POST-AUTHORISATION SAFETY STUDY (PASS) PROTOCOL

PASS INFORMATION

TITLE	A post-authorisation safety study (PASS) to evaluate the long-term cardiovascular and psychiatric safety profile of methylphenidate in adult patients with attention deficit/hyperactivity disorder (ADHD) in European Countries
PROTOCOL VERSION IDENTIFIER	5.2
DATE OF LAST VERSION OF PROTOCOL	2 February 2024
EU PAS REGISTER NUMBER	EUPAS39745
ACTIVE SUBSTANCE	Methylphenidate (MPH) hydrochloride - ATC WHO code: N06BA04
MEDICINAL PRODUCT(S)	Methylphenidate hydrochloride
PRODUCT REFERENCE	N/A
PROCEDURE NUMBER	DE/H/0690/004-010/II/043/G
MARKETING AUTHORISATION HOLDER(S) (MAH)	Medice Arzneimittel Pütter GmbH Co. KG
JOINT PASS	No
RESEARCH QUESTION AND OBJECTIVES	**Overall aim** 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 (lisdexafetamine, 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. **Primary objective** 1. To compare the incidence rate of first-time cardiovascular events (composite of: hospitalisation for myocardial infarction, cardiomyopathy, left-ventricular hypertrophy, hospitalisation for

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	stroke, ventricular arrhythmia, sudden cardiac death or all other causes of cardiovascular death of interest) in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time newly treated with non-MPH ADHD medication. **Secondary objectives** 2. 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 not receiving ADHD medication. 3. To compare the incidence rate of 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) in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time newly treated with non-MPH ADHD medication. 4. To compare the incidence rate of first-time psychiatric events of interest (composite) in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time not receiving ADHD medication. 5. To quantify the crude cumulative incidence, describe the time to onset and define the high risk periods and selected risk factors for cardiovascular events of interest (composite and separately) in adults newly diagnosed with ADHD between (i) cumulative person-time newly exposed to MPH, (ii) cumulative person-time newly treated with non-MPH ADHD medication and (iii) cumulative person-time not receiving ADHD medication. 6. To quantify the crude cumulative incidence, describe the time to onset and define the high risk periods and selected risk factors for psychiatric events of interest (composite and separately) in adults newly diagnosed with ADHD between (i) cumulative person-time newly exposed to MPH, (ii) cumulative person-time newly treated with non-MPH ADHD medication and (iii) cumulative person-time not receiving ADHD medication. **Exploratory objectives** 7. 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 treated with non-MPH ADHD medication, by calendar time prior to and post introduction of extended release MPH formulations. 8. 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 treated with non-MPH ADHD medication, by cumulative dose. 9. 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

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	person-time newly treated with non-MPH ADHD medication, by sex and age. 10. To compare, separately, the incidence rate of hospitalisation for myocardial infarction, cardiomyopathy, left-ventricular hypertrophy, hospitalisation for stroke, ventricular arrhythmia, sudden cardiac death or all other causes of cardiovascular death of interest, in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time newly treated with non-MPH ADHD medication. 11. To compare, separately, the incidence rate of all-cause death, and incidence rate of hypertension, cardiac valve disease and pulmonary hypertension in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time newly treated with non-MPH ADHD medication. 12. To compare, separately, the incidence rate of first-time psychiatric events of interest (psychotic or manic symptoms; suicidal ideation or behaviour; aggressive and hostile behaviour; anxiety, agitation or tension; depressive symptoms; motor or verbal tics) in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time newly treated with non-MPH ADHD medication. If a significant increase in the incidence rate of the cardiovascular composite endpoint is observed to be associated with cumulative person-time newly exposed to MPH versus cumulative person-time not receiving ADHD medication (objective 2) when pooled across all countries, the following additional objectives will be assessed: 13. 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 not receiving ADHD medication, by calendar time prior to and post introduction of extended release MPH formulations. 14. 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 not receiving ADHD medication, by cumulative dose. 15. 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 not receiving ADHD medication, by sex and age. 16. To compare, separately, the incidence rate of hospitalisation for myocardial infarction, cardiomyopathy, left-ventricular hypertrophy, hospitalisation for stroke, ventricular arrhythmia, sudden cardiac death or all other causes of cardiovascular death of interest, in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time not receiving ADHD medication. 17. To compare, separately, the incidence rate of all-cause death, and incidence rate of hypertension, cardiac valve disease and pulmonary hypertension in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time not receiving ADHD medication.

