Study Report

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

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CONTENTS

Study title	DARWIN EU® - Impact of risk minimisation measures related to the risk of meningioma in women using nomegestrol and chlormadinone
Study report version	V4.0
Date	23/09/2025
EUPAS number	EUPAS1000000455
Active substance	Drug classes of interest included: - Progestogen and oestrogen combination products (WHO ATC codes: G03AA, G03AB, G03FA and G03FB) - Pregnadien derivatives (WHO ATC code: G03DB) Progestogens of interest included: - Nomegestrol - Chlormadinone - Medroxyprogesterone
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 meningioma in November 2022. To contextualise findings, changes of other relevant drug classes were also described, including progestogen and oestrogen combination products and progestogens that are pregnadien derivatives. The specific objectives were: 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. 5. To describe the frequency of patients who develop meningioma during treatment with products containing nomegestrol acetate or chlormadinone acetate, 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
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1. DESCRIPTION OF THE STUDY TEAM

Study team roles	Names	Organisations
Principal Investigator	Berta Raventós Talita Duarte-Salles	Erasmus MC
Data Scientist	Ger Inberg Ioanna Nika* Cesar Barboza Maarten van Kessel Ross Williams	Erasmus MC
Epidemiologist	Julieta Politi Anton Barchuk	Erasmus MC
Study Manager	Natasha Yefimenko	Erasmus MC
Data partner name**	**Data Partner member names**	**Organisations**
IQVIA DA Germany 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

* Included in the study team on the 27th of February 2025.
** Data partners' role is only to execute code at their data source, review and approve their results. These people do not have an investigator role. Data analysts/programmers do not have an investigator role and thus declaration of interests (DOI) for these people is not needed.

2. DATA SOURCES

Country	Name of Database	Health Care setting[1]	Type of Data[2]	Number of active subjects[3]	Calendar period covered by each data source[4]
Germany	IQVIA DA Germany	Primary care	EHR	4.48 M	2010–2024
Belgium	IQVIA LPD Belgium	Primary care	EHR	196 k	2015–2024
Croatia	NAJS	Primary care, hospital care (IP, OP)	Registries	4.3 M	2017–2025

1. IP=inpatient, OP=outpatient.
2. EHR = Electronic health records.
3. Defined as the maximum number of persons in an observation period in the last 6 months of available data.
4. Calendar period covered in this study. Restrictions on study period were additionally applied in objectives 1 and 6.

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 several gynaecological and menstrual disorders, hormone replacement therapy (HRT), and contraception. Recent studies have shown a dose-dependent association between these drugs and an increased risk of meningioma. In response, risk minimisation measures (RMM) were introduced in 2022, restricting high-dose products to use at the lowest effective dose for the shortest duration, and advising against their use as first-line treatment. Use of NOMAC or CMA was contraindicated in patients with current or past meningioma, with the requirement to permanently discontinue treatment if diagnosed with meningioma. This contraindication had already been in place for NOMAC, with earlier regulatory actions 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 were also described (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 (2^{nd}/3^{rd} versus 1^{st}) 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

<u>Study design</u>

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

1. A population-level drug utilisation study (DUS) (objective 1).
2. A patient-level DUS (objectives 2 to 5)
3. A trend analyses and effectiveness of risk minimisation measures to assess changes in patient- and population- level analyses (objectives 2 to 5; objective 6 based on results of objective 1)

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

Population

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, with >365 days of data visibility prior to index date. For patient-level DUS, the study population was additionally restricted to new medicine users. These were NOMAC or CMA for objectives 2, 4, and 5, or any of the drug classes or progestogens of interest for objective 3.

Variables

Drug classes of interest:

- Progestogen and oestrogen combination products
- Progestogens that are pregnadien derivatives

Progestogens of interest:

- Medroxyprogesterone
- NOMAC
- 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 (objectives 1, 4 ,6)
- Indication: HRT vs. non-HRT, with age as a proxy (objectives 1, 2, 4, 6)
- WHO ATC 5th level code: For NOMAC and CMA only (objectives 1 and 5).
- Study period: Pre- vs. Post-intervention (objectives 1 to 5).

Sample size

No specific sample size calculations were performed.

Statistical analyses

For objective 1, incidence rates per 100,000 person-years (PY) and period prevalence (%) were calculated for drug classes and progestogens of interest (assessed separately). Estimates were calculated overall, by calendar month, and by study period. End of data for this objective was defined as 31st December 2023 in IQVIA databases and 31st December 2024 in NAJS.

For objective 2, treatment duration was described for the first treatment episode with NOMAC or CMA. Cumulative dose was calculated in IQVIA DA Germany and IQVIA LPD Belgium only, considering all treatments containing these ingredients. For the pre- and post-intervention comparison, duration and cumulative dose were calculated over periods of equal duration (i.e., 12 months).

For objective 3, new users of drug classes and progestogens of interest were described based on pre-specified comorbidities and medications and through large-scale characteristics.

For objective 4, line of treatment (i.e., first vs. non-first treatment) was 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.

For objective 5, the frequency of different treatment strategies occurring 180 days after ending treatment with NOMAC or CMA was described. Strategies included treatment discontinuation and switching to products of other relevant drug classes without these ingredients. The number of meningioma cases occurring at any time during treatment and in the six months prior to treatment discontinuation was reported.

Absolute standardised mean differences (aSMD) of each of the covariates assessed in objectives 2 to 5 were calculated for the pre-RMM and post-RMM periods to assess the impact of the intervention on the characteristics of drug users.

For objective 6, the impact of the restrictions on use of NOMAC or CMA at population-level was estimated using an interrupted time series analysis and was informed by results obtained as part of objective 1. For NOMAC, the intervention implemented in October 2018 was also assessed.

All analyses were conducted overall and stratified by covariates of interest (see “Covariates for stratifications”).

Results

Population-level DUS – Incidence & Prevalence (Objective 1)

Incidence per 100,000 PY of NOMAC prescribing was 22 (21 to 22) in IQVIA DA Germany, 359 (349 to 369) in IQVIA LPD Belgium, and 13 (12 to 13) in NAJS. Corresponding figures for CMA (in the same order and units) were 162 (161 to 163), 130 (124 to 136), and 96 (95 to 98). In general, prescribing incidence rates for both NOMAC and CMA were higher for non-HRT use (defined as women aged 10 to 49 years), especially among women aged 18–34 years. Records of high-dose products were only observed for NOMAC in IQVIA LPD Belgium (incidence per 100,000 PY: 180 [173 to 187]). Regarding period prevalence, less than 1.5% of women had exposure to NOMAC or CMA across databases during the study period. Stratified results were consistent with patterns observed for incidence rates.

Regarding other drugs of interest, progestogens and oestrogens in combination were prescribed with the highest incidence rates in IQVIA DA Germany and IQVIA LPD Belgium, while pregnadien derivatives were prescribed with the highest rates in NAJS.

Incidence and prevalence of prescribing during the pre-intervention period were higher or similar than those observed during the post-intervention period, without accounting for underlying trends. However, increases in incidence rates were observed in IQVIA LPD Belgium for all drug classes and progestogens studied (e.g., incidence per 100,000 PY; pre-intervention vs. post-intervention: 346 [336 to 357] vs. 461 (425 to 500) for NOMAC).

Patient-level DUS (Objective 2 to 5)

The study population for objectives 2, 4, and 5 included women newly prescribed NOMAC (n= 10,519 in IQVIA DA Germany; n= 4,078 in IQVIA LPD Belgium; n=1,918 in NAJS) and newly prescribed CMA (n= 61,275 in IQVIA DA Germany; n= 1,582 in IQVIA LPD Belgium; n=13,512 in NAJS). Median age at treatment start varied from 30–37 years for NOMAC and 23–30 years for CMA.

Average treatment duration for the first treatment episode ranged from 4.5 to 9 months. For NOMAC, cumulative dose per treatment episode was 492 mg in IQVIA DA Germany and 615 mg in IQVIA LPD Belgium. Corresponding figures for CMA were 267 mg and 28 mg. Most women were prescribed NOMAC as

a non-first-line treatment in IQVIA DA Germany (first-line vs. non-first-line: 38.9% vs. 61.1%), whereas the opposite pattern was observed in IQVIA LPD Belgium (68.3% vs. 31.7%, respectively). CMA was prescribed as a first-line treatment in approximately 58% of women in both databases. No differences by line of treatment were observed in NAJS. Discontinuation at 180 days occurred in >70% of women in IQVIA DA Germany and IQVIA LPD Belgium, and >55% of women in NAJS. Cases of meningioma during treatment were only observed for CMA in IQVIA DA Germany (n=8).

The study population for objective 3 included women exposed to any drug classes or progestogens of interest (n= 230,027 in IQVIA DA Germany; n= 35,123 in IQVIA LPD Belgium; n=234,919 in NAJS). Median age at treatment start ranged from 29 to 35 years. In this population, meningioma prior to index date was recorded in 370 women (n= 75 in IQVIA DA Germany; n= 6 in IQVIA LPD Belgium; n= 289 in NAJS). Pre-specified conditions related to gynaecological care with higher prevalence across databases were menstrual disorders and menopause/perimenopause. Pre-specified medications showed low prevalence (<2%) across databases, except for antidepressants (9.9% in IQVIA LPD Belgium; 5.8% in NAJS).

