Study Protocol

P3-C3-006

DARWIN EU® - Impact of risk minimisation measures related to the risk of meningioma in women using nomegestrol or chlormadinone

23/01/2025

Version 4.0

Contents

Study title	DARWIN EU® - Impact of risk minimisation measures related to the risk of meningioma in women using nomegestrol and chlormadinone
Protocol version	V4.0
Date	23/01/2025
EU PAS number	EUPAS1000000455
Active substance	Drug classes of interest will be identified based on WHO ATC codes and will include: - Progestogen and oestrogen combination products (G03AA, G03AB, G03FA and G03FB) - Pregnadien derivates (G03DB) Progestogens of interest will include: - Nomegestrol (G03AA14, G03DB04, G03FB12) - Chlormadinone (G03AA15, G03AB07, G03DB06, G03FB03) - Medroxyprogesterone (G03AC06, G03DA02, G03AA17, G03FA12, G03FB06, G03AA08)
Medicinal product	N/A
Research question and objectives	To describe how prescribing of nomegestrol and chlormadinone has changed following the introduction of risk minimisation measures (i.e. restrictions of use) related to the risk of meningoma in November 2022. To contextualise findings, changes of other relevant drug classes will also be described, including progestogen and oestrogen combination products and progestogens that are pregnadien derivates. The specific objectives are: 1. To assess the monthly prevalence and incidence of use of drug classes of interest before and after the implementation of the restrictions of use. 2. To assess duration of use and cumulative dose of nomegestrol- and chlormadinone- containing products before and after the implementation of restrictions of use. 3. To describe characteristics of users of relevant drug classes before and after implementation of the restrictions of use. 4. To describe the line of treatment in users of nomegestrol- and chlormadinone- containing products before and after the implementation of the restrictions of use for high dosed products. 5. To describe the frequency of patients who develop meningioma during treatment with products containing NOMAC or CMA, and

	those who discontinue or switch to alternative treatments before and after implementation of the restrictions of use. 6. To assess the impact of the restrictions of use adopted in 2018 and 2022 in incident prescriptions of nomegestrol- and chlormadinone-containing products.
Countries of study	Belgium, Croatia, Germany
Authors	Talita Duarte Salles (t.duarte@darwin-eu.org) Berta Raventós (b.raventos@darwin-eu.org) Julieta Politi (j.politi@darwin-eu.org) Anton Barchuk (a.barchuk@darwin-eu.org) Ger Inberg (g.inberg@darwin-eu.org)

LIST OF ABBREVIATIONS

Acronyms/terms	Description
ARIMA	Autoregressive Integrated Moving Average
ATC	Anatomical Therapeutic Chemical
CDM	Common Data Model
CI	Confidence Interval
CIPH	Croatian Institute of Public Health
CMA	Chlormadinone acetate
COVID-19	Coronavirus disease 2019
CMHP	Committee for Medicinal Products for Human Use
DARWIN EU®	Data Analysis and Real-World Interrogation Network
DHPC	Direct Healthcare Professional Communication
EHR	Electronic Health Record
EMA	European Medicines Agency
EU	European Union
FinOMOP	Finnish Care Register for Health Care
GDPR	General Data Protection Regulation
GP	General Practitioner
HR	Hazard Ratio
HRT	Hormonal Replacement Therapy
IQVIA DA	IQVIA Disease Analyzer
IQVIA LPD	IQVIA Longitudinal Patient Database
ITS	Interrupted Time Series
MAH	Marketing Authorisation Holders
NAJS	Croatian National Public Health Information System
NOMAC	Nomegestrol acetate
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
PRAC	Pharmacovigilance Risk Assessment Committee
RR	Risk Ratios
RMM	Risk Minimisation Measures
SMD	Standardised Mean Differences
SNOMED	Systematised Nomenclature of Medicine
WHO	World Health Organisation

1. TITLE

DARWIN EU® - Impact of risk minimisation measures related to the risk of meningioma in women using nomegestrol and chlormadinone

2. RESPONSIBLE PARTIES – STUDY TEAM

Study team role	Names	Organisation
Study Project Manager/Principal Investigator	Berta Raventós Talita Duarte-Salles	Erasmus MC
Data Scientist	Ger Inberg Cesar Barboza Maarten van Kessel Ross Williams	Erasmus MC
Epidemiologist	Julieta Politi Anton Barchuk	Erasmus MC
Data Partner*	**Names**	**Organisation**
IQVIA DA Germany and IQVIA LPD Belgium	Gargi Jadhav Isabella Kacmarczyl Akram Mendez Dina Vojinovic	IQVIA
NAJS	Željka Draušnik Maja Vajagić Danijela Fuštin Jakov Vukovic Ivan Pristaš Antea Jezidžić Marko Čavlina Pero Ivanko	Croatian Institute of Public Health

*Data partners' role is only to execute code at their data source, review and approve their results. They do not have an investigator role. Data analysts/programmers do not have an investigator role and thus declaration of interests (DOI) for them is not needed.

3. ABSTRACT

Title

DARWIN EU® – Impact of risk minimisation measures related to the risk of meningioma in women using nomegestrol and chlormadinone

Rationale and background

Nomegestrol acetate (NOMAC) and chlormadinone acetate (CMA) are synthetic progestins indicated for the treatment of several gynaecological and menstrual disorders, as hormone replacement therapy and as hormonal contraception. Recent epidemiological studies have found a dose-dependent association between NOMAC or CMA and meningioma. As a result, risk minimisation measures (RMM) were implemented in 2022, especially for high-dose products, which should be used at the lowest effective dose and for the shortest duration possible and should not be used for first-line treatment. For all products containing NOMAC or CMA, treatment was contraindicated in patients with meningioma or a history of meningioma. All patients should be monitored for symptoms of meningioma and treatment should be permanently discontinued if diagnosed with meningioma during treatment. This contraindication was already in place for NOMAC, with previous regulatory actions implemented in 2018 and 2020.

Research question and objectives

The overall aim of the study is to describe how prescribing of NOMAC and CMA containing medicines (as single active ingredients and combinations with oestrogen) has changed following the EU-wide introduction of RMM in November 2022. To contextualise findings, changes in other relevant drug classes will also be described. This will include progestogen and oestrogen combination products and progestogens that are pregnadien derivates (see "Variables").

The specific objectives are:

1. To assess the monthly prevalence and incidence of use of drug classes of interest before and after the implementation of the restrictions of use.
2. To assess duration of use and cumulative dose of products containing NOMAC or CMA before and after the implementation of restrictions of use.
3. To describe characteristics of users of relevant drug classes before and after implementation of the restrictions of use.
4. To describe the line of treatment (2nd/3rd versus 1st) in users of products containing NOMAC or CMA before and after the implementation of the restrictions of use.
5. To describe the frequency of patients who develop meningioma during treatment with products containing NOMAC or CMA, and those who discontinue or switch to alternative treatments before and after implementation of the restrictions of use.
6. To assess the impact of the restrictions of use adopted in 2018 and 2022 in incident prescriptions of products containing NOMAC or CMA.

Methods

Study design

Retrospective cohort studies will be conducted using routinely collected health data from 3 databases from 3 countries in Europe. The study will comprise of:

1. A population-level drug utilisation study (DUS) to assess incidence/prevalence of drug classes of interest (objective 1).
2. A patient-level DUS to describe:
    a. Treatment duration and cumulative dose over a specific time window spanning 6 or 12 months, depending on data availability (objective 2)
    b. Characteristics of new users (objective 3)
    c. Line of treatment (objective 4)
    d. Switching to alternative treatments (objective 5)
3. A trend analyses and effectiveness of risk minimisation measures to assess changes in:
    a. Patient-level analyses (objective 2 to 5)
    b. Population-level analyses (objective 6, based on results of objective 1)

Population

The source population will comprise all females aged >10 present in the database at any time during the period from 1st of January 2010 (or start according to the database) to end of data availability. All patients need to have at least 365 days of data visibility prior to index date.

For patient-level DUS, the study population will be additionally restricted to new medicine users:

- Objective 2, 4 and 5: Participants newly prescribed with NOMAC or CMA.
- Objective 3: Participants newly prescribed with any drug classes of interest.

Variables

Drug classes of interest:

- Progestogen and oestrogen combination products (WHO ATC G03AA, G03AB, G03FA and G03FB)
- Progestogens that are pregnadien derivates (WHO ATC G03DB)

Progestogens of interest:

- Medroxyprogesterone (WHO ATC G03AC06, G03DA02, G03AA17, G03FA12, G03FB06, G03AA08)
- NOMAC (WHO ATC G03AA14, G03DB04, G03FB12)
- CMA (WHO ATC G03AA15, G03AB07, G03DB06, G03FB03)

Exposures

- Objective 1: N/A
- Objective 2, 4 and 5: First-ever prescription of NOMAC or CMA (assessed separately)
- Objective 3: First-ever prescription of NOMAC or CMA (assessed separately)
- Objective 6: N/A

Outcomes

- Objective 1: Prescribing of drug classes or progestogens of interest (assessed separately)
- Objective 2: N/A (treatment duration and cumulative use of exposures)
- Objective 3: N/A (characterisation)
- Objective 4: Prescribing of alternative drug classes of interest not containing NOMAC or CMA
- Objective 5: Number of meningioma cases during treatment. Discontinuations or switches to alternative drug classes of interest not containing NOMAC or CMA.
- Objective 6: Prescribing of NOMAC or CMA.

Timing of the intervention

- Main intervention of interest: November 2022 to January 2023.
- Additional intervention related to NOMAC (Objective 6 only): October 2018 to January 2019.

Covariates for stratification:

- Age group: 10-17, 18-34, 35-49, 50-64, +65 years (Objective 1)
- Dose: High- vs. low- dose, for NOMAC and CMA only (Objective 1,4,6)
- Indication: HRT (hormonal replacement therapy) vs. non-HRT, with age as a proxy (Objective 1,2,4,6)
- WHO ATC 5th level code: For NOMAC and CMA only (Objective 1 and 5).
- Study period: Pre- vs. Postintervention (Objective 1 to 5).

Data sources

1. IQVIA Disease Analyzer Germany (IQVIA DA Germany)
2. IQVIA Longitudinal Patient Database Belgium (IQVIA LPD Belgium)
3. Croatian National Public Health Information System (NAJS), Croatia

Sample size

No specific sample size calculations have been performed. The expected number of patients exposed to NOMAC or CMA is expected to be roughly between 1,900 in NAJS and 16,800 in IQVIA DA Germany and between 2,4004 in IQVIA LPD Belgium and 173,900 in IQVIA DA Germany, respectively, for the entire source data.