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	If a significant increase in the incidence rate of the psychiatric composite endpoint is observed to be associated with cumulative person-time newly exposed to MPH versus cumulative person-time not receiving ADHD medication (objective 4) when pooled across all countries, the following additional objective will be assessed: 18. To compare, separately, the incidence rate of first-time psychiatric events of interest (psychotic or manic symptoms; suicidal ideation or behaviour; aggressive and hostile behaviour; anxiety, agitation or tension; depressive symptoms; motor or verbal tics) in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time not receiving ADHD medication. The above objectives will be completed over a 5-year follow-up period. If a sufficient number of patients are still available after 5 years (≥30% of cohort) until 10 years (≥10% of cohort), the following additional objectives will be assessed using a 10-year follow-up period: 19. 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 treated with non-MPH ADHD medication. 20. 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 not receiving ADHD medication. 21. To compare the incidence rate of first-time psychiatric events of interest (composite) in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time not receiving ADHD medication. 22. To compare the incidence rate of first-time psychiatric events of interest (composite) in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time newly treated with non-MPH ADHD medication. 23. To quantify the crude cumulative incidence, describe the time to onset for cardiovascular events of interest (composite and separately) in adults newly diagnosed with ADHD between (i) cumulative person-time newly exposed to MPH, (ii) cumulative person-time newly treated with non-MPH ADHD medication and (iii) cumulative person-time not receiving ADHD medication. 24. To quantify the crude cumulative incidence, describe the time to onset for psychiatric events of interest (composite and separately) in adults newly diagnosed with ADHD between (i) cumulative person-time newly exposed to MPH, (ii) cumulative person-time newly treated with non-MPH ADHD medication and (iii) cumulative person-time not receiving ADHD medication.
COUNTRY(-IES) OF STUDY	Denmark, Norway, Sweden
AUTHOR	IQVIA Ltd

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1. ABSTRACT

Full Study Title

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

Rationale and Background

Medikinet® retard, a methylphenidate (MPH) containing product marketed by Medice, is indicated as part of a comprehensive treatment programme for ADHD in children aged 6 years and over and adults when remedial measures alone prove insufficient. Other ADHD treatments include dexamfetamine, lisdexamfetamine, and atomoxetine, which will compose the MPH non-exposed group in this study.

The short- and long-term efficacy of MPH is well established. Long-term safety data on cardiovascular risks in adults treated with MPH showed minor mean pre-post elevations in blood pressure and pulse rate, yet without an increase in serious cardiac outcomes. However, case reports of sudden death, stroke and myocardial infarction reported for adult patients treated with psychostimulants have led to regulatory concerns on the long-term benefit-risk balance and requests for studies to assess these outcomes. Methlyphenidate use is also associated with psychiatric effects, including psychotic, manic and depressive disorders. These adverse cardiovascular and psychiatric events have however been observed mainly in clinical trials. There is limited and inconsistent data from pharmacoepidemiologic studies on MPH use and adverse cardiovascular or psychiatric events, especially among adults.

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Aim:

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 (lisdexafetamine, 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

Primary Objective

1. To compare the incidence rate of first-time cardiovascular events (composite of: hospitalisation for myocardial infarction, cardiomyopathy, left-ventricular hypertrophy, hospitalisation for stroke, ventricular arrhythmia, sudden cardiac death or all other causes of cardiovascular death of interest) in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time newly treated with non-MPH ADHD medication.