In general, aSMD did not suggest there were differences in prescribing treatments before and after the implementation of RMM (aSMD <0.2). However, a shorter treatment duration after the intervention was observed in IQVIA LPD Belgium for NOMAC (aSMD = 0.24; pre-RMM vs. post- RMM: 85 vs. 72 days) and CMA (aSMD = 0.33; pre-RMM vs. post- RMM: 117 vs. 71 days). Regarding treatment strategies, the number of switches among NOMAC users was lower during the post-intervention period in IQVIA DA Germany (aSMD = 0.32, pre-RMM vs. post-RMM: 16.0% vs. 6.2%) and NAJS (aSMD = 0.33, 23.6% vs. 11.3%). The opposite pattern was observed for discontinuation in IQVIA DA Germany (aSMD = 0.36, pre-RMM vs. post-RMM: 72.6% vs. 87.0%). In terms of patient-level characterisation, some differences were seen for conditions identified through large-scale characteristics in NAJS, representing <0.1% of the conditions assessed.

Analyses of RMM Effectiveness at population-level (Objective 6)

The impact of the intervention implemented in 2022 on trends of incidence of NOMAC and CMA prescribing among women aged ≥10 years differed across ingredients and databases.

Regarding NOMAC, a significant negative step change was observed in NAJS (-45.4% [-63.2 to -19]). In contrast, no significant step change was observed in IQVIA DA Germany (-9.4% [95% CI: -28.7 to 15.3]) or in IQVIA LPD Belgium (19.3% [-7.3 to 3.4]). No significant post-intervention slope changes (i.e., per one-month time unit) were observed for NOMAC in all three databases, compared to what would have been expected had the intervention not occurred. Results for high-dose products (available in IQVIA LPD Belgium only) were similar to those observed for low-dose products, with the step and slope changes estimated at 28.3% (95% CI: -5.5 to 74.4) and 0% (95% CI: -4 to 4.2), respectively. Regarding CMA, a significant negative step change was observed in IQVIA LPD Belgium (-35.5% [-56.2 to -4.9]) and NAJS (-24.9% [-41.4 to -3.7]), with a non-significant reduction in IQVIA DA Germany (-9.1% [-19.5 to 2.8]). No significant post-intervention slope changes were observed for CMA, except for a marginally significant change in NAJS (2.4% [0.7 to 4.1]).

The intervention implemented in 2018 (on NOMAC only) was associated with a significant negative step change in IQVIA DA Germany (-28.6% [-46 to -5.7]). This was followed by a positive and marginally statistically significant slope change of 2.5% (0.9 to 4.2). A decrease in incidence rates was observed 3–4 months after the intervention (i.e. May - August 2019). In IQVIA LPD Belgium, non-significant step and slope changes were estimated (-7.5% [-26.9 to 17.2] and -0.2% [-1.6 to 1.2], respectively). Results for NAJS were not provided as the assumption for linearity did not hold.

Discussion

Findings suggested that women had similar characteristics and prescribing treatments between users of drug classes or progestogens of interest before and after the implementation of RMM. However, modest changes were detected in some databases in terms of treatment duration, switches, and discontinuations.

Cumulative doses observed in this study were lower than expected and should be interpreted with caution due to discrepancies in the mapping of some drug records. However, these were non-differential over time and are not expected to affect the comparison between time periods.

The impact of the 2022 intervention on trends in the incidence of NOMAC and CMA prescribing varied across ingredients and databases. The intervention was associated with an immediate decrease in NOMAC prescribing in NAJS, and in CMA prescribing in both IQVIA LPD Belgium and NAJS. In NAJS, a significant positive change in the slope of CMA prescribing was also observed. Results for high-dose products (available in IQVIA LPD Belgium only) were similar to those observed for low-dose products. The 2018 intervention for NOMAC, assessed in IQVIA databases only, suggested statistically significant reductions in incidence rates at the time of implementation, as well as significant positive slope changes thereafter in IQVIA DA Germany.

Overall, we did not observe substantial changes in patient characteristics or NOMAC and CMA prescribing following the RMM assessed in this study. This may be attributed to the predominance of low-dose exposures, whereas the measures introduced in 2022 mostly targeted high-dose products. Future studies should prioritise the inclusion of databases from countries were high-dose products are authorised and use appropriate control series to minimise the risk of historical bias.

4. LIST OF ABBREVIATIONS

Acronyms/terms	Description
ACF	Autocorrelation Function
AIC	Akaike Information Criterion
aSMD	Absolute Standardised Mean Differences
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
DUS	Drug Utilisation Study
EHR	Electronic Health Records
EMA	European Medicines Agency
EU	European Union
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
LHR	Likelihood ratio
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
PACF	Partial Autocorrelation Function
PRAC	Pharmacovigilance Risk Assessment Committee
RR	Risk Ratios
RMM	Risk Minimisation Measures
SMD	Standardised Mean Differences
SNDS	Système National des Données de Santé

SNOMED	Systematised Nomenclature of Medicine
WHO	World Health Organisation

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Study deliverable	Timelines (planned)	Timelines (actual)
Final Study Protocol	January 2025	23rd January 2025
Creation of Analytical code	February 2025	February – May 2025
Execution of Analytical Code on the data	March/April 2025	March – May 2025
Draft Study Report	May 2025	5th June 2025
Final Study Report	May 2025	15th July 2025
Draft Manuscript (if agreed on)	September 2025	-
Final Manuscript (if agreed on)	October 2025	-

7. 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.(2-6) According to the first epidemiological studies conducted in France, the hazard ratio (HR) of intracranial meningioma adjusted for age among women exposed to NOMAC and CMA was estimated at 4.5 (95% CI 3.5–5.7) and 4.4 (3.4–5.8), respectively.(5, 6) Prolonged exposure to progestogens other than NOMAC such as cyproterone acetate (7) and medroxyprogesterone acetate (8) 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.(9) The initial review was requested by the French medicines agency following new data at the time from two epidemiological studies conducted in France.(5, 6) 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 advised updating the summary of product characteristics for products containing these progestogens 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 patients are diagnosed with meningioma.(10) 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.(9) Following this decision, a direct healthcare professional communication (DHPC) was sent to prescribers (8th November 2022) 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 was 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 was 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.

8. RESEARCH QUESTION AND OBJECTIVES

The overall aim of the study was 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 were also described.

The specific objectives were:

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.

Objectives 1 and 3 were assessed for all relevant drug classes. These included progestogen and oestrogen combination products, progestogens that are pregnadien derivatives, and medroxyprogesterone-containing products.

Objectives 2 and 6 focused on products containing NOMAC or CMA. Objectives 4 and 5 focused on these two compounds but considered 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 and progestogens 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 were 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 would decrease after the implementation of restrictions. Objective 3: The number of new users of NOMAC or CMA would be reduced after the implementation of restrictions. Objective 4: The number of users initiating NOMAC or CMA as first-line treatment would be reduced after the implementation of restrictions. Objective 5: The number of switches and discontinuations from NOMAC or CMA to other drug classes would increase after the implementation of restrictions. Objective 6: The incidence of NOMAC or CMA would be reduced after the implementation of restrictions, especially for high-dose products. This reduction would not be observed for other drug classes of interest.

9. RESEARCH METHODS

9.1. Study type and study design

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

1. A population-level drug utilisation study (DUS) to assess incidence/prevalence of drug classes and progestogens of interest (objective 1).
2. 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)
3. A trend analyses and RMM effectiveness to assess changes in:
    a. Patient-level analyses (objectives 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	New drug/s user cohort	Off the shelf
Trend analyses and RMM effectiveness	Population-level cohort and New drug user cohort	Complex

9.2. Study setting and data sources

This study was 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 considered fit for purpose were:

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 used 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[6]
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	EHR	4.48M	16.8k	173.9k	30-09-2024
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	EHR	196k	6.7k	2.4k	30-09-2024
Croatia	NAJS	Suitable denominator population for population-level rates.	Primary care, hospital care (IP, OP)	Registry	4.3 M	1.9k	15.3k	30-01-2025

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[6]
		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.						

[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 of available data.
[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 acetate; CMA = Chlormadinone acetate.
[6] Based on latest observation end date.

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), Belgium

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 September 2014 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.

9.3. Study period

Databases provided data from 1st of January 2010 (or from the start of available data, if later) to end of data availability. IQVIA LPD provided data starting from 2015 and NAJS from 2017 onward.

9.4. Follow-up

For the population-level DUS (objective 1), study participants in the denominator population started 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 turned 10 years old, 3) date at which they had a year of prior history recorded. Participants stopped 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 ended (e.g., loss to follow-up, death).

For the patient-level DUS (objectives 2 to 5), participants were 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 ended (e.g., loss to follow-up, death), or 180 days after ending treatment (objective 5). For objectives 2, 4, and 5, index date was defined as the date of the first-ever prescription of NOMAC or CMA. For objective 3, this was defined as the date of the first-ever prescription of any of the drug classes or progestogens of interest (see **9.6.2. Outcomes**).

For objective 4, line of treatment was 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 was 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 or progestogen of interest was assessed separately, with the washout window specific to the drug class being studied (e.g., when studying NOMAC, the washout window was applied with respect to this substance only). For objective 3, the washout was 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[4]	Incident with respect to…
General population (objectives 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 (objectives 2, 4 and 5)	Date of prescription	Single entry	Incident	[-Inf, -1]	IP, OP	RxNorm	NOMAC
New users of CMA (objectives 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 (objectives 1 and 6) was 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 turned 10 years old, 3) date at which they had 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 were identified based on the vocabulary hierarchy, with codes of ingredients or clinical drug forms being ancestors.

9.5. Study population with in and exclusion criteria

The source population comprised all females aged 10 or older 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 were required to have at least 365 days of data visibility prior to index date.