Statistical analyses

Objective 1:

We will calculate incidence rates and period prevalence of drug classes and progestogens of interest (assessed separately). Results will be reported overall and stratified by study period, age group, dose, indication (HRT vs. non-HRT) and WHO 5th ATC level codes (if counts allow).

Objective 2:

Treatment duration will be reported for the first prescribed treatment. Cumulative dose will be calculated considering all treatments containing NOMAC or CMA recorded during the study period. For the pre- and postintervention comparison, cumulative dose and treatment will be calculated for all treatments initiated over one year before (or six months, if insufficient follow-up data is available) and after the intervention.

Exposures of interest (NOMAC vs. CMA) will be assessed separately. Results will be reported overall and stratified by study period and indication at first use.

Objective 3:

Characteristics will be described by means of large-scale characterisation. Pre-specified comorbidities and concomitant medications will also be described. Covariates will be reported as counts and proportions. Results will be reported overall and stratified by study period.

Objective 4:

Line of treatment will be retrospectively assessed by looking at the occurrence of records indicating the use of other drug classes of interest not containing NOMAC or CMA from the day before index date to the start

of the study period. Line of treatment will be reported as first vs. non-first treatments. Exposures of interest (NOMAC vs. CMA) will be assessed separately. Results will be reported overall and stratified by study period, dose at index date and indication at index date.

Objective 5:

We will describe the frequency of switches of treatment with NOMAC or CMA to products of other relevant drug classes not containing NOMAC or CMA within 180 days after the end of treatment. We will also describe the number of patients discontinuing treatment. The number of meningioma cases occurring any time during treatment with NOMAC or CMA, and in the six months prior to treatment discontinuation will also be reported. Exposures of interest (NOMAC vs. CMA) will be assessed separately.

Results will be reported overall and stratified by study period and WHO 5th ATC level codes (if counts allow).

Objective 2 to 5:

Standardised mean differences of each of the covariates for the comparison of drug users in the pre-RMM and post-RMM period as a measure of the impact of the profile of drug users. These covariates will include: duration and cumulative dose (objective 2), patient characteristics in terms of prior comorbidities (objective 3) and line of treatment (objective 4). For objective 5, these will include the proportion of patients discontinuing orswitching treatments (assessed separately), and the proportion of patients diagnosed with meningioma during treatment.

Objective 6:

The impact of the restrictions of use will be estimated using an interrupted time series analysis (segmented regression) and will be informed by results obtained as part of objective 1, only if trends can be transformed to be linear and if no residual autocorrelation is detected. For NOMAC, the intervention adopted in October 2018 will also be assessed. Results will be reported overall and stratified by dose and indication.

4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

Study milestones and deliverables	Planned dates
Draft Study Protocol	November 2024
Final Study Protocol	January 2025
Creation of Analytical code	February 2025
Execution of Analytical Code on the data	March/April 2025
Draft Study Report	May 2025
Final Study Report	May 2025

6. RATIONALE AND BACKGROUND

Medicines containing nomegestrol acetate (NOMAC) or chlormadinone acetate (CMA) are synthetic progestins with antiandrogenic effects. Approved indications for NOMAC and CMA in monotherapy or in combination with oestrogens differ between different strengths and different countries. In general, they are indicated for gynaecological and menstrual disorders, hormone replacement therapy (HRT) and, at lower doses, as hormonal contraception.

Meningioma is a rare tumour that forms from the meninges. Known risk factors for meningioma are being female, exposure to ionising radiation and neurofibromatosis type 2.(1) Recently published studies have found a dose-dependent association between NOMAC or CMA and meningioma.(2-5) The hazard ratio (HR) of intracranial meningioma adjusted for age was 4.5 (3.5-5.7) and 4.4 (95% CI 3.4-5.8) among women exposed to NOMAC and CMA, respectively.(2, 3) The risk of meningioma increased with dose and duration of treatment and diminished one year after the discontinuation of treatment. Prolonged exposure to progestogens other than NOMAC such as cyproterone acetate (6) and medroxyprogesterone acetate (7) has also been linked to an increased risk of meningioma.

The risk of meningioma associated with NOMAC is known since 2018 and has been assessed within different regulatory procedures.(8) In October 2018, the Pharmacovigilance Risk Assessment Committee (PRAC) recommended to amend the product information of monotherapy products containing NOMAC to include the contraindication for patients who have, or have had, meningioma. PRAC also recommended permanently discontinuing treatment in patients who develop meningioma. In 2020, the product information of products containing NOMAC in combination with oestradiol was updated with similar contraindications and warnings.

In July 2022, PRAC issued further recommendations for both NOMAC and CMA. PRAC recommended to update the summary of product characteristics for products containing NOMAC or CMA to inform of the risk of meningioma. PRAC recommended that medicines containing high-dose chlormadinone (5 – 10 mg) or high-dose NOMAC (3.75 – 5 mg) should be used at the lowest effective dose and for the shortest duration possible. These medications should only be used when other interventions are not appropriate and should no longer be considered for first-line treatment. Similar to what was already established for NOMAC, treatment with products containing NOMAC or CMA was contraindicated in patients with current or prior history of meningioma. PRAC also recommended monitoring patients for symptoms, and permanently discontinuing treatment if the patients develop meningioma.(9) Measures recommended by PRAC were endorsed by the Committee for Medicinal Products for Human Use (CHMP) and the European Commission issued final legally binding decisions applicable in all the European Union (EU) Member States, between 28th of October and 28th November 2022.(10) Following this decision, a direct healthcare professional communication (DHPC) was sent to prescribers (8th November 2022)(11) and Marketing Authorisation Holders (MAH) had one month to implement changes (28th December 2022). Dates for national-level interventions varied, especially in the case of France, where additional interventions were put in place between 2018 and 2021.

The overall aim of the study is to describe how prescribing of NOMAC and CMA has changed following the introduction of risk minimisation measures (RMM) in November 2022. To contextualise findings, it is also of interest to study changes in prescribing of other relevant drug classes, including progestogen and oestrogen combination products and progestogens that are pregnadien derivatives, and to study the impact of prior EU-level restrictions in trends of NOMAC prescribing.

7. RESEARCH QUESTION AND OBJECTIVES

The overall aim of the study is to describe how prescribing of NOMAC and CMA has changed following the introduction of EU-level RMM related to the risk of meningioma ('restrictions to use' from now on) in November 2022. To contextualise findings, changes of other relevant drug classes will also be described.

The specific objectives are:

1. To assess the monthly prevalence and incidence of use of drug classes of interest before and after the implementation of the restrictions of use.
2. To assess duration of use and cumulative dose of products containing NOMAC or CMA before and after the implementation of restrictions of use.
3. To describe characteristics of users of relevant drug classes before and after implementation of the restrictions of use.
4. To describe the line of treatment (2nd/3rd versus 1st) in users of products containing NOMAC or CMA before and after the implementation of the restrictions of use
5. To describe the frequency of patients who develop meningioma during treatment with products containing NOMAC or CMA, and those who discontinue or switch to alternative treatments before and after implementation of the restrictions of use.
6. To assess the impact of the restrictions of use adopted in 2018 and 2022 in incident prescriptions of products containing NOMAC or CMA.

Objective 1 and 3 will be assessed for all relevant drug classes. These will include progestogen and estrogen combination products, progestogens that are pregnadien derivates, and medroxyprogesterone-containing products.

Objective 2 and 6 will focus on products containing NOMAC or CMA. Objective 4 and 5 will focus on these two compounds but will consider relevant drug classes to establish line of treatment or switches.

A description of the proposed objectives is described in **Table 1**.

Table 1. Primary and secondary research questions and objective.

A. Primary research question and objective.

Objective:	Objective 1: To examine incidence/prevalence of drug classes of interest. Objective 2: To assess duration of use and cumulative dose of products containing NOMAC or CMA. Objective 3: To describe users of relevant drug classes. Objective 4: To describe the line of treatment in users of products containing NOMAC or CMA. Objective 5: To describe the frequency of patients who develop meningioma during treatment with products containing NOMAC or CMA,

	and the frequency of users who discontinue or switch to alternative treatments. Objective 6: To assess the impact of the restrictions of use in incident prescriptions of products containing NOMAC or CMA. All objectives will be focused on comparing changes before and after the implementation of restrictions.
Hypothesis:	Objective 1: N/A, descriptive analysis. Objective 2: Cumulative dose and duration of treatments with NOMAC or CMA will be lower after the implementation of restrictions. Objective 3: The number of new users of NOMAC or CMA will be reduced after the implementation of restrictions. Objective 4: The number of users initiating NOMAC or CMA as first-line treatment will be reduced after the implementation of restrictions. Objective 5: The number of switches and discontinuations from NOMAC or CMA to other drug classes will increase after the implementation of restrictions. Objective 6: The incidence of NOMAC or CMA will be reduced after the implementation of restrictions, especially for high-dose products. This reduction will not be observed for other drug classes of interest.
Population*:*	All objectives: The study population will be restricted to females aged >10 years old with >1 year of prior data history available. Additional criteria: • Objective 1 (subgroup analysis): Individuals with a prior history of meningioma. • Objective 2, 4 and 5: Individuals newly exposed to products containing NOMAC or CMA. • Objective 3: Individuals newly exposed to drug classes of interest.
Exposure:	Objective 1: N/A Objective 2: First-ever prescription of NOMAC or CMA (assessed separately). Objective 3: First-ever prescription of drug classes of interest (any), including: - Combined hormonal contraceptives

	- Progestogens that are pregnadien derivates (including medroxyprogesterone and medroxyprogesterone alone) - Progestogen and oestrogen combination products. Objective 4: Same as Objective 2. Objective 5: Same as Objective 2. Objective 6: N/A
Comparator:	Before vs. After the implementation of restrictions
Outcome:	Objective 1: Prescribing of drug classes of interest (assessed separately) Objective 2: N/A (treatment duration and cumulative use of the exposure). Objective 3: N/A (characterisation of users) Objective 4: Prescribing of alternative treatments not containing NOMAC or CMA (assessed retrospectively to identify line of treatment). Objective 5: Number of patients diagnosed with meningioma during treatment and number of patients discontinuing treatment or switching to alternative treatments not containing NOMAC or CMA 180 days after the end of the index treatment. Objective 6: Prescribing of products containing NOMAC or CMA (assessed separately).
Time*:*	01/01/2010 to end of data availability
Setting:	Routinely collected data from 3 databases in 3 European countries.
Main measure of effect:	Objective 1: Incidence rates (new prescriptions per 100,000 person-years of the population at risk) and prevalence (proportions). Objective 2 to 5: - Objective 2: Median with minimum, maximum and interquartile range. - Objective 3-5: Counts and proportions - All objectives: Standardised Mean Differences (SMD) for comparing changes before and after the implementation of restrictions. Objective 6: Risk ratios derived from the interrupted time series analysis (ITS). ITS will be based on results obtained as part of Objective 1.

