A post-authorisation safety study (PASS) to evaluate the long-term cardiovascular and psychiatric safety profile of methylphenidate (MPH) in adult patients with attention deficit/hyperactivity disorder (ADHD) in European Countries (PASS on methylphenidate in adults)

First published: 04/03/2021

Last updated: 10/12/2025

Study Finalised

Administrative details

EU PAS number

EUPAS39745

Study ID

47509

DARWIN EU® study

No

Study countries

- ☐ Denmark
- ☐ Norway
- ☐ Sweden

Study description

There is limited and inconsistent data from pharmacoepidemiologic studies on MPH use and adverse cardiovascular or psychiatric events, especially among adults. The overall aim of the PASS is to compare the risk of first-time cardiovascular or psychiatric events in association with new use of MPH monotherapy versus new use of non-MPH ADHD medications (lisdexamfetamine, dexamfetamine and atomoxetine, monotherapy) and versus no use of ADHD medication in adult patients aged ≥18 years newly diagnosed with ADHD, in healthcare databases of three European countries.

Study status

Finalised

Research institutions and networks

Institutions

IQVIA

☐ United Kingdom

First published: 12/11/2021

Last updated: 22/04/2024

Institution | Non-Pharmaceutical company | ENCePP partner

Contact details

Study institution contact

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Study contact

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Primary lead investigator

Sofia Correia

Primary lead investigator

Study timelines

Date when funding contract was signed

Actual: 27/09/2018

Study start date

Planned: 31/03/2021

Actual: 31/03/2021

Data analysis start date

Planned: 01/10/2021

Date of interim report, if expected

Planned: 30/06/2022

Actual: 21/09/2022

Date of final study report

Planned: 30/03/2025

Actual: 29/01/2025

Sources of funding

- Pharmaceutical company and other private sector

More details on funding

Medice

Study protocol

PASS_Medice_ADHD_ Protocol_v5.2_20Feb2024_abstract for HMA-EMA.pdf
(420.57 KB)
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(420.57 KB)

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)

Regulatory procedure number

EMEA/H/N/PSP/S/0064

Methodological aspects

Study type

Study type list

Study topic:

Disease /health condition

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Safety study (incl. comparative)

Data collection methods:

Secondary use of data

Study design:

This was a retrospective observational cohort study conducted in 3 European countries (Denmark, Norway, and Sweden) using secondary data. A new user design was applied.

Main study objective:

To compare the incidence rate of first-time cardiovascular events (composite) in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time newly exposed to MPH versus cumulative person-time newly treated with non-MPH ADHD medication.

Study Design

Non-interventional study design

Cohort

Non-interventional study design, other

Retrospective cohort study (new user design)

Study drug and medical condition

Study drug International non-proprietary name (INN) or common name

ATOMOXETINE

METHYLPHENIDATE HYDROCHLORIDE

Anatomical Therapeutic Chemical (ATC) code

(N06BA02) dexamfetamine

dexamfetamine

(N06BA04) methylphenidate

methylphenidate

(N06BA09) atomoxetine

atomoxetine

(N06BA12) lisdexamfetamine

lisdexamfetamine

Medical condition to be studied

Attention deficit hyperactivity disorder

Myocardial infarction

Cardiomyopathy

Left ventricular hypertrophy

Cerebrovascular accident

Ventricular arrhythmia

Psychotic symptom

Manic symptom

Suicidal ideation

Suicidal behaviour

Aggression

Anxiety

Agitation

Tension

Depressive symptom

Tic

Sudden cardiac death

Hypertension

Cardiac valve disease

Pulmonary hypertension

Additional medical condition(s)

All causes of cardiovascular death

Population studied

Short description of the study population

Adults newly diagnosed with ADHD, on or after the age of 18 years, in Denmark, Norway, and Sweden

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Age groups

- **Adult and elderly population (≥18 years)**
  - Adults (18 to < 65 years)
    - Adults (18 to < 46 years)
    - Adults (46 to < 65 years)
  - Elderly (≥ 65 years)
    - Adults (65 to < 75 years)
    - Adults (75 to < 85 years)
    - Adults (85 years and over)

Estimated number of subjects

500000

Study design details

Setting

The study period of started from 13 June 2008 for Sweden, 06 May 2011 for Norway, and from 29 September 2006 for Denmark through to 31 December 2019,

in order to allow for the minimum lookback period for confounders before the enrolment (12 months) and to start the study not prior to the availability of prescription data for MPH and at least one active comparator in the selected European Union (EU) market(s).