For patient-level DUS, the study population was additionally restricted to new medicine users (see **9.6. Variables** for further details). For objectives 2, 4, and 5, these were restricted to participants newly prescribed with NOMAC or CMA. For objective 3, these were all drug classes and progestogens of interest. A list of concepts for meningioma can be found in **Appendix I**.

Further information on exposures can be found in **9.6.1. Exposures**. The operational definitions of the inclusion and exclusion criteria are presented in **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 were excluded	Before	[-365, -1]	IP, OP	N/A	N/A	General population (objectives 1 and 6)
Prior database history	Study participants with less than 365 days of prior history observed at index date were excluded	After	[-365, -1]	IP, OP	N/A	N/A	All except general population (objectives 1 and 6)
Prior use of NOMAC	Individuals with prior prescriptions of NOMAC were excluded	After	[-Inf, -1]	IP, OP	N/A	N/A	New users of NOMAC (objectives 2, 4 and 5)
Prior use of CMA	Individuals with prior prescriptions of CMA were excluded	After	[-Inf, -1]	IP, OP	N/A	N/A	New users of CMA (objectives 2, 4 and 5)
Prior use of drug classes of interest (any)	Individuals with prior prescriptions of any of the drug classes or progestogens of interest were 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).

9.6. Variables

Drug classes of interest were identified based on Anatomical Therapeutic Chemical (ATC) codes, and included:

- Progestogens and oestrogens combinations
- Progestogens that are pregnadien derivatives

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

- Medroxyprogesterone
- NOMAC
- CMA

Progestogens of interest were identified using ingredient-level codes (all descendants included). Drug classes of interest were identified based on corresponding clinical drug forms (all descendants included). For all drug classes and progestogens studied, we used a 90-day gap to combine individual drug exposures (e.g., prescriptions) into drug eras (e.g., treatment episodes). A list of codes can be found in **Appendix I**.

9.6.1. Exposures

Exposures were considered for patient-level DUS (objectives 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 derivatives, medroxyprogesterone, NOMAC and CMA.
- NOMAC (objectives 2, 4, and 5)
- CMA (objectives 2, 4, and 5)

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

9.6.2. Outcomes

Outcomes were considered for the population-level DUS (objective 1) and consisted of the 2 drug classes and 3 progestogens of interest described in **9.6. Variables**. They were also 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 was also considered as an outcome for objective 5.

The operational definition of the outcomes is presented in **Table 8**. Concepts used to identify exposures are detailed in **Appendix I**.

Table 7. Operational definitions of exposures.

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.	[-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.	[-Inf, -1]	0	IP, OP	RxNorm	New users of NOMAC (objectives 2, 4, and 5) New users of CMA (objectives 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 (objectives 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 were identified based on the vocabulary hierarchy, with codes of ingredients or clinical drug forms 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 oestrogen combination products	For incidence/prevalence calculations (objective 1).	Yes	Count	[-365, -1]	IP, OP	RxNorm	General population (objectives 1 and 6)
Progestogens that are pregnadien derivatives	For incidence/prevalence calculations (objective 1).	Yes	Count	[-365, -1]	IP, OP	RxNorm	General population (objectives 1 and 6)
Medroxyprogesterone	For incidence/prevalence calculations (objective 1).	Yes	Count	[-365, -1]	IP, OP	RxNorm	General population (objectives 1 and 6)
NOMAC	For incidence/prevalence calculations (objectives 1 and 6).	Yes	Count	[-365, -1]	IP, OP	RxNorm	General population (objectives 1 and 6)
CMA	For incidence/prevalence calculations (objectives 1 and 6).	Yes	Count	[-365, -1]	IP, OP	RxNorm	General population (objectives 1 and 6)
Progestogen and oestrogen combination products not containing NOMAC or CMA	To assess line of treatment and switches to alternative treatments (objectives 4 and 5).	Yes	Binary	N/A	IP, OP	RxNorm	New users of NOMAC or CMA (objectives 2, 4, and 5)
Progestogens that are pregnadien derivatives not containing NOMAC or CMA	To assess line of treatment and switches to alternative treatments (objectives 4 and 5).	Yes	Binary	N/A	IP, OP	RxNorm	New users of NOMAC or CMA (objectives 2, 4, and 5)
Meningioma	Diagnosis of meningioma	Yes	Binary	[-Inf,-1]	IP, OP	SNOMED	New users of NOMAC or CMA (objectives 2, 4, and 5)

[1] NOMAC = nomegestrol, CMA = chlormadinone
[2] For outcomes relative to objectives 1 and 6, the washout window was applied for incidence calculations only

9.6.3. 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 **14.2 Limitations of the research methods** for further details).

Regarding the restrictions implemented in 2022, a transition period of three months (November 2022 to January 2023) was considered to reflect the period during which the intervention was being implemented. This transition period was applied to all pre- and post-intervention comparisons. For objectives 1 to 5, treatments initiated during this period were 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 for this period were excluded.

Covariates for stratification:

Covariates for stratification varied across objectives and included:

- Age group:

  10–17, 18–34, 35–49, 50–64, +65 years.

- Indication:

  Non-HRT vs. HRT. Indication was 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 included amounts from 3.75mg to 5mg. For CMA, high doses included amounts from 5mg to 10mg. Low doses were any amounts less than those specified.

- WHO 5th ATC level codes:

  For NOMAC or CMA only, if counts allow. For NOMAC codes included were: G03AA14, G03DB04, G03FB12. For CMA, codes included were: 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 were assessed separately (**9.6. Variables**).Covariates for stratification included:

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

Objective 2:

NOMAC and CMA were assessed separately. Covariates for stratification included:

- Indication
- Time period

Objective 3:

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

- Time period

Objective 4:

NOMAC and CMA were assessed separately. Covariates for stratification included:

- Dose
- Indication
- Time period

Objective 5:

NOMAC and CMA were assessed separately. Covariates for stratification were:

- WHO 5th ATC level codes
- Time period

Objective 6:

NOMAC and CMA were assessed separately. Covariates for stratification included:

- Dose
- Indication

Please see **14.2. Limitations of the research methods** for important information on these covariates.

Covariates for Objective 3 (characterisation):

For objective 3, pre-specified comorbidities and comedications were reported. Pre-specified comorbidities included meningioma and conditions that may modify its risk.(11, 12) Potential indications of these drug classes of interest were also 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 (13, 14)
- Type 2 diabetes (15)
- Autoimmune diseases (16, 17)

- Asthma (16-18)
- Epilepsy (16)
- Uterine fibroids (12)

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 consisted of the drug classes of interest included in this study.

Medications of interest:

Drug classes and progestogens of interest:

- Progestogen and oestrogen combination products not including NOMAC or CMA.
- Progestogens that are pregnadien derivatives 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, spironolactone, cyproterone acetate)

A list of concepts to identify pre-specified comorbidities and comedications is detailed in **Appendix I**. Comorbidities were 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 were 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 **Table 9**.

Table 9. Operational definition 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 (objectives 1 and 6)
Dose (NOMAC and CMA)	High vs. low doses. For NOMAC, high doses included amounts from 3.75mg to 5mg. For CMA, high doses included amounts from 5mg to 10mg. Low doses were any amounts less than those specified.	Categorical	0	IP, OP	N/A	N/A	General population (objectives 1 and 6)
Indication	Non-HRT vs. HRT. Age was 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 (objectives 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 included: meningioma, obesity, type 2 diabetes, 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 included: progestogen and oestrogen combination products not containing NOMAC or CMA, progestogens that are pregnadien derivatives not containing NOMAC or CMA, NOMAC, CMA, medroxyprogesterone, antidepressants, metformin, bisphosphonates, clonidine, gonadotropin releasing hormone antagonists and anti-androgens.

9.7. Study size

Based on the feasibility assessment, the expected number of exposed patients was estimated to be approximately between 1,900 in NAJS and 16,800 in IQVIA DA Germany for NOMAC, and between 2,4004 in IQVIA LPD Belgium and 173,900 in IQVIA DA Germany for CMA.

No specific sample size calculations were performed. Given that meningioma is a rare tumour, we expected to have limited sample size in objective 1, when restricting the population to individuals with prior history of meningioma. For objectives 3, 4, and 5, we expected an adequately large sample size to estimate Standardised Mean Differences (SMD). For objective 2, this was expected to be more limited as we only considered 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.(19) 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.(20) Unbalanced designs (i.e. unequal number of time points before and after the intervention) have been found to have less power than balanced designs.(19, 20) As the intervention is located at the end of the time series, we restricted the pre-intervention period to balance the number of observations for objective 6 and to ensure a more recent contrafactual for comparison (see **9.9.2. Main statistical methods**).

9.8. Data transformation

Analyses were conducted separately for each database. Before study initiation, test runs of the analytics were performed and quality control checks were performed. After all the tests were passed (see **11. Quality Control**), the final package was released in the version-controlled Study Repository for execution against all the participating data sources.

The data partners locally executed the analytics against the OMOP CDM in R Studio and reviewed and approved the by default aggregated results before returning them to the Coordination Centre. Sometimes multiple execution iterations were performed, and additional fine tuning of the code base was needed. The study results of all data sources were checked after which they were made available to the team and the Dissemination Phase started. All results were locked and timestamped for reproducibility and transparency.

9.9. Statistical methods

9.9.1. Main summary measures

Main measures used were counts, proportions, mean, median, standard deviation, interquartile range, incidence rates, prevalence proportions, and risk ratios (RR).