8. RESEARCH METHODS

8.1 Study type and study design

Retrospective cohort studies will be conducted using routinely collected health data from 3 databases from 3 countries in Europe. The study will comprise of:

4. A population-level drug utilisation study (DUS) to assess incidence/prevalence of drug classes of interest (objective 1).
5. A patient-level DUS to describe:
    a. Treatment duration and cumulative dose (objective 2).
    b. Characteristics of new users (objective 3)
    c. Line of treatment (objective 4)
    d. Switching to alternative treatments (objective 5)
6. A trend analyses and RMM effectiveness to assess changes in:
    a. Patient-level analyses (objective 2 to 5)
    b. Population-level analyses (objective 6, based on results of objective 1)

The study types with related study designs are described in **Table 2**.

Table 2. Description of potential study types and related study designs.

Study type	Study design	Study classification
Population Level DUS	Population Level Cohort	Off the shelf
Patient-level DUS	Cohort analysis	Off the shelf
Trend analyses and RMM effectiveness	Population-level cohort and New drug user cohort	Complex

8.2 Study setting and data sources

This study will be conducted using routinely collected data from 3 databases in 3 European countries selected from the DARWIN EU® Database Catalogue. All databases were previously mapped to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM).

The selection process was based on the size of the databases, the number of individuals exposed to drug classes of interest, the suitability of denominator population for population-level rates, geographical spread, and available follow-up data. Based on the feasibility assessment performed, the suggested databases are considered fit for purpose:

1. IQVIA Disease Analyzer Germany (IQVIA DA Germany)
2. IQVIA Longitudinal Patient Database Belgium (IQVIA LPD Belgium)
3. Croatian National Public Health Information System (NAJS), Croatia

Information on data sources planned to be used with a justification for their choice in terms of ability to capture the relevant data is described in **Table 3**.

Table 3. Description of the selected data sources.

Country	Name of Database[1]	Justification for Inclusion	Health Care setting[2]	Type of Data[3]	Number of active subjects[4]	Feasibility count of NOMAC[5]	Feasibility count of CMA[5]	Data lock for the last update
Germany	IQVIA DA Germany	Suitable denominator population for population-level rates. Observed records of individuals exposed to nomegestrol and chlormadinone. Contribute to the geographical diversity of data sources.	Primary care	EHRs	4.35M	16.8k	173.9k	30-09-2023
Belgium	IQVIA LPD Belgium	Suitable denominator population for population-level rates. Follow-up data up to > 1 year after the implementation of restrictions of use. Observed records of individuals exposed to nomegestrol and chlormadinone. Contribute to the geographical diversity of data sources.	Primary care	EHRs	213k	6.7k	2.4k	31-12-2023

Country	Name of Database[1]	Justification for Inclusion	Health Care setting[2]	Type of Data[3]	Number of active subjects[4]	Feasibility count of NOMAC[5]	Feasibility count of CMA[5]	Data lock for the last update
Croatia	NAJS	Suitable denominator population for population-level rates. Follow-up data up to 1 year after the implementation of restrictions of use. Observed records of individuals exposed to nomegestrol and chlormadinone. Contribute to the geographical diversity of data sources.	Primary care, hospital care (IP, OP)	Registry	2.68M	1.9k	15.3k	17-11-2023

1. IQVIA DA= IQVIA Disease Analyzer; IQVIA LPD= IQVIA Longitudinal Patient Database; NAJS= Croatian National Public Health Information System
2. IP= inpatient, OP= outpatient.
3. EHR = Electronic health records
4. Defined as the maximum number of persons in an observation period in the last 6 month
5. Person counts provided as part of the feasibility assessment using preliminary concepts. Counts correspond to the whole database, without restriction on age, sex or study period. All counts are rounded to the nearest multiple of 100. NOMAC= Nomegestrol acetat; CMA = Chlormadinone acetate.

IQVIA Disease Analyzer (IQVIA DA) Germany, Germany

IQVIA Disease Analyzer (DA) Germany is a database of de-identified electronic medical records from specialised and GP practices in Germany since 1992. This dataset encompasses approximately 3% of all outpatient practices within Germany, ensuring a substantial representation of the national healthcare landscape. The sampling methods used for practice selection, considering physician's demographics, specialty focus, community size category and federal state location, was instrumental in constructing a database that accurately mirrors the diverse spectrum of healthcare providers in the country. Consequently, data within IQVIA DA Germany database has been demonstrated to be representative of general and specialised practices throughout Germany.

The database contains demographics records, basic medical data, disease diagnosis, and prescription records. While the database partly records information on deaths and procedures, it currently does not support linkage with external data sources. Routine updates are conducted at regular intervals. The quality of data is assessed based on several criteria including completeness of information and correctness (e.g. linkage between diagnosis and prescriptions).

IQVIA Belgium Longitudinal Patient Data (IQVIA LPD), Germany

Belgium Longitudinal patient data (LPD) is collected from GP prescribing systems and contains patient records on all signs and symptoms, diagnoses and prescribed medications. The information recorded allows patients and doctors to be monitored longitudinally. Data are recorded directly in the LPD from doctors' surgeries in real-time during patient consultations via a practice management software system. It is used in studies to provide various market insights such as treatment trends, patient pathway analysis and treatment compliance. The panel of contributing physicians (a stable 300 GPs) is maintained as a representative sample of the primary care physician population in Belgium according to three criteria known to influence prescribing: age, sex and geographical distribution. Currently, the database is covering 1.1 M cumulative patients and covers from 2012 through to the present. The panel consists of a stable 300 GPs that are geographically well spread. The total number of active GPs in Belgium is 15.602. The regional geographical spread of physicians in the LPD data is also representative of the distribution across the country: 57% GPs in the North (compared to 54% nationally), 31% in the South (33% nationally) and 12% in Brussels (13%). The provider of the data has more than 2.250 GPs under contract so in case of a drop out a replacement is easily found. Drugs obtained over the counter by the patient outside the prescription system are not reported. No explicit registration or approval is necessary for drug utilisation studies.

Croatian National Public Health Information System (NAJS), Croatia

The National Public Health Information System (Nacionalni javnozdravstveni informacijski sustav - NAJS) is an organised system of information services by Croatian Institute of Public Health (CIPH). NAJS enables data collecting, processing, recording, managing and storing of health-related data from health care providers as well as production and management of health information. NAJS contains medical and public health data collected and stored in health registries and other health data collections including cancer registry, mortality, work injuries, occupational diseases, communicable and non-communicable diseases, health events, disabilities, psychosis and suicide, diabetes, drug abuse and others.

8.3 Study period

From 1st of January 2010 to end of data availability. For some databases the start date will be defined later (see "11. Limitations" for further details).

8.4 Follow-up

For the population-level DUS (objective 1), study participants in the denominator population will start contributing person time on the latest of the following: 1) study start date (1st January 2010, or as defined according to the database), 2) date on which they turn 10 years old, 3) date at which they have a year of prior history recorded. Participants will stop contributing person time at the earliest date of the following: 1) end of available data in each of the data sources, 2) date at which their observation period ends (e.g. loss to follow-up, death).

For the patient-level DUS (objective 2 to 5), participants will be followed up from the day of incident prescription of medication (index date), until the earliest end of data availability, date at which their observation period ends (e.g. loss to follow-up, death), or 180 days after ending treatment (objective 5). For objective 2, 4 and 5, index date will be defined as the date of the first-ever prescription of NOMAC or CMA. For objective 3, this will be defined as the date of the first-ever prescription of any of the 6 drug classes of interest (see "8.6.2 Outcomes").

For objective 4, line of treatment will be assessed retrospectively by looking at prior records of alternative treatments, from the date of initiation of treatment with products containing NOMAC or CMA to start of the study period (1st January 2010, or as defined according to the database).

For objective 6, follow-up will be the same as that for objective 1.

Information on the operational definition of index date is described in **Table 4**. Please note that, for objectives 1 and 6, each drug class of interest will be assessed separately, with the washout window specific to the drug class being studied (e.g., when studying NOMAC, the washout window will be applied with respect to this substance only). For objective 3, the washout will be applied to all the drug classes of interest combined.

Table 4. Operational definition of time 0 (index date) and other primary time anchors.

Study population names	Time Anchor Description (e.g. time 0)[1]	Number of entries[2]	Type of entry	Washout window	Care Setting[3]	Code Type[3]	Incident with respect to…
General population (objective 1 and 6)	Study entry date	Multiple entry	Incident, prevalent	[-365, -1]	IP, OP	N/A	Outcome drug class (assessed separately)
Patients with prior history of meningioma (objective 1, subgroup analysis)	Date of diagnosis	Single entry	Incident	[-Inf, 0]	IP, OP	SNOMED	Meningioma
New users of NOMAC (objective 2, 4 and 5)	Date of prescription	Single entry	Incident	[-Inf, -1]	IP, OP	RxNorm	NOMAC
New users of CMA (objective 2, 4 and 5)	Date of prescription	Single entry	Incident	[-Inf, -1]	IP, OP	RxNorm	CMA
New users of drug classes or progestogens of interest (objective 3)	Date of prescription	Single entry	Incident	[-Inf, -1]	IP, OP	RxNorm, SNOMED	Drug classes of interest (any)

[1] Study entry date (objective 1 and 6) will be defined as the latest of the following: 1) study start date (1st January 2010, or as defined according to the database), 2) date on which they turn 10 years old, 3) date at which they have a year of prior history recorded.
[2] Indicating whether patients are allowed to enter the study population only once or multiple times
[3] IP = inpatient, OP = outpatient
[4] RxNorm codes will be identified based on ATC codes.

8.5 Study population with inclusion and exclusion criteria

The source population will comprise all females aged >10 present in the database at any time during the period from 1st of January 2010 (or start according to the database) to end of data availability. All patients will need to have at least 365 days of data visibility prior to index date.

For patient-level DUS, the study population will be additionally restricted to new medicine users (see "8.6. Variables" for further details). For objective 2, 4 and 5 these will be restricted to participants newly

prescribed with NOMAC or CMA. For objective 3, these will be all drug classes of interest. A preliminary list of concepts for meningioma can be found in **Appendix I**.