Secondary Objectives

2. 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 not receiving ADHD medication.
3. To compare the incidence rate of first-time psychiatric events of interest (composite of: psychotic or maniac symptoms, suicidal ideation or behaviour, aggressive and hostile behaviour, anxiety or agitation or tension, depressive symptoms, motor or verbal tics) in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time newly treated with non-MPH ADHD medication.
4. To compare the incidence rate of first-time psychiatric events of interest (composite) in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time not receiving ADHD medication.
5. To quantify the crude cumulative incidence, describe the time to onset and define the high risk periods and selected risk factors for cardiovascular events of interest (composite and separately) in adults newly diagnosed with ADHD between (i) cumulative person-time newly exposed to MPH, (ii) cumulative person-time newly treated with non-MPH ADHD medication and (iii) cumulative person-time not receiving ADHD medication.
6. To quantify the crude cumulative incidence, describe the time to onset and define the high risk periods and selected risk factors for psychiatric events of interest (composite and separately) in adults newly diagnosed with ADHD between (i) cumulative person-time newly exposed to MPH, (ii) cumulative person-time newly treated with non-MPH ADHD medication and (iii) cumulative person-time not receiving ADHD medication.

Exploratory Objectives

7. 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 treated with non-MPH ADHD medication, by calendar time prior to and post introduction of extended release MPH formulations.

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8. 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 treated with non-MPH ADHD medication, by cumulative dose.
9. 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 treated with non-MPH ADHD medication, by sex and age.
10. To compare, separately, the incidence rate of hospitalisation for myocardial infarction, cardiomyopathy, left-ventricular hypertrophy, hospitalisation for stroke, ventricular arrhythmia, sudden cardiac death or all other causes of cardiovascular death of interest, in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time newly treated with non-MPH ADHD medication.
11. To compare, separately, the incidence rate of all-cause death, and incidence rate of hypertension, cardiac valve disease and pulmonary hypertension in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time newly treated with non-MPH ADHD medication.
12. To compare, separately, the incidence rate of first-time psychiatric events of interest (psychotic or manic symptoms; suicidal ideation or behaviour; aggressive and hostile behaviour; anxiety, agitation or tension; depressive symptoms; motor or verbal tics) in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time newly treated with non-MPH ADHD medication.

If a significant increase in the incidence rate of the cardiovascular composite endpoint is observed to be associated with cumulative person-time newly exposed to MPH versus cumulative person-time not receiving ADHD medication (objective 2) when pooled across all countries, the following additional objectives will be assessed:

13. 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 not receiving ADHD medication, by calendar time prior to and post introduction of extended release MPH formulations.
14. 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 not receiving ADHD medication, by cumulative dose.
15. 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 not receiving ADHD medication, by sex and age.
16. To compare, separately, the incidence rate of hospitalisation for myocardial infarction, cardiomyopathy, left-ventricular hypertrophy, hospitalisation for stroke, ventricular arrhythmia, sudden cardiac death or all other causes of cardiovascular death of interest, in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time not receiving ADHD medication.
17. To compare, separately, the incidence rate of all-cause death, and incidence rate of hypertension, cardiac valve disease and pulmonary hypertension in adults newly

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diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time not receiving ADHD medication.

If a significant increase in the incidence rate of the psychiatric composite endpoint is observed to be associated with cumulative person-time newly exposed to MPH versus cumulative person-time not receiving ADHD medication (objective 4) when pooled across all countries, the following additional objective will be assessed:

18. To compare, separately, the incidence rate of first-time psychiatric events of interest (psychotic or manic symptoms; suicidal ideation or behaviour; aggressive and hostile behaviour; anxiety, agitation or tension; depressive symptoms; motor or verbal tics) in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time not receiving ADHD medication.

