Multinational, multi-database cohort study to assess adverse cardiovascular and cerebrovascular outcomes and mortality in association with inhaled NVA237 in Europe (NVA237 PASS)

First published: 25/10/2013

Last updated: 14/03/2024

Study Finalised

Administrative details

EU PAS number

EUPAS5035

Study ID

38133

DARWIN EU® study

No

Study countries

- ☐ Denmark
- ☐ Italy

- [ ] Netherlands
- [ ] Spain
- [ ] United Kingdom

Study description

In the context of the NVA237 marketing application in Europe, the Committee for Medicinal Products for human use (CHMP) required the conduct of a post-authorization safety study (PASS) to assess the association between the use of NVA237 and cardiovascular and cerebrovascular events. The objectives of this study are to assess the incidence rates and hazard ratio of 1) cardiovascular and cerebrovascular outcomes and 2) mortality among new users of inhaled NVA237 with COPD compared to new users of comparator drugs (long acting antimuscarinic antagonists LAMAs excluding NVA237) or long acting β2 agonists (LABAs) with COPD.This study will be a multinational, multi-database cohort study using information from five European electronic health care databases from the Netherlands, Italy, United Kingdom (UK), Denmark and Spain in new users of NVA237 vs. new users of two comparator drug classes.

Study status

Finalised

Research institutions and networks

Institutions

Novartis Pharmaceuticals

First published: 01/02/2024

Last updated: 01/02/2024

Institution

Aarhus University & Aarhus University Hospital DEPARTMENT OF CLINICAL EPIDEMIOLOGY

Denmark

First published: 20/07/2021

Last updated: 02/04/2024

Institution | Educational Institution | ENCePP partner

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

Società Italiana di Medicina Generale e delle Cure Primarie (SIMG)

First published: 01/02/2024

Last updated: 01/02/2024

Institution | Patient organisation/association

SIDIAP Jordi Gol Spain

Networks

EU-ADR Alliance

First published: 01/02/2024

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Network

Contact details

Study institution contact

Clinical Disclosure Officer Novartis

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Study contact

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Primary lead investigator

Clinical Disclosure Officer Novartis

Primary lead investigator

Study timelines

Date when funding contract was signed
Actual: 07/05/2013

Study start date
Actual: 01/11/2012

Data analysis start date
Planned: 25/10/2013

Actual: 25/10/2013

Date of interim report, if expected
Planned: 04/12/2013

Date of final study report
Planned: 30/11/2017

Actual: 17/11/2017

Sources of funding

- Pharmaceutical company and other private sector

More details on funding

Novartis

Study protocol

NVA237A2402T-v03--protocol_Redacted.pdf (2.76 MB)

Regulatory

Was the study required by a regulatory body?

Yes

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

EU RMP category 1 (imposed as condition of marketing authorisation)

Other study registration identification numbers and links

CNVA237A2402T

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 use of data

Main study objective:

To assess the incidence rates and hazard ratio of cardiovascular and cerebrovascular outcomes, and of mortality among new users of inhaled NVA237 with COPD compared to new users of LAMA (non-NVA237) or new users of LABA in patients with COPD.

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

Anatomical Therapeutic Chemical (ATC) code

(R03BB06) glycopyrronium bromide

glycopyrronium bromide

Medical condition to be studied

Chronic obstructive pulmonary disease

Population studied

Short description of the study population

Population of patients, 40 years of age or older with at least 1 year of valid database history and a recorded diagnosis of COPD.

Inclusion criteria

All patients aged 40 years or older who were diagnosed with COPD and had at least one year of database history and a first time prescription/dispensing for one of the following medications after 01 November 2012 were included in the study: NVA237 or a single ingredient LAMA (other than NVA237) or a single-ingredient LABA.

Exclusion criteria

Patients with 1) missing data on age or gender, 2) a recorded diagnosis of asthma only and thus, no recorded diagnosis of COPD prior to or within six months after the first prescription/dispensing of any of the drugs of interest, or 3) who received the study drug of interest (NVA237, LAMA [excluding NVA237] or LABA) in the one year prior to the index date (= time of first prescription) of the respective study cohorts were excluded. Patients thus needed to be treatment-naïve to the exposure of interest for a minimum of one year. In addition, patients treated with both LABA and LAMA at the time of first prescription/dispensing of the study drug of interest were excluded from the study. As this was a non-interventional study using real-world data, it was decided to not exclude patients with non-cardiovascular life-threatening conditions (i.e., defined as patients with underlying cancer.

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

Chronic obstructive pulmonary disease (COPD) patients

Estimated number of subjects

3000

Study design details

Outcomes

• Major cardiovascular events •Ischemic heart disease including myocardial infarction and angina pectoris•Cardiac arrhythmias •Atrial fibrillation/flutter •Cerebrovascular disorders •Mortality

Data analysis plan

As primary analysis, the risk of overall mortality as well as the risk of the different endpoints of interest among new users of NVA237 will be compared to the risk in the new users of LABA and other LAMA using Cox regression analysis. Cox regression analyses will be conducted to estimate both crude and adjusted relative risks (expressed as hazard ratios HRs with 95% confidence intervals 95% CIs), allowing for time-varying exposures. All analyses will at first be performed for each database separately. Effect estimates will be pooled across the databases, using a random effects meta-analytical approach. In addition, a pooled mega-analysis will be done by combining the data sources on a patient-level and adjusting for the database.As secondary analysis, subsequent episodes, with or without treatment, will be taken into account. For this analysis, the HR of the events of interest will be estimated for NVA237 vs. no use of NVA237.

Documents

Study results

NVA237A2402T-Redacted-Final-Study-Report.pdf (6.63 MB)

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)

THIN® (The Health Improvement Network®)

Danish registries (access/analysis)

Health Search/IQVIA Health Longitudinal Patient Database

Integrated Primary Care Information (IPCI)

The Information System for Research in Primary Care (SIDIAP)

Data sources (types)

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