Further information on exposures can be found in see "8.6.1. Exposures". The operational definitions of the inclusion and exclusion criteria are presented by means of **Table 5** and **Table 6**, respectively.

Table 5. Operational definitions of inclusion criteria.

Criterion	Details	Order of application[1]	Assessment window	Care Settings[2]	Code Type	Diagnosis position[3]	Applied to study populations:
Observation period during the study period	All individuals present after the study start date	N/A	N/A	IP, OP	N/A	N/A	All
Sex	Females only	N/A	N/A	IP, OP	N/A	N/A	All
Age	Individuals aged >10	Before	N/A	IP, OP	N/A	N/A	All
History of meningioma	Individuals with prior history of meningioma	Before	[-Inf, -1]	IP, OP	SNOMED	Any	Patients with prior history of meningioma (objective 1, subgroup analysis)

[1] Relative to the study entry date
[2] IP = inpatient, OP = outpatient
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

Table 6. Operational definitions of exclusion criteria.

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type	Diagnosis position[2]	Applied to study populations:
Prior database history	Study participants with less than 365 days of prior history observed at index date will be excluded	Before	[-365, -1]	IP, OP	N/A	N/A	General population (objective 1 and 6)
Prior database history	Study participants with less than 365 days of prior history observed at index date will be excluded	After	[-365, -1]	IP, OP	N/A	N/A	All except general population (objective 1 and 6)
Prior use of NOMAC	Individuals with prior prescriptions of NOMAC will be excluded	After	[-Inf, -1]	IP, OP	N/A	N/A	New users of NOMAC (objective 2, 4 and 5)
Prior use of CMA	Individuals with prior prescriptions of CMA will be excluded	After	[-Inf, -1]	IP, OP	N/A	N/A	New users of CMA (objective 2, 4 and 5)

Prior use of drug classes of interest (any)	Individuals with prior prescriptions of any of the drug classes of interest will be excluded	After	[-Inf, -1]	IP, OP	N/A	N/A	New users of drug classes or progestogens of interest (objective 3)

[1] Relative to the study entry date
[2] IP = inpatient, OP = outpatient
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

8.6 Variables

Drug classes of interest will be identified based on Anatomical Therapeutic Chemical (ATC) codes, and will include:

- Progestogens and oestrogens combinations
- Progestogens that are pregnadien derivates

Progestogens of interest (some included in the groups listed above) will also be assessed as separate groups, including:

- Medroxyprogesterone
- NOMAC
- CMA

Drug classes and progestogens of interest will be reported by combining WHO ATC codes of interest. Drug classes of interest will be identified using WHO ATC 4th level codes, except for progestogens of interest, which will be identified using WHO ATC 5th level codes. If possible, products containing medroxyprogesterone will be limited to those for non-oncological purposes. A preliminary list of codes can be found in **Appendix I**.

8.6.1. Exposures

Exposures will be considered for patient-level DUS (objective 2 to 5), which consists of individuals with a first-ever prescription of:

- Drug classes of interest and progestogens of interest (objective 3): Progestogens and oestrogens combinations, progestogens that are pregnadien derivates, medroxyprogesterone, NOMAC and CMA.
- NOMAC (objective 2, 4 and 5)
- CMA (objective 2, 4 and 5)

The operational definition of exposures is described by means of **Table 7**. Preliminary concepts for the exposures are detailed in **Appendix I**.

8.6.2 Outcomes

Outcomes will be considered for the population-level DUS (objective 1) and will consist of the 2 drug classes and 3 progestogens of interest described in “8.6 Variables”. They will also be considered to study records of drug classes of interest not containing NOMAC nor CMA for objectives aiming to assess line of treatment (objective 4) and switching (objective 5). Meningioma will also be considered as an outcome for Objective 5.

The operational definition of the outcomes is presented in the **Table 8**. Preliminary concepts for the exposures are detailed in **Appendix I**.

Table 7. Operational definitions of exposure.

Exposure group names[1]	Details	Washout window	Assessment Window	Care Setting[2]	Code Type[3]	Applied to study populations	Incident with respect to…
Drug classes of interest (any)	To characterise users of any of the drug classes or progestogens of interest(objective 3). Consisting of first-ever prescription to any of the drug classes or progestogens of interest (see "8.6 Variables").	[-Inf, -1]	0	IP, OP	RxNorm	New users of drug classes or progestogens of interest (objective 3)	Drug classes or progestogens of interest (any)
NOMAC	First-ever prescription to NOMAC. To identify study participants exposed to the drug for objective 2, 4 and 5.	[-Inf, -1]	0	IP, OP	RxNorm	New users of NOMAC (objective 2, 4 and 5) New users of CMA (objective 2, 4 and 5)	NOMAC
CMA	First-ever prescription to CMA.	[-Inf, -1]	0	IP, OP	RxNorm	New users of NOMAC (objective 2, 4 and 5) New users of CMA (objective 2, 4 and 5)	CMA

[1] NOMAC = nomegestrol, CMA = chlormadinone

[2] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable

[3] RxNorm codes will be identified based on the vocabulary hierarchy, with ATC codes being ancestors.

Table 8. Operational definitions of outcomes.

Outcome name[1]	Details	Primary outcome?	Type of outcome	Washout window[2]	Care Settings[3]	Code Type[4]	Applied to study populations
Progestogen and estrogen combination products	For incidence/prevalence calculations (Objective 1).	Yes	Count	[-365, -1]	IP, OP	RxNorm	General population (objective 1 and 6)
Progestogens that are pregnadien derivates	For incidence/prevalence calculations (Objective 1).	Yes	Count	[-365, -1]	IP, OP	RxNorm	General population (objective 1 and 6)
Medroxyprogesterone	For incidence/prevalence calculations (Objective 1).	Yes	Count	[-365, -1]	IP, OP	RxNorm	General population (objective 1 and 6)
NOMAC	For incidence/prevalence calculations (Objective 1 and 6).	Yes	Count	[-365, -1]	IP, OP	RxNorm	General population (objective 1 and 6)
CMA	For incidence/prevalence calculations (Objective 1 and 6).	Yes	Count	[-365, -1]	IP, OP	RxNorm	General population (objective 1 and 6)
Progestogen and oestrogen combination products not containing NOMAC or CMA	To assess line of treatment and switches to alternative treatments (Objective 4 and 5).	Yes	Binary	N/A	IP, OP	RxNorm	New users of NOMAC or CMA (objective 2, 4 and 5)
Progestogens that are pregnadien derivates not containing NOMAC or CMA	To assess line of treatment and switches to alternative treatments (Objective 4 and 5).	Yes	Binary	N/A	IP, OP	RxNorm	New users of NOMAC or CMA (objective 2, 4 and 5)
Meningioma	Diagnosis of meningioma	Yes	Binary	[-Inf,-1]	IP, OP	SNOMED	New users of NOMAC or CMA (objective 2, 4 and 5)

[1] NOMAC = nomegestrol, CMA = chlormadinone

[2] For outcomes relative to objective 1 and 6, the washout window will be applied for incidence calculations only.

[3] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable.

[4] RxNorm codes will be identified based on the vocabulary hierarchy, with ATC codes being ancestors.

8.6.3 Other covariates

Time of the intervention:

Restrictions for NOMAC were first introduced in 2018, with a transition period from October 2018 to January 2019. Additional EU-level restrictions were implemented in 2020 for products with NOMAC in combination with oestradiol, which were not considered for the study (see limitations for further details).

Regarding the restrictions implemented in 2022, a transition period of three months (November 2022 to January 2023) will be considered to reflect the period during which the intervention was being implemented. This transition period will be applied for all pre- and post-intervention comparisons. For objectives 1 to 5, treatments initiated during this period will be considered for the overall results but not for the stratification by time period (see "Covariates for stratification" below for more information). For objective 6, aggregate monthly figures of this time period will be excluded.

Relevant dates related to the implementation of restrictions in 2018 and 2022 are detailed in **Appendix II.**

Covariates for stratification:

Covariates for stratification will vary across objectives and will include:

- Age group:
  10-17, 18-34, 35-49, 50-64, +65 years.
- Indication:
  Non-HRT vs. HRT. Indication will be assessed using age as a proxy (non-HRT in women aged 10-49 years, HRT in women aged >50 years).
- Dose:
  High- vs low- dose, for NOMAC or CMA only. For NOMAC, high doses will include amounts from 3.75mg to 5mg. For CMA, high doses will include amounts from 5mg to 10mg. Low doses will be any amounts less than those specified.
- WHO 5th ATC level codes:
  For NOMAC or CMA only, if counts allow. For NOMAC codes included will be: G03AA14, G03DB04, G03FB12. For CMA, codes included will be: G03AA15, G03AB07, G03DB06, G03FB03.
- Time period:
  Preintervention: from start date to October 2022; Postintervention: from February 2023 to study end.

See below which covariates apply according to each objective.

Objective 1:

Drug classes and progestogens of interest will be assessed separately ("8.6. Variables"). Covariates for stratification will include:

- Age group
- Indication
- Dose
- WHO 5th ATC level codes
- Time period

Objective 2:

NOMAC and CMA will be assessed separately. Covariates for stratification will include:

- Indication
- Time period

Objective 3:

Drug classes of interest will be described as part of the characterisation (see "Covariates for Objective 3" for more information).

- Time period

Objective 4:

NOMAC and CMA will be assessed separately. Covariates for stratification will include:

- Dose
- Indication
- Time period

Objective 5:

NOMAC and CMA will be assessed separately. Covariates for stratification will include:

- WHO 5th ATC level codes
- Time period

Objective 6:

NOMAC and CMA will be assessed separately. Covariates for stratification will include:

- Dose
- Indication

Please see the "11 Limitations" for important information on these covariates.

Covariates for Objective 3 (characterisation):

For objective 3, pre-specified comorbidities and comedications will be reported. Pre-specified comorbidities will include meningioma and conditions that might play a role in modifying its risk.(12, 13) Potential indications of these drug classes of interest will also be considered, including gynaecological disorders and menopause.