The above objectives will be completed over a 5-year follow-up period. If a sufficient number of patients are still available after 5 years (≥30% of cohort) until 10 years (≥10% of cohort), the following additional objectives will be assessed using a 10-year follow-up period:

19. 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 treated with non-MPH ADHD medication.
20. 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 not receiving ADHD medication.
21. To compare the incidence rate of first-time psychiatric events of interest (composite) in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time not receiving ADHD medication.
22. To compare the incidence rate of first-time psychiatric events of interest (composite) in adults newly diagnosed with ADHD between cumulative person-time newly exposed to MPH versus cumulative person-time newly treated with non-MPH ADHD medication.
23. To quantify the crude cumulative incidence, describe the time to onset for cardiovascular events of interest (composite and separately) in adults newly diagnosed with ADHD between (i) cumulative person-time newly exposed to MPH, (ii) cumulative person-time newly treated with non-MPH ADHD medication and (iii) cumulative person-time not receiving ADHD medication.
24. To quantify the crude cumulative incidence, describe the time to onset for psychiatric events of interest (composite and separately) in adults newly diagnosed with ADHD between (i) cumulative person-time newly exposed to MPH, (ii) cumulative person-time newly treated with non-MPH ADHD medication and (iii) cumulative person-time not receiving ADHD medication.

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Study Design

This is an observational cohort study conducted in three European countries (Sweden, Norway, Denmark) using secondary data. A new user design will be applied. The study population will be comprised of a cohort of adults newly diagnosed with ADHD, on or after the age of 18 years. Cohorts will be constructed for each of the two grouped adverse effects (cardiovascular disorders or psychiatric disorders). Comparisons will be made according to contributed treatment episodes of person-time of new use of MPH, episodes of new use of non-MPH or episodes of no treatment:

(i) Patient contributed person-time during first episode of new use of MPH (MPH person-time)

(ii) Patient contributed person-time during first episode of new use of other treatments for ADHD (dexamfetamine, lisdexmfetamine, atomoxetine) (non-MPH person-time)

(iii) Patient contributed person-time of no use of any ADHD medication post diagnosis (untreated person-time).

Patients will be followed during the study period to assess the occurrence of cardiovascular or psychiatric events of interest, as appropriate.

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Population

Setting

The study period of primary interest will start 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 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 are aged 18 years or more and have a diagnosis of ADHD will be identified as eligible for inclusion into the study using the National Patient Register. Individual patient data will thereafter be linked to the National Dispensed Drug Register and the Cause of Death Register.

The following selection criteria will be 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. These patients by definition cannot be considered 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 (cardiovascular or psychiatric) two cohorts will be created, and additional selection criteria, nested within the criteria for data extraction, will be applied. These cohorts will be referred as the cardiovascular and psychiatric cohorts, respectively.

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Primary Endpoint

The primary endpoint for the cardiovascular cohort is a composite of at least one of the following cardiovascular events of interest:

- Hospitalisation for myocardial infarction
- Hospitalisation for stroke
- Ventricular arrythmia
- Cardiomyopathy
- Left-ventricular hypertrophy
- Sudden death
- All causes of cardiovascular death

Secondary Endpoints

The secondary endpoints will be the following:

Psychiatric events

The endpoint for analysis of the psychiatric cohort is a composite of at least one of the following psychiatric events of interest:

- Psychotic or manic symptoms
- Suicidal ideation or behaviour
- Aggressive and hostile behaviour
- Anxiety, agitation or tension
- Depressive symptoms
- Motor or verbal tics

Cardiovascular events

Secondary endpoints for the cardiovascular cohort will also include the components of the primary composite cardiovascular endpoint as individual endpoints:

- Hospitalisation for myocardial infarction
- Hospitalisation for stroke
- Ventricular arrythmia
- Cardiomyopathy
- Left-ventricular hypertrophy
- Sudden death
- All causes of cardiovascular death

as well as following additional cardiovascular endpoints:

- All-cause death
- Hypertension
- Cardiac valve disease
- Pulmonary hypertension

Exploratory endpoints for the psychiatric cohort will also include the components of the primary composite psychiatric endpoint as individual endpoints:

- Psychotic or manic symptoms

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▪ Suicidal ideation or behaviour ▪ Aggressive and hostile behaviour ▪ Anxiety, agitation or tension ▪ Depressive symptoms ▪ Motor or verbal tics
Data Sources • The National registries from Sweden, Norway, and Denmark
Study Size The databases populations are expected to yield about 130,600, 59,200 and 77,400 adult patients with incident ADHD from start of data collection period in Sweden (2008), Norway (2011) and Denmark (2006), respectively. Since the long-term cardiovascular and psychiatric risks of MPH used by adults with ADHD remains to be defined, the sample size calculation assumes an effect size of 1.8 being observed at the end of 5-years follow-up, where the incidence in the reference group is 3/1,000, with 80% power and 5% significance.