9.9.2. Main statistical methods

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

Table 10. Description of study types and types 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 - Measures of patient-level DUS (descriptives of treatment duration)

Objective 1:

Monthly incidence rates with 95% CI were 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 was treated as a separate outcome (see **9.6.2. Outcomes** for more information).

A washout window of 365 days was applied after each treatment episode. Therefore, participants with an outcome record did not contribute time to the study during the 365 days following the end of each treatment episode. Participants were able to re-enter the study after the washout window had passed. This washout was applied for each outcome separately and was specific to the drug class or progestogen of interest being under study. Please note that a treatment episode could consist of several consecutive prescriptions (see **9.6. Variables** for more information).

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

Objective 1 was only 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 was considered). In IQVIA DA Germany and IQVIA LPD Belgium, the study period was restricted up to 31st December 2023 (see **9.10. Deviations from protocol**).

Results were 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 was 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 were included, irrespective of the time elapsed since their diagnosis, and contributed time to the analysis from the date of diagnosis.

Objective 2:

Treatment duration was reported for the first prescribed treatment. Duration was derived from the start and end of the first treatment episode (i.e., drug era). Cumulative dose was calculated considering all treatments containing NOMAC or CMA recorded during the study period, and was calculated in IQVIA DA Germany and IQVIA LPD Belgium only (see **9.10. Deviations from protocol**). If two eras with different doses were separated by less than 90 days, the time between the two was considered as exposed by the first era (**Figure 1**, first row). If two eras started at the same date, the overlapping period was 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 were 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 spanned from October 2021 to September 2022, the year preceding the request for PRAC to review current evidence on NOMAC and CMA. The post-intervention period for comparison spanned from February 2023 to January 2024. For databases with less available data (see **Table 3**), the comparison was limited to 6 months (post-intervention: February to July 2023; pre-intervention: February to July 2022). Time periods for comparison covered the same calendar months to avoid any differences arising from seasonality.

NOMAC and CMA were assessed separately. Results were reported overall and stratified by study period (pre- vs. postintervention) and indication at first use (non-HRT vs. HRT). Cumulative dose was not assessed in NAJS.

Objective 3:

Characteristics were described by database using pre-specified conditions and medications and by means of large-scale characterisation. The number of patients initiating high- or low-doses of NOMAC and CMA (assessed separately) and the number of years since meningioma diagnosis were also described. Characterisation results were reported within specific time windows (see **9.6.3. Other covariates**).To facilitate the reporting of the large-scale characterisation results, only the top 10 conditions and the top 10 medications are described in the report.

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

Objective 4:

For each participant initiating treatment with NOMAC or CMA, we retrospectively assessed the occurrence of records indicating the use of other drug classes of interest not containing NOMAC or CMA. This assessment was 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 described the order in which treatments of interest were prescribed, as first vs. non-first treatments.

NOMAC and CMA were assessed separately. Results were 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 were assessed at index date (i.e., date of treatment initiation with NOMAC or CMA). Please see **14.2. Limitations of the research methods** for more information.

Objective 5:

We described the number and proportion of patients who followed different treatment strategies in the 180 days following the end of treatment. These strategies were 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 were considered. The proportion of individuals following each treatment strategy (e.g., switching) was 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 treatment started.

Figure 2 illustrates some of these scenarios.

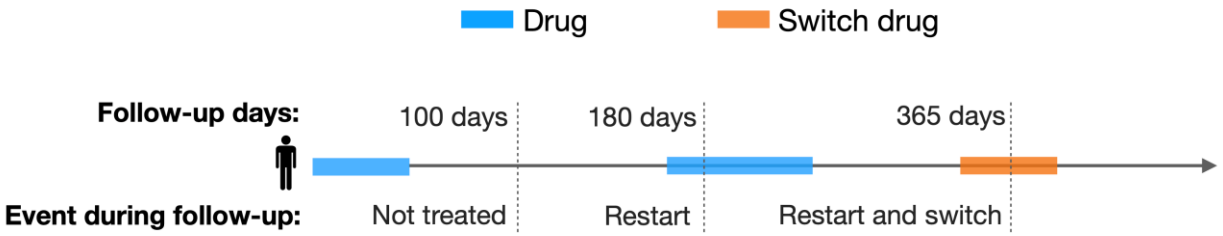

Figure 2. Outcomes after the drug exposure of interest (in blue) over different time periods.

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 was also reported. For cases identified in the six months prior, we reported the treatment strategy followed after treatment (i.e., restart, switch, both, or discontinuation).

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

Objective 25:

For objectives 2 to 5, SMD of each covariate were calculated to compare drug users in the pre-RMM and post-RMM periods, serving as a measure of the RMM's impact on the profile of drug users. These covariates included: duration and cumulative dose (objective 2), patient characteristics (objective 3) and line of treatment (objective 4). For patient characteristics, only conditions were compared, with the assessment window set as any time prior to 1 day before index date. For objective 5, covariates included the proportion of patients diagnosed with meningioma during treatment, and the proportion of patients who discontinued or switched to alternative treatments (assessed separately). To aid interpretation, absolute SMD (aSMD) were reported.

Objective 6:

The impact of the restrictions of use was estimated using an ITS. This analysis was restricted to NOMAC and CMA (assessed separately) and was informed by results of objective 1 (main analysis without the meningioma restriction). For NOMAC, the intervention that took place in 2018 was also assessed.

Time series was assessed using segmented regression. Monthly incident counts of patients prescribed with NOMAC or CMA were modelled using a Poisson regression model, using the number of person-years as an offset variable to convert the outcome into a rate and to adjust any potential changes in the population over time.(21) We assessed the assumption of the Poisson distribution (i.e., that the variance equals the expected count) by examining the dispersion parameter (i.e., residual deviance divided by the number of degrees of freedom). We used Poisson when the dispersion parameter was similar to 1. If higher, we used negative binomial models to account for overdispersion.

The assumption of linearity (i.e., the underlying trend is well approximated by a linear term of time) was assessed by adding a non-linear term to the model. We compared both models (with and without the non-linear term) by visually inspecting the data and residuals, as well as through statistical goodness-of-fit tests (the Pearson test).(22, 23) The likelihood ratio (LHR) and the Akaike Information Criterion (AIC) were used to compare models with and without non-linear terms.(22, 23) To allow for a nonlinear relationship, we added a restricted cubic spline transformation of time using 2 interior knots and 2 boundary knots.(24) Autocorrelation was assessed by examining the plot of residuals and the partial autocorrelation function and conducting statistical tests where possible. Seasonality was assessed by visual inspection of the time series and residuals, and was controlled for by including a Fourier term consisting of a sine/cosine pair in the model.(25) AIC values were also considered to assess whether adjustment for seasonality was needed. We did not report results when trends were non-linear or when residual autocorrelation was present, due to the complexity of predicting the counterfactual and isolating the effects of the intervention.(21)

The impact model of the intervention (i.e., how we expected the intervention to have impacted the outcome) was anticipated to show an abrupt change in the level and a gradual change in the gradient of the trend (step and slope change). **Figure 3** illustrates the ITS with a level and slope change model.

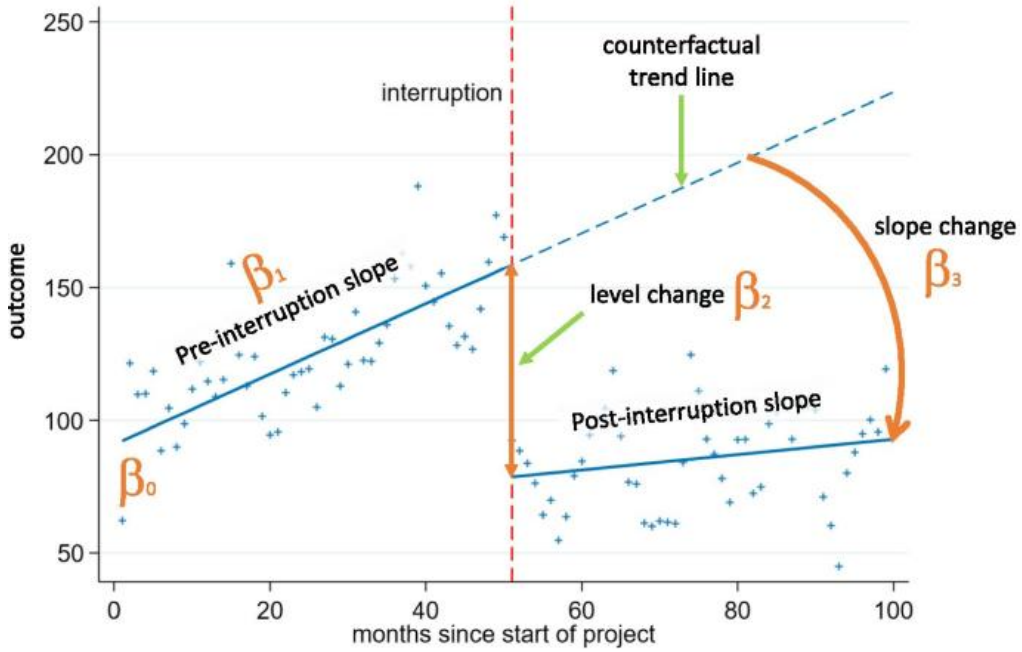

Figure 3. Graphical depiction of a segmented linear regression model with a level and slope change.

Reproduced from BMC Med Res Methodol. 2021;21(1):134, doi: 10.1186/s12874-021-01306-w.