Comorbidities of interest:

Relevant conditions considering the restrictions of use:

- Meningioma

Comorbidities that might play a role in meningioma risk:

- Type 2 neurofibromatosis (1)
- Obesity (14, 15)
- Diabetes mellitus (16)
- Autoimmune diseases (17, 18)
- Asthma (17-19)
- Epilepsy (17)
- Uterine fibroids (13)

Potential indications for drug classes of interest:

- Menopause / Perimenopause
- Primary ovarian insufficiency
- Endometriosis
- Polycystic ovary syndrome
- Menstrual disorders

- Neoplasm of endometrium

Other comorbidities:

- Hyperlipidaemia
- Hypertensive disorder
- Osteoporosis
- Neoplasm of the brain
- Neoplasm of the breast
- Cancer (any malignancy)
- Venous thromboembolism

Pre-specified concomitant medications will consist of the drug classes of interest included in this study.

Medications of interest:

Drug classes of interest:

- Progestogen and oestrogen combination products not including NOMAC or CMA.
- Progestogens that are pregnadien derivates not including NOMAC or CMA.
- NOMAC (high- and low-dose products, assessed separately)
- CMA (high- and low-dose products, assessed separately)
- Medroxyprogesterone

Drugs used in the management of conditions for which medications of interest might be prescribed:

- Antidepressants
- Antihyperglycemics (Metformin)
- Bisphosphonates
- Clonidine
- Gonadotropin Releasing Hormone antagonists
- Anti-androgens (bicalutamide, flutamide, finasteride, spirolactone, cyproterone acetate)

A preliminary list of concepts to identify pre-specified comorbidities and comedications is detailed in the **Appendix I**. Comorbidities will be measured for any time prior to 1 day before index date, 365 days prior to 1 day before index date and at index date. Concomitant medications will be described 365 days prior to 31 days before index date, and 30 days to 1 day before index date, and at index date.

The operational definition of the covariates is described in the **Table 9**.

Table 9. Operational definitions of covariates.

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type	Diagnosis Position[2]	Applied to study populations
Age groups	Defined as: 10-17, 18-34, 35-49, 50-64, +65.	Categorical	N/A	IP, OP	N/A	N/A	General population (objective 1 and 6)
Dose (NOMAC and CMA)	High vs. low doses. For NOMAC, high doses will include amounts from 3.75mg to 5mg. For CMA, high doses will include amounts from 5mg to 10mg. Low doses will be any amounts less than those specified.	Categorical	0	IP, OP	N/A	N/A	General population (objective 1 and 6)
Indication	Non-HRT vs. HRT. Age will be used as a proxy (non-HRT in women aged 10-49 years, HRT in women aged >50 years).	Categorical	0	IP, OP	N/A	N/A	General population (objective 1 and 6)
Comorbidities	Large-scale characterisation and pre-specified conditions[3]	Binary	[-Inf, -1], [-365,-1], 0	IP, OP	SNOMED	Any	New users of drug classes or progestogens of interest (objective 3)
Concomitant medications	Large-scale characterisation and pre-specified medications[4]	Binary	[-365, -31], [-30,-1], 0	IP, OP	RxNorm		New users of drug classes of interest or progestogens (objective 3)
Time period	Preintervention: January 2010 (or study start) to October 2022 Postintervention: February 2023 to end of available data	Categorical	N/A	IP, OP	N/A	N/A	All.

[1] IP = inpatient, OP = outpatient

[2] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

[3] These will include: meningioma, obesity, diabetes mellitus, type 2 neurofibromatosis, asthma, autoimmune diseases, epilepsy, uterine fibroids, menopause/perimenopause, primary ovarian insufficiency, endometriosis, polycystic ovarian syndrome, menstrual disorders, neoplasm of the endometrium, neoplasm of the brain, neoplasm of the breast, cancer (any malignancy), hyperlipidaemia, hypertensive disorder, osteoporosis, venous thromboembolism.

[4] These will include: progestogen and oestrogen combination products not containing NOMAC or CMA, progestogens that are pregnadien derivates not containing NOMAC or CMA, progestogen and oestrogen combination products not containing NOMAC or CMA, NOMAC, CMA, medroxyprogesterone, antidepressants, metformin, bisphosphonates, clonidine, gonadotropin releasing hormone antagonists and anti-androgens.

8.7 Study size

The expected number of patients exposed to NOMAC or CMA is expected to be roughly between 1,900 in NAJS and 16,800 in IQVIA DA Germany and between 2,4004 in IQVIA LPD Belgium and 173,900 in IQVIA

DA Germany, respectively. These counts were provided as part of the feasibility assessment and correspond to the entire source data, without restriction on age, sex or study period.

No specific sample size calculations have been performed. Given that meningioma is a rare tumour, we expect to have limited sample size in Objective 1, when restricting the population to individuals with prior history of meningioma. For Objective 3, 4 and 5, we expect an adequately large sample size to estimate Standardised Mean Differences (SMD) accurately. For Objective 2, this might be more limited as we will only consider users initiating treatment within a period of 6 to 12 months.

Several factors have been identified to potentially influence the power to estimate the impact of the intervention, including the total number of time points, the average sample size per time point, the expected effect size, the location of intervention in time series or the impact model used.(20) In previous studies, ITS have been found to have more than 80% power to detect effect sizes of 1.0 or greater in a range of situations with 24 or more points, depending on the degree of autocorrelation and the impact model used.(21) Unbalanced designs (i.e. unequal number of time points before and after the intervention) have been found to have less power than balanced designs.(20, 21) As the intervention is located at the end of the time series, we will delay the study period start to balance the number of observations for Objective 6 and to ensure a more recent contrafactual for comparison (see "8.8 Analysis").

8.8 Analysis

The type of analysis by study type is fixed as can be observed from **Table 10**.

Table 10. Description of study types and type of analysis.

Study type	Study classification	Type of analysis
Population Level DUS	Off-the-shelf	- Population-based incidence rates - Population-based prevalence of use of a drug/drug class
Patient Level DUS	Off-the-shelf	- Characterisation of patient-level features - Frequency and % of indication/s - Estimation of minimum, p25, median, p75, and maximum initially prescribed or dispensed dose/strength - Estimation of minimum, p25, median, p75, and maximum treatment duration
Trend analyses and RMM effectiveness	Complex	- Incidence and prevalence rate/s of drug/s use over time - For patient-level analyses, standardised mean differences of each of the covariates for the comparison between new drug user/s in the pre-RMM vs post-RMM period will be obtained - Measures of patient-level DUS (descriptives of treatment duration) will be provided

The analyses that will be performed for each objective are detailed below. A summary can be found in

Table 11.

Objective 1:

Monthly incidence rates with 95% CI will be calculated as the number of new prescriptions per 100,000 person-years of the population at risk during the study period. Each of the drug classes and progestogens of interest will be treated as a separate outcome (see "8.6.2. Outcomes" for more information).

A washout window of 365 days will be applied after each treatment episode. Therefore, participants with an outcome record will not contribute time to the study during the 365 days following the end of each treatment episode. Participants will be able to re-enter the study after the washout window has passed. This washout will be applied for each outcome separately and will be specific to the drug class or progestogen of interest being under study. Please note that a treatment episode might consist of several consecutive prescriptions (see "8.6. Variables" for more information).

Period prevalence with 95% CI will be calculated as the proportion of study participants who were prescribed with an outcome medication monthly.

Objective 1 will only be conducted for complete calendar months observed in the database (e.g., if the end of available data is 15th of June 2023, only data up to 31st May 2023 will be considered). Results will be reported overall and stratified by study period (pre- vs. postintervention), age group (10-17, 18-34, 35-49, 50-64, +65), dose (high- vs. low- dose products, for NOMAC and CMA only), indication (non-HRT vs. HRT) and WHO 5th ATC level codes (if counts allow).

A subgroup analysis will be conducted restricting the study population to those individuals with a prior history of meningioma. All individuals within the study population with a documented history of meningioma will be included, irrespective of the time elapsed since their diagnosis, and will contribute time to the analysis from the date of diagnosis. Given the limited number of feasibility counts for this condition, results will only be reported overall and by calendar years. Please see the limitation section for further details.

Objective 2:

Treatment duration will be reported for the first prescribed treatment. Duration will be derived from the start and end of the prescription.

Cumulative dose will be calculated considering all treatments containing NOMAC or CMA recorded during the study period. If two eras with different doses are separated by less than 30 days, the time between the two eras will be considered as exposed by the first era (**Figure 1**, first row). If two eras start at the same date, the overlapping period will be considered exposed by both.

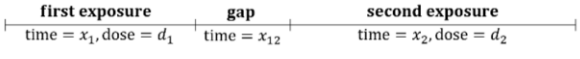
Gap era joint mode	Schematics	Dose in between	Cumulative dose	Cumulative time
"first"		d_1	$d_1 \cdot (x_1 + x_{12}) + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"second"		d_2	$d_1 \cdot x_1 + d_2 \cdot (x_2 + x_{12})$	$x_1 + x_{12} + x_2$
"zero"		0	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"join"		NA	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_2$

Figure 1. Gap era joint mode

Cumulative dose and treatment duration will be calculated for all treatments initiated during the study period and occurring over one year before and after the intervention to compare time periods of equal duration. The pre-intervention period for comparison will span from October 2021 to September 2022,

the year prior the request for PRAC to review current evidence on NOMAC and CMA. The post-intervention period for comparison will span from February 2023 to January 2024. For databases with less available data (see Table 3) we will limit the comparison to 6 months (post-intervention: February to July 2023; pre-intervention: February to July 2022). Time periods for comparison will cover the same calendar months in case seasonality is detected.

NOMAC and CMA will be assessed separately. Results will be reported overall and stratified by study period (pre- vs. postintervention) and indication at first use (non-HRT vs. HRT).

Objective 3:

Characteristics will be described by means of large-scale characterisation. The top 10 of disease codes and top 10 of drug codes will be described in the report to simplify dissemination. Pre-specified comorbidities and concomitant medications will also be reported within specific time windows (see "8.6.3. Other covariates"). The number of patients initiating high- or low-doses of NOMAC and CMA (assessed separately) and the number of years since meningioma diagnosis will also be described.

Results will be reported overall and stratified by study period (pre- vs. postintervention).

Objective 4:

For each participant initiating treatment with NOMAC or CMA, we will retrospectively assess the occurrence of records indicating the use of other drug classes of interest not containing NOMAC or CMA. This assessment will be performed from the day before index date to the earliest of the start of the study period or the start of the observation period for each patient. We will describe the order in which treatments of interest were prescribed, as first vs. non-first treatments. NOMAC and CMA will be assessed separately.

NOMAC and CMA will be assessed separately. Results will be reported overall and stratified by study period (pre- vs. postintervention), dose (high- vs. low-dose products), and indication (non-HRT vs. HRT). Dose and indication will be assessed at index date (i.e. date of treatment initiation with NOMAC or CMA). Please see "11. Limitations" for more information.