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Data Analysis:

- **Descriptive analyses**
  - Descriptive analysis will be conducted for each cohort post-data extraction to provide insight into general patterns, functional form and any outliers of exposure and covariates.
  - The proportion and summary characteristics of patients excluded from the analysis for the cardiovascular and psychiatric cohorts, including Strengthening The Reporting Of Observational Studies In Epidemiology (STROBE) diagram, will be provided.
  - Patients' characteristics at index and at initiation of treatment will be described, including all potential confounders relevant to the specific cohort/sub-cohort.
  - Crude cumulative incidence proportion and rate of the individual outcomes (cardiovascular and psychiatric 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. Data will also be stratified by potential confounders.
  - An unadjusted Cox proportional hazards regression model will be fitted to describe the time-to-event, which will be presented graphically for each person-time treatment pattern.
  - High and low risk periods will be identified by calculating and comparing crude incidence densities (ID) between intervals within the person-time.
- **Comparative analyses**
  - Univariate analysis will be performed within each cohort (overall cardiovascular and psychiatric) to characterise differences in the potential confounders between treatment pathways (first treatment episode MPH vs first treatment episode non-MPH and first treatment episode MPH vs untreated) to inform on risk factors.
  - Cardiovascular and psychiatric risk scores will be determined within each cohort (overall cardiovascular and psychiatric) via Cox proportional hazard regression modelling the impact of relevant risk factors on the probability of the occurrence of the composite event in order to reduce the dimension of potential confounders in the outcome regression model.
  - For each sub-cohort and the relevant composite or singular outcome, time-varying analysis of cardiovascular and psychiatric hazard rates will be performed using time-varying Cox regression models. For secondary objectives 1and 3 and exploratory objectives 6 - 11 the comparison will be made using hazard ratios (HRs) of each outcome as a result of cumulative exposure to MPH vs cumulative exposure to non-MPH. For objectives secondary objectives 2 and 3 and exploratory objectives 11 and 12 the comparison will be made using HRs of each outcome comparing cumulative exposure of MPH to untreated patient-time.
  - Assuming country specific analyses have been completed, results may be combined using a meta-analyses approach. Hazard ratios for the composite

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outcomes from the time-varying Cox regression analyses will be pooled across data sources with random effects meta-analysis. Between-database heterogeneity will be quantified with the I-squared measure.

- **Exploratory analyses**
  - The primary analysis will be repeated for the cardiovascular composite outcome using cumulative dose in place of cumulative exposure. The fractional polynomial method will be used to find the best polynomial model (number permitting).
  - The primary analysis will be repeated for the cardiovascular composite outcome for each stratum after stratifying by time before and after the market launch of the extended release formula (number permitting). Crude cumulative incidence will be provided for each stratum.
  - The primary analysis will be repeated for the cardiovascular composite outcome stratified by age and sex (separately) (number permitting). Crude cumulative incidence will be provided for each stratum.

Milestones

- Study period of primary focus: 2006 (Denmark), 2008 (Sweden) and 2011 (Norway) through to 31 December 2019 (all countries)
- Registration in the EU Post-Authorisation Study (PAS) register: completed in Q1 2021
- Start of data collection: Q1 2021 (Sweden); Q3 2021 (Norway and Denmark)
- End of data collection: Q4 2021 (Sweden); Q1 2022 (Denmark), Q4 2023 (Norway)
- Interim report of study results: Q2 2022 (Sweden)
- Final report of study results: Q1 2025 (Sweden, Norway, Denmark)

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