The key variables for an ITS analysis with a slope and step change have been described elsewhere,(26) and include:

- t : the time elapsed since the start of the study, measured in units that correspond to the frequency of observations (e.g., monthly or yearly), with the interruption occurring at time T_I.
- Y_t : the outcome at time point t.
- X_t : dummy variable indicating the pre-RMM period (coded as 0) or the post-RMM period (coded as 1).
- ε_t : error term to allow for deviation from the fitted model.

$$Y_t = \beta_0 + \beta_1 t + \beta_2 X_t + \beta_3 [t - T_I] X_t + \varepsilon_t$$

Equation 1. Segmented linear regression model with a level and slope change.

In **Equation 1**, β are the model parameters representing the baseline intercept at T= 0 (β_0), the pre-interruption slope (β_1); the level change following the intervention (β_2) and the slope change following the intervention (β_3). The impact of the intervention considering both step and slope change can be estimated at a given time point (p), as: $\beta_2 + \beta_3 [p - T_I]$.

The effect size of the intervention was estimated using RR. The amount of pre-intervention data to include for this analysis was 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 was 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, we used data from 1st January 2021 onwards. For NOMAC, the intervention adopted in 2018 was assessed using data from 1st January 2017 onwards.

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

All objectives:

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

A summary of the analysis specification is described in **Table 11**.

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 would be lower after the implementation of restrictions. Objective 3: The number of new users of NOMAC or CMA with prior history of meningioma would be reduced after the implementation of restrictions. Objective 4: The number of users initiating NOMAC or CMA as first-line treatment would be reduced after the implementation of restrictions. Objective 5: The number of discontinuations and switches from NOMAC or CMA to other drug classes would increase after the implementation of restrictions. Objective 6: The incidence of NOMAC or CMA would be reduced after the implementation of restrictions, especially for high-dose products. This reduction would 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) Objectives 3 to 6: Pre-intervention vs. Post-intervention
Outcome:	Objective 1: Incidence rates and prevalence of drug classes and progestogens 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 were assessed separately.
Analytic software:	R
Model(s):	Objective 1: Not applicable, descriptive analysis. Objectives 2 to 5: Standardised mean differences. Objective 6: Segmented regression.
Confounding adjustment method	
	Stratification.
Missing data methods	
	The absence of a record for a condition or medication was 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 was 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.

9.9.3. Missing values

All missing values were assumed to occur at random. For incidence and prevalence calculations, individuals with missing part of their follow-up were censored at the time of follow-up or end of data availability, and the reported figures assumed that censoring occurred at random.

9.9.4. Sensitivity analysis

Not applicable.

9.10. Deviations from protocol

Since the last publication of the protocol, this has been amended to incorporate the following changes:

1. **Study Period Modification**
   The study period for IQVIA LDP Belgium was initially described as beginning in 2012, but was modified to start in September 2014, based on the start date of data availability of this database (i.e., September 2015 considering the 365 days prior history requirement). Since approving the protocol, data partners have provided new data releases with more follow-up data. This information has been updated in **Table 3**.

   For both IQVIA DA Germany and IQVIA LPD Belgium, the final months of available data were excluded from analyses requiring a population denominator only (i.e., incidence and prevalence calculations for objectives 1 and 6). Although the protocol specified excluding the last 6 months of data to prevent capturing artefactual increases in incidence and prevalence estimates, results from the initial execution showed that the artefactual increase extended beyond this six-month window. This led to restricting the data to 31st December 2023. Please refer to **14.2. Limitations of the research methods** for further details.

2. **Drug records**
   Drug records in NAJS were initially mapped at ingredient level (e.g., “Chlormadinone”), without additional data such as dosage or clinical drug form. NAJS updated the mapping of drugs during the conduction of the study, mapping most drug records at clinical drug box level (e.g., “Chlormadinone 2 MG and Ethinyl Estradiol 0.03 MG Oral Tablet, Box of 21”). This allowed for a more granular and accurate analysis of the data. However, lower daily doses of drugs were detected during the onboarding process and are now being investigated, as it is likely related on how data on quantity and box sizes are mapped and analysed in the current analytical pipelines. Consequently, cumulative dose (objective 2) was not assessed in this database. Stratification by dose was possible, as dose was identified based on the name of the concept id (e.g., 2 mg for CMA in the prior example).

We have clarified that treatment duration was assessed based on the start and end dates of the first treatment episode instead of the first individual prescription, as described in the protocol (see **9.9.2 Main statistical methods**). Based on insights on drug exposures duration gained through *DrugExposureDiagnostics*, we used a 90-day gap to combine individual drug exposures (i.e., prescriptions) into drug eras (i.e., treatment episodes). This gap was specified in **9.6. Variables** and was consistently applied across databases. No additional procedure was used in NAJS to infer treatment duration.

3. **Identification of drug classes and progestogens of interest**
Progestogens of interest (NOMAC, CMA and medroxyprogesterone) were identified at the ingredient level. It was not possible to restrict medroxyprogesterone records to non-oncological use only. Drug classes of interest (progestogens and oestrogens in combination; progestogens that are pregnadien derivatives) were identified using clinical drug forms corresponding to WHO ATC 4th-level codes of interest. Stratification by WHO ATC 5th-level codes for NOMAC and CMA (applicable for objectives 1 and 5) was also attempted using clinical drug forms. However, not all 5th-level codes could be assessed separately. Therefore, these were grouped into two categories per progestogen, as it was not possible to distinguish between fixed combinations of progestogens and oestrogens (G03AA) and sequential preparations (G03FB). For NOMAC, G03AA14, and G03FB12 were grouped together, and similarly, G03AA15, G03AB07, and G03FB03 were combined into a single group for CMA. WHO ATC 5th-level codes corresponding to pregnadien derivatives (G03DB) were described separately (NOMAC: G03DB04; CMA: G03DB06).

4. **Patient-level characteristics**

Diabetes mellitus was specified in the protocol as a pre-specified condition for patient-level characterisation. However, we have described the occurrence of type 2 diabetes in this report. The impact of this deviation is expected to be minimal, as previous estimates suggest that type 2 diabetes accounts for over 90% of all diabetes cases in high-income countries.(27)

5. **Methods for RMM Analyses**

We have expanded **9.9.2. Main statistical methods** to provide additional details on the analyses performed. These revisions enhance clarity and transparency but do not represent major deviations from the methodology outlined in the original protocol.

Regarding patient-level analyses, we have replaced SMD for aSMD for better interpretation. For population-level analyses, we now describe the equation used in the ITS model to aid reader understanding. Further elaboration has also been added regarding the methods used for modelling and testing the assumptions specified in the protocol, including the assumptions of the Poisson distribution and linearity (restricted cubic splines). We also specified the approach followed to adjust for seasonality (fitting Fourier terms in the model). In the protocol, we specified that quasi-Poisson models would be used instead of Poisson models to account for overdispersion if detected in the data, which was the case for some of the time series studied. The primary methodological change relative to the protocol is the use of negative binomial models in place of quasi-Poisson models. Both quasi-Poisson and negative binomial models provide the same estimates than the Poisson model, with the only difference being that standard errors and confidence intervals are inflated to account for overdispersion. The rationale for using negative binomial instead of quasi-Poisson models was to allow the calculation of the AIC and the use LHR tests for model comparison (see **12.7.1. Model Diagnostics** for more details).

10. 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 was written in R. Each data partner executed the study code against their database containing patient-level data and returned the results set which only contained aggregated data. The results from each of the contributing data sites were combined in tables and figures for the study report.

Data storage and protection

For this study, participants from various European Union member states processed 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 were run, which generated non-identifiable aggregate summary results.

11. 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 *DataQualityDashboard* 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 were developed and assessed using the following R packages: *CodelistGenerator*, *CohortDiagnostics* and *DrugExposureDiagnostics*. The study code was 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 included numerous automated unit tests to ensure the validity of the codes, alongside software peer review and user testing. For the ITS analysis, functions from several R packages were used: “MASS” and “stats” for fitting regression models, from “Epi” for exponentiating model parameters and from “splines” for incorporating natural splines.

12. RESULTS

All results are available in a web application ("Shiny App") at: https://data.darwin-eu.org/P3-C3-006-Meningioma/.

12.1. Participants

This section describes the number of participants participating in analysis performed at population-level (objective 1) and patient-level (objectives 2 to 5). Objective 6 was derived from aggregate results derived from objective 1.

12.1.1. Population-level DUS (Objective 1)

Objective 1 included data from 9,560,010 women in IQVIA DA Germany, 343,270 in IQVIA LPD Belgium, and 2,204,945 in NAJS. Details on attrition and the number of women contributing to the denominator population created for incidence and prevalence calculations (objective 1) are described by database in **Appendix II – Table 1**.

The subgroup analysis, limited to women with a prior history of meningioma, included 18,467 women in IQVIA DA Germany, 127 in IQVIA LPD Belgium, and 8,682 in NAJS. Details on attrition for the subgroup analysis are described in **Appendix II – Table 2**.

12.1.2. Patient-level DUS (Objective 2-5)

New-users of progestogens of interest

Table 12 includes information on the attrition and number of patients included for patient-level DUS (objectives 2, 4 and 5), which included data on first-ever users of NOMAC and CMA (assessed separately).

The cohort of women newly prescribed with NOMAC comprised 10,519 women in IQVIA DA Germany, 4,078 in IQVIA LPD Belgium, and 1,918 in NAJS. For CMA, corresponding numbers (in the same order) were 61,275, 1,582, and 13,512.

Table 12. Attrition of individuals included in the study population of Objectives 2, 4, and 5.