Objective 5:

We will describe the number and proportion of patients that follow different treatment strategies in the 180 days following the end of treatment. These strategies are defined as:

- Restart the same treatment
- Switch to a different treatment
- Restart and switch to a different treatment
  Discontinued treatment (not treated, neither with the original treatment nor any potential switch)

For this objective (time period comparison), both incident and prevalent users will be considered. The proportion of individuals following each treatment strategy (e.g. switching) will be calculated using the number of people exposed to the product of interest during the time period under study (e.g. pre-intervention) as the denominator regardless of when the initiation started.

Figure 2 illustrates some of these scenarios.

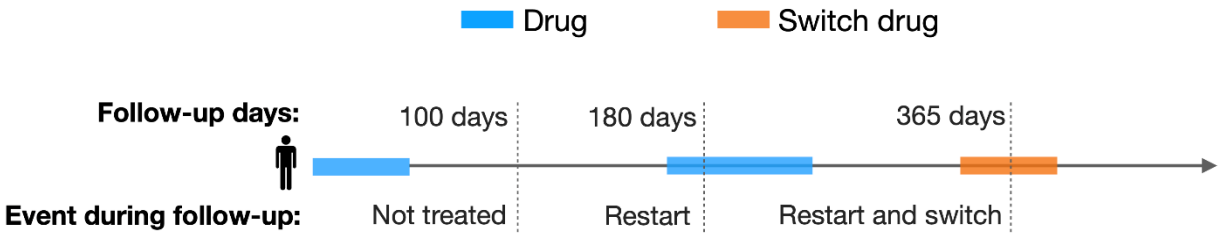


Figure 2. Outcomes after the drug exposure of interest (in blue) over different time periods.

Source: DrugUtilisation R package website (22)

The number of meningioma cases occurring any time during treatment with NOMAC or CMA, and in the six months prior to the end of treatment will also be reported. For cases identified in the six months prior, we will report the treatment strategy followed after treatment (i.e. restart, switch, both, or discontinuation).

NOMAC and CMA will be assessed separately. Results will be reported overall and stratified by study period (pre- vs. postintervention) and WHO 5th ATC level codes (if counts allow). For the pre- and post-intervention comparison, treatments initiated during the 180 days before the intervention will not be considered, to ensure sufficient time for assessing outcomes (e.g., switches, discontinuations) prior to the intervention.

Objective 2-5:

For objectives 2 to 5, SMD of each of the covariates for the comparison of drug users in the pre-RMM and post-RMM period as a measure of the impact of the profile of drug users. These covariates will include: duration and cumulative dose (objective 2), patient characteristics (objective 3) and line of treatment (objective 4). For patient characteristics, only conditions will be compared, with the assessment window set as any time prior to 1 day before the index date. For objective 5, covariates will include the proportion of patients diagnosed with meningioma during treatment, and the proportion of patients who discontinue or switch to alternative treatments (assessed separately).

Objective 6:

The impact of the restrictions of use will be estimated using an ITS. This analysis will be restricted to NOMAC and CMA (assessed separately) and will be informed by results of the main analysis obtained as part of objective 1 (no meningioma restriction). For NOMAC, the intervention taken place in 2018 will also be assessed.

Time series will be assessed using segmented regression. Monthly incident counts of patients prescribed with NOMAC or CMA will be modelled using a Poisson regression model. Quasi-Poisson models will be considered in the presence of overdispersion. The effect size of the intervention will be estimated using risk ratios (RR).

The assumption of linearity will be assessed by visually inspecting the data and residuals, as well as through statistical goodness-of-fit tests. Autocorrelation will be assessed by examining the plot of residuals and the partial autocorrelation function and conducting statistical tests where possible. If seasonality is detected, it will be controlled for by including variables representing them in the regression model. If the trends are not (or cannot be transformed to be linear) or in the presence of residual autocorrelation, ITS will not be conducted due to the complexity of predicting the counterfactual and to disentangle the intervention effects.(23)

The impact model of the intervention (i.e. how we expect the intervention has impacted the outcome) is anticipated to show an abrupt change in the level and a gradual change in the gradient of the trend (step and slope change). Potential impact models will be further discussed and agreed with EMA and defined a priori.(23, 24)

The amount of pre-intervention data to include for this analysis will be based on defining a valid counterfactual for the ITS analysis. Given the large amount data (12 years before the intervention), the range of pre-intervention data will be restricted to ensure the validity of the comparison (i.e. historical trends might differ from the most recent ones). To analyse the impact of restrictions adopted in 2022, analysis will be conducted using data from 1st January 2021 onwards. For NOMAC, the intervention adopted in 2018 will be assessed using data from 1st January 2017 onwards. Methodological considerations will be evaluated based on the visual assessment of the trends. This may include adjustments on the amount of pre-intervention data or the frequency of data points, if deemed necessary to support the analysis.

Results will be reported overall and stratified by dose (high- vs. low- dose products) and indication (non-HRT vs. HRT).

All objectives:

All analyses will be conducted separately for each database, and will be carried out in a federated manner, allowing analyses to be run locally without sharing patient-level data. A minimum cell counts of 5 will be used when reporting results, with any smaller counts reported as "<5" to comply with privacy protection regulations.

Table 11. Primary, secondary, and subgroup analysis specification.

A. Primary analysis

Hypothesis:	Objective 1: Not applicable, descriptive analysis. Objective 2: Cumulative dose and duration of treatments with NOMAC or CMA will be lower after the implementation of restrictions. Objective 3: The number of new users of NOMAC or CMA with prior history of meningioma will be reduced after the implementation of restrictions. Objective 4: The number of users initiating NOMAC or CMA as first-line treatment will be reduced after the implementation of restrictions. Objective 5: The number of discontinuations and switches from NOMAC or CMA to other drug classes will increase after the implementation of restrictions. Objective 6: The incidence of NOMAC or CMA will be reduced after the implementation of restrictions, especially for high-dose products. This reduction will not be observed for other drug classes of interest.
Exposure contrast:	Objective 1: Not applicable, descriptive analysis. Objective 2: Pre-intervention (1-year period) vs. Post-intervention (1-year period) Objective 3 to 6: Pre-intervention vs. Post-intervention
Outcome:	Objective 1: Incidence rates and prevalence of drug classes of interest Objective 2: Cumulative dose and treatment duration of NOMAC or CMA.

	Objective 3: Number and characteristics of users of drug classes of interest. Objective 4: Line of treatment when initiating NOMAC or CMA. Objective 5: Diagnosis with meningioma during treatment. Discontinuations and switches from treatments with NOMAC or CMA to others. Objective 6: Incidence rates of NOMAC or CMA. Drug classes of interest, NOMAC and CMA will be assessed separately.
Analytic software:	R
Model(s):	Objective 1: Not applicable, descriptive analysis. Objective 2 to 5: Standardised mean differences. Objective 6: Segmented regression (Poisson models).
Confounding adjustment method	
	Stratification.
Missing data methods	
	The absence of a record for a condition or medication will be considered as the absence of the disease or use of the medication.
Subgroup Analyses	
	Objective 1: Age groups, indication, study period. For NOMAC or CMA only: dose, WHO ATC 5th level (if counts allow). A subgroup analysis will be performed restricting the study population to individuals with a prior history of meningioma. Objective 2: Study population, indication, study period. Objective 3: Study period. Objective 4: Study population, study period, exposure of interest (NOMAC vs. CMA), dose and indication. Objective 5: Study population, WHO ATC 5th level (if counts allow), study period, dose. Objective 6: Dose (high-dose products only), indication.

8.9 Evidence synthesis

Results from analyses described in section 8 will be presented separately for each database and no meta-analysis of results will be conducted.

9. DATA MANAGEMENT

Data management

All databases are mapped to the OMOP CDM. This enables the use of standardised analytics and tools across the network since the structure of the data and the terminology system is harmonised. The OMOP CDM is developed and maintained by the Observational Health Data Sciences and Informatics (OHDSI) initiative and is described in detail on the wiki page of the CDM: https://ohdsi.github.io/CommonDataModel and in The Book of OHDSI: http://book.ohdsi.org.

The analytic code for this study will be written in R. Each data partner will execute the study code against their database containing patient-level data and will then return the results set which will only contain aggregated data. The results from each of the contributing data sites will then be combined in tables and figures for the study report.

Data storage and protection

For this study, participants from various European Union member states will process personal data from individuals which is collected in national/regional electronic health record databases. Due to the sensitive nature of this personal medical data, it is important to be fully aware of ethical and regulatory aspects and to strive to take all reasonable measures to ensure compliance with ethical and regulatory issues on privacy.

All databases used in this study are already used for pharmaco-epidemiological research and have a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control are adhered to. In agreement with these regulations, rather than combining person level data and performing only a central analysis, local analyses will be run, which generate non-identifiable aggregate summary results.

10. QUALITY CONTROL

General database quality control

Several open-source quality control mechanisms for the OMOP CDM have been developed (see Chapter 15 of The Book of OHDSI http://book.ohdsi.org/DataQuality.html). In particular, data partners are expected to run the OHDSI Data Quality Dashboard tool (https://github.com/OHDSI/DataQualityDashboard). This tool provides numerous checks relating to the conformance, completeness and plausibility of the mapped data. Conformance focuses on checks that describe the compliance of the representation of data against internal or external formatting, relational, or computational definitions, completeness in the sense of data quality is solely focused on quantifying missingness, or the absence of data, while plausibility seeks to determine the believability or truthfulness of data values. Each of these categories has one or more subcategories and are evaluated in two contexts: validation and verification. Validation relates to how well data align with external benchmarks with expectations derived from known true standards, while verification relates to how well data conform to local knowledge, metadata descriptions, and system assumptions.

Study specific quality control

Concepts and phenotypes of interest will be developed and assessed using the following R packages: “CodelistGenerator”, “CohortDiagnostics” and “DrugExposureDiagnostics”. The study code will be based on different R packages to: 1) estimate incidence rates and period prevalence (“IncidencePrevalence”), 2) characterise patients “PatientProfiles” and “CohortCharacteristics”) and 3) summarise patient-level drug

use ("DrugUtilisation"). These packages will include numerous automated unit tests to ensure the validity of the codes, alongside software peer review and user testing.