In each country, patients who were aged 18 years or more and had a diagnosis of

ADHD were identified as eligible for inclusion into the study using the National Patient Register. Individual patient data were thereafter linked to the National Dispensed Drug Register and the Cause of Death Register.

The following selection criteria were applied for the data extraction:

Inclusion criteria for data extraction:

• A diagnosis recorded at any time in the data source of ADHD based on International Statistical Classification of Diseases, 10th Revision (ICD-10) codes F90 (Hyperkinetic disorders) or F98.8 (Other specified behavioural and emotional

disorders with onset usually occurring in childhood and adolescence).

• Age 18 years or more at ADHD diagnosis.

• Continuous enrolment in the database for >12 months prior to date of first diagnosis.

• No dispensed prescription for ADHD medication in the prior 12 months before

cohort entry (defined as the index diagnosis of ADHD).
Exclusion criteria for data extraction:
• Patients with missing age or sex.
• ADHD diagnosis prior to and including age 17 years. These patients by definition
cannot be considered as adults newly diagnosed with ADHD in this study and are
instead prevalent cases of the indication for treatment.
To address the research questions related to the primary and secondary endpoints
separate cohorts were created, and cohort-specific selection criteria, nested within
the criteria for data extraction, were applied. These cohorts were referred as the
CV and psychiatric cohorts, respectively.

Outcomes

First-time cardiovascular events (composite of hospitalization for myocardial infarction, cardiomyopathy, left-ventricular hypertrophy, hospitalization for stroke, ventricular arrhythmia, sudden cardiac death or all other causes of cardiovascular death of interest), first-time psychiatric events of interest (composite of psychotic or manic symptoms, suicidal ideation or behaviour, aggressive and hostile behaviour, anxiety or agitation or tension, depressive symptoms, motor or verbal tics)

Data analysis plan

• Descriptive analysis for each cohort post data-extraction,
• Cohort-specific descriptive statistics summarizing demographic, health and clinical patient characteristics will be presented.
• Crude incidence (presented as both proportions and rates) for the relevant

outcomes reported during person-time treated with MPH, treated with Non-MPH, or time untreated will be calculated for 1-year, 2-year, 3-year, 4-year and 5-year intervals cumulatively, stratified by potential confounders

• Time to event, high and low risk periods will be summarized.

• Univariate analyses will be used to inform on potential confounders and risk factors.

• Cardiovascular and psychiatric risk scores will be determined via regression

• Time-varying analysis of cardiovascular and psychiatric hazard rates will be performed using time-varying Cox regression models by country and pooled estimate calculated using random effects meta-analysis.

Documents

Abstract of study report

Medice ADHD final report_v2.0_18Jun2025_abstract_HMA-EMA.pdf (307.34 KB)

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)

Danish registries (access/analysis)

Sweden National Prescribed Drugs Register / Läkemedelsregistret

Norwegian Health Registers

Data source(s), other

Norwegian Prescription Database (NorPD)

Data sources (types)

Administrative healthcare records (e.g., claims)

Disease registry

Electronic healthcare records (EHR)

Other

Data sources (types), other

Exposure registry

Use of a Common Data Model (CDM)

CDM mapping

No

Data quality specifications

Check conformance

Yes

Check completeness

Yes

Check stability

Unknown

Check logical consistency

Yes

Data characterisation

Data characterisation conducted

Yes

Data characterisation moment

after data extraction

Data characterisation details

Routine procedures included checking electronic files, maintaining security and data confidentiality, following analysis plans, and performing quality control checks of all programes. Each data source custodian maintained any patient-identifying information securely on site according to internal standard operating procedures. The study is sub-contracted by IQVIA to a third party in Norway, and the datasets and analytic programes were stored according to the vendor’s procedures.

Security processes were in place to ensure the safety of all systems and data. Every effort was made to ensure that data are kept secure so that they cannot be accessed by anyone except selected study staff.

Appropriate data storage and archiving procedures were followed. Standard procedures to restore files in the event of a hardware or software failure were in place at each data source.

The study sponsor did not have access to health records at the level of the individual patient but only to tables with aggreg