	IQVIA DA Germany		IQVIA LPD Belgium		NAJS	
	NOMAC	CMA	NOMAC	CMA	NOMAC	CMA
Initial qualifying events[1]	49,028	699,988	15,752	4,962	7,782	88,110
Collapse records separated by 90 or less days (assumed continuous use)	24,113	290,082	11,062	3,615	3,526	37,270
Require first cohort entry	17,357	175,491	6,598	2,363	1,938	16,633
Require cohort start date during the study period[2]	17,357	126,274	6,598	2,363	1,935	13,609
Require female	17,335	126,083	6,564	2,348	1,935	13,597
Require age ≥10 years	17,335	126,080	6,561	2,347	1,935	13,596
Require minimum prior observation of 365 days	10,519	61,275	4,078	1,582	1,918	13,512

[1] Number of records.
[2] Study period differed across databases and spanned from study start (or data availability start, if later) to end of data availability.

Table 13 and **Table 14** include demographic information of women included at the date of a first treatment with NOMAC or CMA, respectively, overall and stratified by study period. For NOMAC, median age at treatment initiation was approximately 30–37 years. For CMA, median age was 30 years in IQVIA DA Germany, and 23–24 years in IQVIA LPD Belgium and NAJS. Women aged 10 to 17 years represented <10% of new users except for CMA in IQVIA LPD Belgium, where 19.5% of new users were within this age group.

Women categorised as using treatment for non-HRT purposes, within the 10–49 age range used as a proxy, represented over 85% of new users of NOMAC or CMA. The highest proportion of HRT use (age ≥50) was found for CMA in IQVIA DA Germany (10.5%) and for NOMAC in IQVIA LPD Belgium (14.9%). The proportion of women aged ≥50 was particularly low in NAJS, representing <2% of new users.

Most identified participants initiated NOMAC or CMA during the pre-intervention period, with percentages of approximately 80–90%. Fewer than 5 women aged ≥50 years (i.e., HRT use) initiated NOMAC in NAJS and CMA in IQVIA LPD Belgium during the post-intervention period.

Table 13. Baseline characteristics of first-ever users of NOMAC, overall and stratified by study period.

			IQVIA DA Germany			IQVIA LPD Belgium			NAJS		
			Overall	Pre-RMM	Post-RMM	Overall	Pre-RMM	Post-RMM	Overall	Pre-RMM	Post-RMM
Subjects	-	N	10,519	9,522	837	4,078	3,311	647	1,918	1,701	200
Age	-	Median [Q25 - Q75]	32 [23-42]	32 [23-42]	30 [21 - 41]	37 [24-46]	37 [24 - 47]	34 [23 - 46]	34 [25 - 40]	34 [25 - 40]	31 [24 - 41]
		Mean (SD)	32.4 (10.8)	32.6 (10.7)	31.2 (11.2)	35.7 (12.7)	35.9 (12.6)	34.7 (12.9)	32.9 (9.1)	33.1 (8.9)	31.8 (10.1)
		Range	12 to 79	12 to 79	12 to 59	10 to 79	10 to 79	13 to 76	12 to 61	12 to 61	13 to 53
Age group	10 to 17	N (%)	699 (6.7%)	602 (6.3%)	76 (9.1%)	333 (8.2%)	269 (8.1%)	57 (8.8%)	55 (2.9%)	39 (2.3%)	16 (8.0%)
	18 to 34	N (%)	5,190 (49.3%)	4,707 (49.4%)	408 (48.7%)	1,517 (37.2%)	1,199 (36.2%)	267 (41.3%)	948 (49.4%)	836 (49.1%)	103 (51.5%)
	35 to 49	N (%)	4,108 (39.1%)	3,736 (39.2%)	315 (37.6%)	1,620 (39.7%)	1,352 (40.8%)	226 (34.9%)	890 (46.4%)	804 (47.3%)	78 (39.0%)
	50 to 64	N (%)	517 (4.9%)	472 (5.0%)	38 (4.5%)	584 (14.3%)	471 (14.2%)	94 (14.5%)	25 (1.3%)	22 (1.3%)	-
	> 65	N (%)	5 (0.05%)	5 (0.05%)	-	24 (0.6%)	20 (0.6%)	-	-	-	-
Indication	Non-HRT	N (%)	9,997 (95.0%)	9,045 (95.0%)	799 (95.5%)	3,470 (85.1%)	2,820 (85.2%)	550 (85.0%)	1,893 (98.7%)	1,679 (98.7%)	197 (98.5%)
	HRT	N (%)	522 (5.0%)	477 (5.0%)	38 (4.5%)	608 (14.9%)	491 (14.8%)	97 (15.0%)	25 (1.3%)	22 (1.3%)	-

[1] Study period spanned from study start (or data availability start, if later) to end of data availability. Pre-RMM: from start date to October 2022, Post-RMM: from February 2023 to study end. Women initiating treatment during the transition period (November 2022 to January 2023) were not included in results stratified by study period.

Table 14. Baseline characteristics of first-ever users of CMA, overall and stratified by study period.

			IQVIA DA Germany			IQVIA LPD Belgium			NAJS		
			Overall	Pre-RMM	Post-RMM	Overall	Pre-RMM	Post-RMM	Overall	Pre-RMM	Post-RMM
Subjects	-	N	61,275	56,335	4,146	1,582	1,306	235	13,512	10,955	2,308
Age	-	Median [Q25 - Q75]	30 [22-42]	30 [22-41]	35.5 [26-46]	23 [18-31]	23 [18 - 32]	22 [18 - 29.5]	24 [20 - 30]	24 [20 - 30]	24 [20 - 30]
		Mean (SD)	32.3 (12.1)	31.9 (12)	35.8 (12.1)	25.6 (9.2)	25.8 (9.4)	24.7 (8.8)	25.6 (7.3)	25.6 (7.2)	25.8 (7.5)
		Range	11 to 94	11 to 90	11 to 86	12 to 68	12 to 68	14 to 53	10 to 85	10 to 85	11 to 71
Age group	10 to 17	N (%)	5,206 (8.5%)	4,942 (8.8%)	221 (5.3%)	308 (19.5%)	250 (19.1%)	52 (22.1%)	958 (7.1%)	751 (6.9%)	182 (7.9%)
	18 to 34	N (%)	31,978 (52.2%)	29,953 (53.2%)	1,720 (41.5%)	996 (63.0%)	809 (61.9%)	156 (66.4%)	10,826 (80.1%)	8,816 (80.5%)	1,806 (78.2%)
	35 to 49	N (%)	17,675 (28.9%)	15,728 (27.9%)	1,615 (39.0%)	260 (16.4%)	232 (17.8%)	24 (10.2%)	1,665 (12.3%)	1,341 (12.2%)	305 (13.2%)
	50 to 64	N (%)	6,102 (10.0%)	5,426 (9.6%)	566 (13.7%)	17 (1.1%)	14 (1.1%)	-	50 (0.4%)	36 (0.3%)	13 (0.6%)
	>65	N (%)	314 (0.5%)	286 (0.5%)	24 (0.6%)	-	-	-	13 (0.1%)	11 (0.1%)	-
Indication	Non-HRT	N (%)	54,859 (89.5%)	50,623 (89.9%)	3,556 (85.8%)	1,564 (98.9%)	1,291 (98.9%)	232 (98.7%)	13,449 (99.5%)	10,908 (99.6%)	2,293 (99.4%)
	HRT	N (%)	6,416 (10.5%)	5,712 (10.1%)	590 (14.2%)	18 (1.1%)	15 (1.1%)	-	63 (0.5%)	47 (0.4%)	15 (0.6%)

[1] Study period spanned from study start (or data availability start, if later) to end of data availability. In IQVIA DA Germany and IQVIA LPD Belgium, follow up ended on 31st December 2023. Pre-RMM: from start date to October 2022, Post-RMM: from February 2023 to study end. Women initiating treatment during the transition period (November 2022 to January 2023) were not included in results stratified by study period.

New-users of any of the drug classes or progestogens of interest

Objective 3 included data on women initiating any of the drug classes or progestogens of interest (i.e., progestogens and oestrogens combinations, pregnadien derivatives, NOMAC, CMA, or medroxyprogesterone). This objective included data from 230,027 women in IQVIA DA Germany, 35,123 in IQVIA LPD Belgium, and 234,919 in NAJS). Median age at treatment initiation was 31 [Q25–Q75: 21–42] in IQVIA DA Germany, 29 [19–41] in IQVIA LPD Belgium, and 35 [25–45] in NAJS. Between 45–50% of women were aged between 18 and 34 years old at the time of treatment initiation, with 86–88% considered to be indicated for non-HRT purposes.

Details on their attrition and further information on demographics for this population stratified by study period can be explored in **Appendix II – Table 3** and **Appendix II – Table 4**. Information on the number of people initiating each of the drug classes or progestogens of interest can be found in **12.4. Patient-level characterisation (Objective 3)**.

12.2. Population-level DUS (Objective 1)

In this section, we present incidence rates and prevalence of drug classes and progestogens of interest, overall and stratified by covariates of interest. Results stratified by study period are presented in **12.2.2. Pre- and post-RMM comparison**. This section describes pre- and post-RMM estimates without considering underlying trends and does not represent a formal analysis of the impact of the RMM, which is assessed in Objective 6. Section **12.2.3. Subgroup analysis** includes results derived from restricting the study population to participants with prior history with meningioma.