11. LIMITATIONS OF THE RESEARCH METHODS

General limitations:

The study will be informed by routinely collected health care data and so data quality issues inherent to observational studied need to be considered. As such, the recording of events (e.g. comorbidities, medications) may vary across databases and might be inaccurately recorded or incomplete. In addition, results will only reflect events occurring in the healthcare settings covered by each database, and therefore prescriptions issued outside the healthcare institutions covered by each data partner will not be captured.

Databases:

In IQVIA LPD Belgium and IQVIA DA Germany, the observation period of the patients in these databases is calculated based on the last visit, observation or interaction of the patient with the health care system. This methodology impacts the individuals considered "at risk" for the different medicines of interest of the study (i.e., the individuals included in the denominator populations) during the latest months of available data from the latest data lock, where healthy and/or non-frequent users of the health care system will not be considered active. Consequently, the denominators that will be used to calculate the incident use of drugs in the population may present an artefactual decrease whilst the incident users will remain, incrementing the incidence and prevalence ratios. The presence of these artefacts will be considered when interpreting the results. However, this is likely to affect the amount of follow up available for the study. We expect that the data from the last 6 months may not accurately reflect actual figures of use and, therefore, will be excluded from the analysis for Objective 1 and 6.

Regarding the study period, NAJS will provide data from 2017 onwards only, as prior data might include information on duplicated patients. IQVIA LPD Belgium will provide data from 2012 onwards.

Since information on drug exposure end dates is unavailable in NAJS, treatment duration will not be inferred directly from the start and end dates of drug exposure. Instead, we will infer the treatment period using only the drug exposure start dates, assuming continuous drug exposure between consecutive start dates, if separated by less than 90 days. To account for the final prescription, we apply a 30-day window following the last recorded drug start date. This approach might lead to some uncertainty regarding the exact duration or cumulative dose prescribed.

Medications of interest:

Medicines of interest will be identified based on ATC 5th and 4th level codes. Some ATC codes incorporate attributes that are not immediately visible (e.g. route, indication, mechanism of action, dosage and combinations). Therefore, not every ATC code containing the name of a drug ingredient is automatically the correct classifier for that drug (i.e. some ingredients show up in more than one ATC code). As an example, medroxyprogesterone is the ingredient of 9 ATC concepts that have the same name but different attributes, such as different indications like those relevant to this study as well as the treatment of neoplastic diseases. In prior vocabulary versions, ATC 5th level concepts were mapped to RxNorm ingredients and, therefore, all those additional attributes were not considered. Although recent efforts have improved the hierarchical structure, some inconsistencies between ATC-RxNorm mapping still exit, especially for combination drugs.(25)

The use of medicines of interest will be derived from prescription data, and therefore assumptions about the use and duration of the drug will be unavoidable (e.g. drug prescriptions do not imply the actual

consumption of the medication). In addition, the actual reason for the prescription of the drug is not available in the data and will be assessed using age as a proxy. Age 50 will be used as a threshold to reflect indication, with women older than this age assumed to take this medication for HRT and younger women assumed to take it for non-HRT reasons. This could lead to misclassification, particularly in women who near this threshold age. Misclassification can also occur among women who experience primary ovarian insufficiency (age < 40 years) or early menopause (age 40 to 45), which are estimated to affect 1 to 3% and 5 to 10% of females of high-income countries, respectively.(26)

When assessing the line of treatment (Objective 4), treatment lines will be considered under the assumption that patients receive the treatments of interest for the same indication over time. However, this may not always be accurate, as these treatments can have multiple indications, and patients may be prescribed these medications for different purposes over time.

The cumulative dose and line of treatment for products containing NOMAC or CMA will be assessed based on exposures recorded during the study period. This assessment will ensure the quality of the data being used, as data collected before 2010 might be inconsistently reported in some data patterns. While this could lead to an underestimation of the cumulative dose or an inaccurate assessment of the line of treatment, we believe this will have a very limited impact on the study, given that we will cover over 12 years of follow-up.

Analysis:

Due to the limited number of feasibility counts for meningioma (in the order of hundreds across most databases), studying the effect of the restrictions of use among this population will not be feasible. A subgroup analysis for this population has been included for Objective 1 for descriptive purposes; however, it is unlikely to have a sufficient number of patients to allow for formal analysis.

The dates of the interventions were determined based on EU-level restrictions. However, we excluded the restrictions imposed in 2020 on products containing NOMAC in combination with oestradiol (see the introduction for further details). The rationale for this exclusion is that the 2020 intervention is likely to have been affected by the coronavirus disease (COVID-19) pandemic. Including this restriction could result in biased estimates, as any observed effects might be attributed to the pandemic rather than the intervention itself. The effect of the COVID-19 pandemic might still be seen in 2021, which will affect the ability to capture stable trends for Objective 6. Methodological considerations for Objective 6 will be thoroughly evaluated based on the visual assessment of the trends. Regarding the timing of interventions, some countries may have implemented national-level measures prior to the EU restrictions. These measures fall outside the scope of this study and will be considered for context and interpretation only.

The amount of current available data might not fully capture the long-term effects resulting from the RMM implemented in November 2022. Further studies using additional follow-up data (once available) might be needed to assess the long-term impact of the intervention.

Segmented regression (Objective 6) might not be appropriate if trends cannot be transformed to be linear or if there is residual autocorrelation. Other modelling approaches such as Autoregressive Integrated Moving Average (ARIMA) models could be considered. However, these methods require a substantial number of time points before and after the intervention and are not feasible given the currently available post-intervention data.

12. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Adverse events/adverse reactions will not be collected or analysed as part of this evaluation. The nature of this non-interventional evaluation, through the use of secondary data, does not fulfil the criteria for reporting adverse events, according to module VI, VI.C.1.2.1.2 of the Good Pharmacovigilance Practices (https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vi-collection-management-submission-reports_en.pdf).

Only in case of prospective data collection, there is a need to describe the procedures for the collection, management and reporting of individual cases of adverse events/adverse reactions.

13. GOVERNANCE BOARD ASPECTS

All data sources (except for IQVIA DA Germany and IQVIA LPD Belgium) require approval from their respective governance boards.

14. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

A study report including an executive summary, and the specified tables and/or figures will be submitted to EMA by the DARWIN EU® CC upon completion of the study. An interactive dashboard incorporating all the results (tables and figures) will be provided alongside the study report. The full set of underlying aggregated data used in the dashboard will also be made available if requested.

15. OTHER ASPECTS

Not applicable.

16. REFERENCES

1. Cao J, Yan W, Li G, Zhan Z, Hong X, Yan H. Incidence and survival of benign, borderline, and malignant meningioma patients in the United States from 2004 to 2018. International Journal of Cancer. 2022;151(11):1874-88.
2. Nguyen P, Hoisnard L, Neumann A, Zureik M, Weill A. Utilisation prolongée de l'acétate de chlormadinone et risque de méningiome intracrânien: une étude de cohorte à partir des données du SNDS. 2021.
3. Nguyen P, Hoisnard L, Neumann A, Zureik M, Weill A. Utilisation prolongée de l'acétate de nomégestrol et risque de méningiome intracrânien: une étude de cohorte à partir des données du SNDS. . 2021

4. Nguyen P, Roland N, Neumann A, Hoisnard L, Passeri T, Duranteau L, et al. Prolonged use of nomegestrol acetate and risk of intracranial meningioma: a population-based cohort study. The Lancet Regional Health - Europe. 2024;42:100928.
5. Hoisnard L, Laanani M, Passeri T, Duranteau L, Coste J, Zureik M, et al. Risk of intracranial meningioma with three potent progestogens: A population-based case–control study. European Journal of Neurology. 2022;29(9):2801-9.

6. Weill A, Nguyen P, Labidi M, Cadier B, Passeri T, Duranteau L, et al. Use of high dose cyproterone acetate and risk of intracranial meningioma in women: cohort study. BMJ. 2021:n37.
7. Roland N, Neumann A, Hoisnard L, Duranteau L, Froelich S, Zureik M, et al. Use of progestogens and the risk of intracranial meningioma: national case-control study. BMJ. 2024:e078078.
8. European Medicines Agency. Nomegestrol and chlormadinone Article-31 referral - Annex II. 2022. Available from: https://www.ema.europa.eu/en/documents/referral/nomegestrol-and-chlormadinone-article-31-referral-annex-ii_en.pdf
9. European Medicines Agency. Medicines containing nomegestrol or chlormadinone: PRAC recommends new measures to minimise risk of meningioma 2022. Available from: https://www.ema.europa.eu/en/news/medicines-containing-nomegestrol-or-chlormadinone-prac-recommends-new-measures-minimise-risk-meningioma.
10. European Medicines Agency. Nomegestrol and chlormadinone - referral. Available from: https://www.ema.europa.eu/en/medicines/human/referrals/nomegestrol-chlormadinone.
11. European Medicines Agency. Nomegestrol / chlormadinone - direct healthcare professional communication (DHPC). Available from: https://www.ema.europa.eu/en/medicines/dhpc/nomegestrol-chlormadinone#key-facts.
12. Barnholtz-Sloan JS, Kruchko C. Meningiomas: causes and risk factors. Neurosurgical Focus. 2007;23(4):E2.
13. Johnson DR, Olson JE, Vierkant RA, Hammack JE, Wang AH, Folsom AR, et al. Risk factors for meningioma in postmenopausal women: results from the Iowa Women's Health Study. Neuro-Oncology. 2011;13(9):1011-9.
14. Zhang D, Chen J, Wang J, Gong S, Jin H, Sheng P, et al. Body mass index and risk of brain tumors: a systematic review and dose–response meta-analysis. European Journal of Clinical Nutrition. 2016;70(7):757-65.
15. Niedermaier T, Behrens G, Schmid D, Schlecht I, Fischer B, Leitzmann MF. Body mass index, physical activity, and risk of adult meningioma and glioma. Neurology. 2015;85(15):1342-50.
16. Gheorghiu A, Brunborg C, Johannesen TB, Helseth E, Zwart J-A, Wiedmann MKH. Lifestyle and metabolic factors affect risk for meningioma in women: a prospective population-based study (The Cohort of Norway). Frontiers in Oncology. 2024;14.
17. Schwartzbaum J, Jonsson F, Ahlbom A, Preston-Martin S, Lönn S, Söderberg KC, et al. Cohort studies of association between self-reported allergic conditions, immune-related diagnoses and glioma and meningioma risk. International Journal of Cancer. 2003;106(3):423-8.
18. Brenner AV, Linet MS, Fine HA, Shapiro WR, Selker RG, Black PM, et al. History of allergies and autoimmune diseases and risk of brain tumors in adults. International Journal of Cancer. 2002;99(2):252-9.
19. Berg-Beckhoff G, Schüz J, Blettner M, Münster E, Schlaefer K, Wahrendorf J, et al. History of allergic disease and epilepsy and risk of glioma and meningioma (INTERPHONE study group, Germany). European Journal of Epidemiology. 2009;24(8):433-40.
20. Hawley S, Ali MS, Berencsi K, Judge A, Prieto-Alhambra D. Sample size and power considerations for ordinary least squares interrupted time series analysis: a simulation study</p&gt. Clinical Epidemiology. 2019;Volume 11:197-205.
21. Zhang F, Wagner AK, Ross-Degnan D. Simulation-based power calculation for designing interrupted time series analyses of health policy interventions. Journal of Clinical Epidemiology. 2011;64(11):1252-61.
22. Català M, Guo Y, Lopez-Guell K, Burn E, Mercade-Besora N, Chen X. DrugUtilisation (0.7.1): Assessing drug restart and switching after treatment. Available from: https://darwin-eu-dev.github.io/DrugUtilisation/articles/drug_restart.html.
23. Lopez Bernal J, Soumerai S, Gasparrini A. A methodological framework for model selection in interrupted time series studies. Journal of Clinical Epidemiology. 2018;103:82-91.

