) and cancer outcomes among antimuscarinic drug users and to validate outcome-specific case-identification algorithms based on electronic diagnosis codes in the Clinical Practice Research Datalink (CPRD) in the United Kingdom. Upon validation these algorithms will be used to evaluate CV and cancer risk associated with mirabegron as part of the required post-approval safety program to be implemented in the US and the EU.The study period is January 2004 through December 2012. The study will calculate incidence rates of the following endpoints: - CV: including acute myocardial infarction, stroke, all-cause mortality, CV mortality and a composite endpoint.- Neoplasm endpoint: including the 10 most commonly occurring in the general population.The data retrieved from primary care data, which contains prescriptions issued by the general practitioners (GP) and medical information recorded by GPs as part of their routine clinical practice, will be compared with information from other sources. The data are linkable, at least for a large subset of patients, with other health care data sets (e.g., hospitalization records, national mortality data, census data, cancer registry).

Study status

Finalised

Research institutions and networks

Institutions

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

Contact details

Study institution contact

Alejandro Arana aarana@rti.org

Study contact

aarana@rti.org

Primary lead investigator

Alejandro Arana

Primary lead investigator

Study timelines

Date when funding contract was signed
Planned: 05/04/2013

Actual: 12/06/2013

Study start date
Planned: 15/03/2014

Actual: 31/03/2014

Data analysis start date
Planned: 01/07/2014

Actual: 27/08/2014

Date of interim report, if expected
Actual: 31/03/2015

Date of final study report
Planned: 28/08/2015

Actual: 28/08/2015

Sources of funding

- Pharmaceutical company and other private sector

More details on funding

Astellas Pharma Global Development, Inc.

Study protocol

178-CL-116 Validation Protocol_sigs-redacted.pdf (1.04 MB)

178-cl-116-clp-02-reissue-en-v3dot2_Redacted.pdf (1.2 MB)

Regulatory

Was the study required by a regulatory body?

Yes

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

EU RMP category 3 (required)

Methodological aspects

Study type

Study type list

Study topic:

Disease /health condition

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Drug utilisation

Other

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

Validation of the CPRD database for the study of CV and neoplasm events in users of treatments for overactive bladder

Data collection methods:

Secondary use of data

Main study objective:

Characterize users of OAB drugs. Describe patterns of usage of OAB drugs. Validate algorithms used for the diagnosis of study endpoints. Describe the availability of potential confounders in the CPRD, to help in the design of the PASS studies of mirabegron. Estimate IRs of study endpoints in new users of OAB drugs. Estimate the IRRs of CV outcomes in users of OAB drugs compared with tolterodine.

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

Anatomical Therapeutic Chemical (ATC) code

(G04BD04) oxybutynin

oxybutynin

(G04BD07) tolterodine

tolterodine

(G04BD08) solifenacin

solifenacin

(G04BD09) trospium

trospium

(G04BD10) darifenacin

darifenacin

(G04BD11) fesoterodine

fesoterodine

Medical condition to be studied

Urinary incontinence

Population studied

Short description of the study population

Patients in the study had at least 12 months of continuous enrollment in the database, followed by an index prescription for oxybutynin, tolterodine, darifenacin, solifenacin, trospium, or fesoterodine, provided that the agent was not prescribed during the previous 12 months; patients were aged 18 years or older at the time of the index prescription.

Subjects in the program will be required to meet all of the following inclusion criteria:

1. Have at least 12 months of continuous enrollment in the database (thereby providing medical and prescription history data) before the first prescription or dispensing of an OAB drug of interest.
2. For most covariates (e.g., history of bilateral mastectomy, menopause status, use of hormone-replacement therapy), all available information without time limitation will be used, although the 12-month period prior to the cohort entry date will be used to estimate measures of health care utilization.
3. Have a first recorded prescription or dispensing for oxybutynin, tolterodine, darifenacin, solifenacin, trospium, or fesoterodine.
4. Be aged 18 years or older at the time of first prescription of a drug of interest.

Patients will be excluded if they meet any of the following criteria at any time prior to cohort entry:

1. Had a diagnosis of cancer other than non-melanoma skin cancer.
2. Had a diagnosis of human immunodeficiency virus (HIV) infection. These patients often receive health care through specialty clinics or separate health plans, and their health service use might not be fully captured in the data sources.

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

Other

Special population of interest, other

Overactive bladder patients

Estimated number of subjects

400000

Study design details

Outcomes

CV endpoints: AMI, stroke, CV mortality, all-cause mortality, major adverse cardiac events (MACE).Composite cancer endpoints: lung & bronchus, colon & rectum, melanoma of skin, urinary bladder, non-Hodgkin lymphoma, kidney & renal pelvis, pancreas, prostate (males), breast (females), corpus uteri

(females).

Data analysis plan

Summary statistics of the covariates will be generated. The characteristics of the users at cohort entry and the patterns of use of the study medications will be described. CV cases will be classified as definite, probable, possible or noncases after patient profile review.A random sample of definite, probable and noncases will be selected for validation. GPs will be asked to review patients' medical records and charts and complete a questionnaire. Based on this assessment, the PPV will be calculated for the definite, probable and possible cases.The screening and validation method of neoplasm endpoints will depend on whether the medical practice where the study subject is enrolled consented to have its information linked to other health care data within the NHS system. Characteristics of subjects in practices without and with data linkage will be compared. The concordance between diagnosis derived from the CPRD, the Hospital Episodes Statistics and the cancer registry will be described

Documents

Study results

178-cl-116-clrr-03-disc01-en-final-02_redacted2.pdf (9.33 MB)

Study publications

Arana, A, Margulis, AV, Varas-Lorenzo, C, et al. Validation of cardiovascular o...
Kaye JA, Margulis AV, Fortuny J, McQuay LJ, Plana E, Bartsch JL, Bui CL, Perez-...
Arana A, Margulis AV, McQuay LJ, Ziemiecki R, Bartsch J, Franks B, D´Silva M, A...
Margulis AV, Fortuny J, Kaye JA, Calingaert B, Reynolds M, Plana E, et al. Vali...
Margulis AV, Fortuny J, Kaye JA, Calingaert B, Reynolds M, Plana E, McQuay LJ, ...

Data management

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)

Clinical Practice Research Datalink

Data source(s), other

Office for National Statistics (ONS) mortality data, National Cancer Data Repository (NCDR)

Data sources (types)

Administrative healthcare records (e.g., claims)

Disease registry

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