12.2.1. Main results

Incidence

Trends in incidence rates of drug classes and progestogens of interest are shown in **Figure 4**. For visualisation purposes, this figure only includes results for June of each calendar year. Results across all calendar months can be explored in the "Shiny App". Overall findings described in **Table 15**, with additional details in **Appendix II – Table 5**.

Incidence per 100,000 PY of NOMAC was 22 (95%CI 21 to 22) in IQVIA DA Germany, 359 (349 to 369) in IQVIA LPD Belgium, and 13 (12 to 13) in NAJS. Corresponding figures for CMA (in the same order and units) were 162 (161 to 163), 130 (124 to 136), and 96 (95 to 98). Incidence of CMA was higher than that observed for NOMAC across databases except for IQVIA LPD Belgium, where incidence of NOMAC exceeded that observed for CMA and obtained higher figures than that observed for other databases (**Figure 4**). In general, incidence rates were higher among women aged 18–34 years, followed by women aged 10-17 or 35–49 years (**Appendix II – Figure 1**). In general, women aged 18–34 years obtained the highest rates across drug classes studied. In NAJS, women aged 35–49 obtained the highest rates of medroxyprogesterone (776 [95%CI 767 to 786]), followed by those aged 50–64 (341 per 100,000 PY [334 to 347]).

Incidence rates stratified by indication, which was assessed using age as a proxy (non-HRT: 10–49 years; HRT: >50 years), were higher for non-HRT than HRT (**Appendix II – Figure 2**). Incidence rates of NOMAC and CMA for HRT use was approximately 0 or had <5 incident events, except for NOMAC in IQVIA LPD Belgium (112 per 100,000 PY [104 to 120]) and CMA in IQVIA DA Germany (26 per 100,000 PY [25 to 26]).

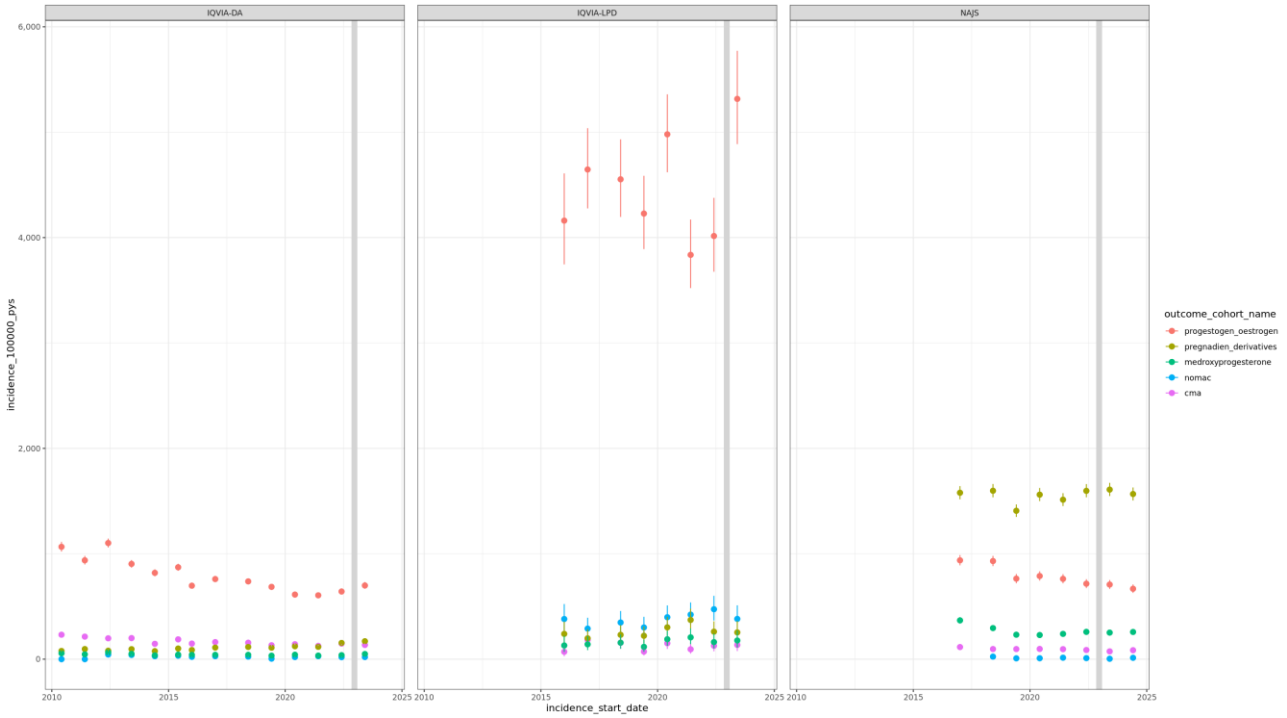

Figure 4. Incidence rates of drugs of interest by database as of June each year (2010–2024). The grey-shaded area represents the intervention (November 2022 to January 2023).

Regarding stratification by dose, incident records of high-dose products containing NOMAC (i.e., defined as amounts from 3.75mg to 5mg) were only captured in IQVIA LPD Belgium (n=2,529 events; PY=1,407,135), resulting in an incidence rate of 180 [173 to 187] per 100,000 PY. No incident records of high-dose products containing CMA (i.e., defined as amounts from 5mg to 10mg) were observed across participating databases. Incidence of low-dose products (i.e., defined as amounts lower than the lowest threshold for high-dose products) aligned with that observed for overall NOMAC or CMA (**Table 15**), except for IQVIA LPD Belgium, where the incidence of products containing low-dose products of NOMAC was 160 [154 to 167] per 100,000 PY.

Regarding ATC groups, incident records of NOMAC or CMA pertaining to pregnadien derivatives groupings (NOMAC: G03DB04; CMA: G03DB06) were only captured for NOMAC in IQVIA LPD Belgium (incidence per 100,000 PY: 180 [173 to 187]) and CMA in IQVIA DA Germany (incidence per 100,000 PY: 62 [62 to 63]). Incidence rates of combination products (NOMAC: G03AA14, F03FB12; CMA: G03AA15, G03AB07, G03FB03), aligned with those seen overall (**Table 15**), except for NOMAC in IQVIA LPD Belgium (incidence per 100,000 PY: 180 [173 to 187]) and CMA in IQVIA DA Germany (incidence per 100,000 PY: 101 [100 to 102] per 100,000 PY).

Considering the other drug classes studied, progestogens and oestrogens in combination had the highest incidence rates per 100,000 PY in IQVIA DA Germany (770 [767 to 772]) and IQVIA LPD Belgium (4,061 [4,026 to 4,097]), with the latter showing substantially higher rates than those observed for the other classes (**Table 15**). In NAJS, pregnadien derivatives obtained the highest rates per 100,000 PY (1,616 [1,609 to 1,622]) and were followed by progestogens and oestrogens in combination (814 [810 to 819]). These patterns were also observed when considering yearly rates (**Figure 4**).

Prevalence

The proportion of patients who were prescribed with a drug class or progestogen of interest (i.e., period prevalence) by calendar year is shown in **Figure 5**. For visualisation purposes, this figure only includes results calculated in June of each calendar month. Results across all calendar months can be explored in the "Shiny App". Overall findings described in **Table 15**, with additional details in **Appendix II – Table 6**.

Period prevalence of NOMAC, CMA or medroxyprogesterone was less than 2% across databases when considering the entire study period (**Table 15**). Results stratified by covariates of interest during the entire study period aligned with those seen for incidence results, showing similar patterns across age groups (**Appendix II – Figure 3**) and indications (**Appendix II – Figure 4**).

For IQVIA LPD Belgium, prevalence of NOMAC was estimated at 0.8% [95%CI 0.8 to 0.8] for high-dose products and 0.7% [0.6 to 0.7] for low-dose products. In databases without high-dose products, results for low-dose products aligned with the overall prevalence. Regarding ATC, pregnadien groups (NOMAC: G03DB04; CMA: G03DB06) were only captured for NOMAC in IQVIA LPD Belgium and CMA in IQVIA DA Germany. For databases with no counts in these groups, results for combination products *(*NOMAC: G03AA14, F03FB12; CMA: G03AA15, G03AB07, G03FB03), aligned with those seen overall. For IQVIA LPD Belgium, prevalence of G03DB04 was equal to that observed for combination products containing NOMAC (0.8% [0.8 to 0.8]). For IQVIA DA Germany, prevalence of CMA was 0.3% (0.3 to 0.3) for pregnadien derivatives (G03DB06) and 0.8% (0.8 to 0.8) for combination products containing CMA.

Considering the other drug classes studied, progestogens and oestrogens in combination obtained the highest prevalence estimates in IQVIA DA Germany (5.7 [5.7 to 5.7]) and IQVIA LPD Belgium (16.6 [16.5 to 16.8]). In NAJS, the highest figures were observed for pregnadien derivatives, obtaining substantially higher figures than those observed for other databases (IQVIA DA Germany: 0.6 [0.6 to 0.6]; IQVIA LPD Belgium: 1.1 [1.0 to 1.1]; NAJS: 9.4 [9.3 to 9.4]) (**Table 15**). These patterns were also observed when considering yearly rates (**Figure 5**).