24. Lopez Bernal J, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: a tutorial. International Journal of Epidemiology. 2016:dyw098.
25. Ostropolets A, Talapova P, De Wilde M, Abedtash H, Rijnbeek P, Reich CG. A High-Fidelity Combined ATC-Rxnorm Drug Hierarchy for Large-Scale Observational Research. IOS Press; 2024.
26. Mishra GD, Chung H-F, Cano A, Chedraui P, Goulis DG, Lopes P, et al. EMAS position statement: Predictors of premature and early natural menopause. Maturitas. 2019;123:82-8.

17. ANNEXES

Appendix I: List with preliminary concept definitions.

Meningioma:

Concept ID	Concept Name
4250780	Angiomatous meningioma
4029200	Atypical meningioma
609195	Atypical meningioma of cerebral meninges
4260192	Benign meningeal neoplasm
37110097	Benign meningioma
608204	Benign meningioma
376063	Benign neoplasm of cerebral meninges
4003171	Benign neoplasm of meninges
135767	Benign neoplasm of spinal meninges
4130540	Cerebellopontine angle meningioma
4098901	Cerebral meningioma
4212098	Clear cell meningioma
4300672	Cutaneous meningioma
35622955	Familial multiple benign meningioma
4176436	Fibrous meningioma
4261967	Hemangioblastic meningioma
4118992	Intracranial meningioma
4102396	Lymphoplasmocyte-rich meningioma
4189335	Malignant meningeal neoplasm
37017114	Malignant meningioma of meninges of brain
4112969	Malignant meningioma of optic nerve sheath
4177240	Malignant tumor of meninges
4133829	Meningeal neoplasm (morphology)
763799	Meningioma of cerebellum
4114200	Meningioma of optic nerve sheath
4186247	Meningioma of orbit
608281	Meningioma of uncertain behavior
608280	Meningioma uncertain whether benign or malignant

4266488	Meningioma, chordoid
4301120	Meningioma, malignant
4164328	Meningioma, rhabdoid
4164954	Meningiomatosis
4288742	Meningothelial meningioma
608205	Metaplastic meningioma
4099822	Microcystic meningioma
4130542	Neoplasm of cerebral meninges
4131105	Neoplasm of meninges
4130041	Neoplasm of spinal meninges
4314637	Neoplasm of uncertain behavior of cerebral meninges
438997	Neoplasm of uncertain behavior of meninges
4317020	Neoplasm of uncertain behavior of spinal meninges
4030268	Papillary meningioma
36716634	Primary malignant meningioma
436926	Primary malignant neoplasm of cerebral meninges
4002340	Primary malignant neoplasm of meninges
134295	Primary malignant neoplasm of spinal meninges
4303729	Primary optic nerve sheath meningioma
4243303	Psammomatous meningioma
4303730	Secondary optic nerve sheath meningioma
4100554	Secretory meningioma
4098902	Spinal meningioma
4277603	Transitional meningioma
4175395	Xanthomatous meningioma

Drug classes:

Drug class	Analysis	WHO ATC 4th level codes[1]	WHO ATC 5th level codes[1]
Progestogens that are pregnadien derivates	Objective 1	G03DB	All descendants included
Progestogen and oestrogen combination products	Objective 1	G03AA, G03AB, G03FA, G03FB	All descendants included

Medroxyprogesterone[2]	Objective 1	N/A	G03AC06, G03DA02, G03AA17, G03FA12, G03FB06, G03AA08, L02AB02
Nomegestrol	Objective 1 and 6	N/A	G03AA14, G03DB04, G03FB12
Chloramidinone	Objective 1 and 6	N/A	G03AA15, G03AB07, G03DB06, G03FB03
Progestogen and estrogen combination products not containing nomegestrol or chlormadinone.	Objective 4 and 5	G03AA, G03AB, G03FA, G03FB	All descendants included, except: G03AA14, G03AA15, G03AB07, G03FB12 and G03FB03
Progestogens that are pregnadien derivates not containing nomegestrol or chlormadinone.	Objective 4 and 5	G03DB	All descendants included, except: G03DB04 and G03DB06.
Drug classes of interest (any)	Objective 3	G03AA, G03AB, G03DB, G03FA, G03FB	All descendants included

[1] All descendants included.

[2] If possible, products for oncological purposes will be excluded (L02AB02).

Pre-specified comorbidities:

Pre-specified comorbidities	Concept IDs[1]
Asthma	317009
Autoimmune diseases	434621
Cancer (any malignancy)	443392
Diabetes mellitus	201820
Endometriosis	433527
Epilepsy	380378
Hyperlipidaemia	432867
Hypertensive disorder	316866
Menopause/Perimenopause	4129547, 4141640, 439082
Neoplasm of the brain	373724
Neoplasm of the breast	81251
Neoplasm of the endometrium	4095749
Menstrual disorders	443431, 443800, 4302555, 194696, 439081
Obesity	433736
Osteoporosis	80502

Polycystic ovary syndrome	40443308
Primary ovarian insufficiency	4279913
Type 2 neurofibromatosis	380975
Uterine fibroids	197236
Venous thromboembolism	4133004, 440417

[1] All descendants included.

Pre-specified medications:

Pre-specified medications	WHO ATC codes[1]
Antidepressants	N06A
Anti-androgens	L02BB, C03DA01, G04CB01, G03H
Biophosphonates	M05BA
Clonidine	C02AC01
Metformin	A10BA02
Gonadotropin Releasing Hormone antagonists	L02AE02
Selective Estrogen Receptor Modulators	G03XC

[1] All descendants included.

Appendix II: Relevant dates of the assessment of nomegestrol acetate and chlormadinone acetate.

Date	Procedure
10/2018	Adoption of CMDh position
1/12/2018	Transmission to the National Competent Authorities of the translation of the annexes to the position
30/01/2019	Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder)

CMDh= Coordination Group for Mutual Recognition and Decentralised Procedures-Human

Source: European Medicines Agency. Nomegestrol: CMDh Scientific conclusions and grounds for variation, amendments to the Product Information and timetable for the implementation - PSUSA/00002181/201801.

https://www.ema.europa.eu/en/medicines/psusa/psusa-00002181-201801

Date	Procedure
22/09/2021	Date of request for PRAC assessment by France
30/09/2021	Procedure start date
07/07/2022	PRAC recommendation date
01/09/2022	CHMP opinion date (endorsement of PRAC's assessment risk)
8/11/2022	DHPC dissemination date
28/11/2022	European Commission decision date
28/12/2022	Timeline for Marketing Authorisation Holders to implement changes

PRAC= Pharmacovigilance Risk Assessment Committee; CHMP = Committee for Medicinal Products for Human Use.

Source: European Medicines Agency. Nomegestrol and chlormadinone -referral.
https://www.ema.europa.eu/en/medicines/human/referrals/nomegestrol-chlormadinone

Appendix III: ENCePP checklist for study protocols

Study title: DARWIN EU® – Impact of risk minimisation measures related to the risk of meningioma in women using nomegestrol and chlormadinone

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	5, 8.2
1.1.2 End of data collection[2]	☒	☐	☐	
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7, 8.8
2.1.2 The objective(s) of the study?	☒	☐	☐	
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	
2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	8.1.

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 3: Study design		Yes	No	N/A	Section Number
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8.2.
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	8.8.
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	8.8.
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	

Comments:

Section 4: Source and study populations		Yes	No	N/A	Section Number
4.1	Is the source population described?	☒	☐	☐	8.5
4.2	Is the planned study population defined in terms of:				8.3, 8.4, 8.5
	4.2.1 Study time period	☒	☐	☐	
	4.2.2 Age and sex	☒	☐	☐	
	4.2.3 Country of origin	☒	☐	☐	
	4.2.4 Disease/indication	☒	☐	☐	
	4.2.5 Duration of follow-up	☒	☐	☐	
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	8.5

Comments:

Section 5: Exposure definition and measurement		Yes	No	N/A	Section Number
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3	Is exposure categorised according to time windows?	☐	☐	☒	

Section 5: Exposure definition and measurement		Yes	No	N/A	Section Number
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6	Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement		Yes	No	N/A	Section Number
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8.6.2
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.6.2
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☒	☐	
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias		Yes	No	N/A	Section Number
7.1	Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	
7.2	Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☐	☒	
7.3	Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☐	☐	☒	

Comments:

Section 8: Effect measure modification	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources	Yes	No	N/A	Section Number
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☒	
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	8.2
9.1.3 Covariates and other characteristics?	☒	☐	☐	8.2
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	8.2
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☒	☐	
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	8.6.2
9.3.3 Covariates and other characteristics?	☒	☐	☐	8.6.3
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	8.2

Comments:

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	8.8

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.2 Is study size and/or statistical precision estimated?	☐	☒	☐	8.7
10.3 Are descriptive analyses included?	☒	☐	☐	8.8
10.4 Are stratified analyses included?	☒	☐	☐	8.8
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	8.8
10.8 Are relevant sensitivity analyses described?	☐	☒	☐	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9
11.2 Are methods of quality assurance described?	☒	☐	☐	9
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☒	☐	
12.1.2 Information bias?	☒	☐	☐	11
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☐	☐	☐	8.2, 8.7,11

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	13
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	9

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	14
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	14

Comments:

Name of the main author of the protocol: Berta Raventós

Date: 12/11/2024

Signature: BR