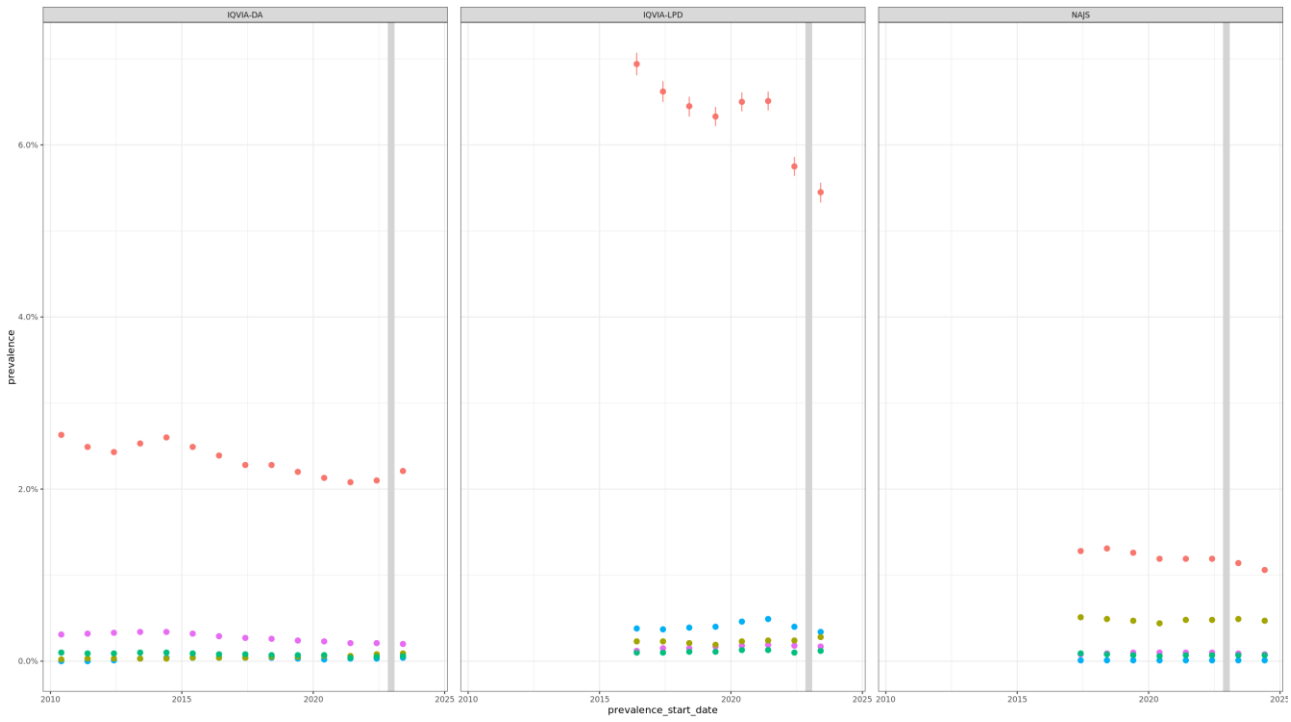

Figure 5. Prevalence of drugs of interest by database, for the month of June each year (2010–2024). The grey-shaded area represents the intervention. (November 2022 to January 2023).

12.2.2. Pre- and post-RMM comparison

In general, incidence rates estimated during the pre-intervention period were similar or higher than those observed after (**Table 15**). In IQVIA LPD Belgium, increases were seen for all drug classes and progestogens studied. For NOMAC, incidence rates per 100,000 PY increased from 350 (339 to 361) to 462 (435 to 490). Increases were consistent across dose-strata in IQVIA LPD Belgium. In this database, rates of NOMAC per 100,000 PY increased from 150 (143 to 157) to 243 (217 to 272) for low doses, and from 177 (170 to 185) to 203 (179 to 229) for high doses. For CMA, incidence rates per 100,000 PY increased from 128 (122 to 135) to 149 (134 to 165). Results for low-dose products aligned with the overall incidence for databases without high-dose products (**Appendix II – Figure 5**).

Period prevalence of drug classes or progestogens of interest during the post-intervention period was lower than that observed for the pre-intervention period (**Table 15**). This pattern was consistent across databases and outcomes assessed.

Additional information on incidence and prevalence results can be found in **Appendix II – Table 7** to **Appendix II – Table 10**.

Table 15. Incidence and prevalence of drug classes and progestogens of interest by database, overall and stratified by study period.

Outcome	Database name[1]	Incidence per 100,000 PY (95% CI)			Prevalence (95% CI)		
		Overall	Pre-RMM	Post-RMM	Overall	Pre-RMM	Post-RMM
Progestogens and oestrogens in combination	IQVIA DA Germany	770 (767 to 772)	779 (776 to 782)	782 (774 to 790)	5.7 (5.7 to 5.7)	5.7 (5.7 to 5.7)	3.1 (3.1 to 3.2)
	IQVIA LPD Belgium	4,061 (4,026 to 4,097)	3,971 (3,932 to 4,010)	4,424 (4,337 to 4,513)	16.6 (16.5 to 16.8)	15.4 (15.3 to 15.6)	11.2 (11.1 to 11.4)
	NAJS	814 (810 to 819)	872 (866 to 877)	663 (655 to 671)	6.1 (6 to 6.1)	5.3 (5.3 to 5.4)	2.7 (2.7 to 2.8)
Pregnadien derivates	IQVIA DA Germany	108 (107 to 109)	104 (104 to 105)	186 (182 to 190)	0.6 (0.6 to 0.6)	0.5 (0.5 to 0.5)	0.3 (0.3 to 0.3)
	IQVIA LPD Belgium	249 (241 to 258)	245 (236 to 254)	292 (271 to 314)	1.1 (1.0 to 1.1)	0.9 (0.9 to 1.0)	0.7 (0.7 to 0.7)
	NAJS	1,616 (1,609 to 1,622)	1,640 (1,632 to 1,647)	1,548 (1,536 to 1,561)	9.4 (9.3 to 9.4)	7.6 (7.6 to 7.7)	3.2 (3.2 to 3.3)
NOMAC	IQVIA DA Germany	22 (21 to 22)	22 (21 to 22)	22 (21 to 24)	0.14 (0.1 to 0.14)	0.1 (0.1 to 0.1)	0.1 (0.1 to 0.1)
	IQVIA LPD Belgium	359 (349 to 369)	350 (339 to 361)	462 (435 to 490)	1.5 (1.5 to 1.6)	1.4 (1.3 to 1.4)	1.0 (1.0 to 1.1)
	NAJS	13 (12 to 13)	16 (15 to 16)	6 (5 to 7)	0.1 (0.1 to 0.1)	0.1 (0.1 to 0.1)	0.0 (0.0 to 0.0)
CMA	IQVIA DA Germany	162 (161 to 163)	165 (164 to 166)	141 (138 to 145)	1.1 (1.1 to 1.1)	1.1 (1.1 to 1.1)	0.4 (0.4 to 0.4)
	IQVIA LPD Belgium	130 (124 to 136)	128 (122 to 135)	149 (134 to 165)	0.6 (0.6 to 0.6)	0.5 (0.5 to 0.5)	0.4 (0.4 to 0.4)
	NAJS	96 (95 to 98)	106 (104 to 108)	72 (70 to 75)	0.7 (0.7 to 0.7)	0.6 (0.6 to 0.6)	0.2 (0.2 to 0.3)
Medroxyprogesterone	IQVIA DA Germany	41 (41 to 42)	41 (41 to 42)	49 (47 to 51)	0.3 (0.3 to 0.3)	0.3 (0.3 to 0.3)	0.1 (0.1 to 0.1)
	IQVIA LPD Belgium	151 (145 to 158)	149 (142 to 156)	172 (156 to 190)	0.7 (0.7 to 0.7)	0.6 (0.6 to 0.6)	0.4 (0.4 to 0.5)
	NAJS	272 (269 to 274)	280 (277 to 283)	248 (243 to 253)	1.7 (1.7 to 1.8)	1.4 (1.4 to 1.4)	0.5 (0.5 to 0.5)

[1] Study period spanned from study start (or data availability start, if later) to end of data availability. In IQVIA DA Germany and IQVIA LPD Belgium, follow up ended on 31st December 2023.
Pre-RMM: from start date to October 2022, Post-RMM: from February 2023 to study end.

12.2.3. Subgroup analysis

In the subgroup analysis, we restricted the denominator for incidence and prevalence calculations to women who had a prior history of meningioma (n= 18,467 in IQVIA DA Germany; n= 127 in IQVIA LPD Belgium; n=8,682 in NAJS). Given the limited number of women contributing to the denominator, results are described overall and by study period. Incidence and prevalence results calculated over the entire study period can be found in **Appendix II – Table 11** and **Appendix II – Table 12.**

The number of incident prescriptions was <5 or 0 for NOMAC (in all databases) and CMA (with ≥5 events in IQVIA DA Germany only). Incidence rates per 100,000 PY for CMA was 13 (6 to 23) in IQVIA DA Germany. The number of prevalent events captured for NOMAC or CMA was <5 or 0 in most cases, with the exception of NOMAC in IQVIA LPD Belgium (n= 5), and CMA in IQVIA DA Germany (n= 12) and NAJS (n=5). In these databases, period prevalence was estimated as <0.1%, except for NOMAC in IQVIA LPD Belgium (3.9 % [95%CI 1.7 to 8.9]).

Regarding other drug classes of interest, incidence rates per 100,000 PY were higher in NAJS, particularly for pregnadien derivatives (940 [845 to 1043]), which was followed by progestogen and oestrogens in combination (254 [206 to 310]) and medroxyprogesterone (161 [124 to 207]) (**Figure 6**). In IQVIA DA Germany, incidence rates per 100,000 PY were 114 (92 to 139) for progestogens and oestrogens in combination, 20 (12 to 32) for pregnadien derivatives, and 7 (3 to 15) for medroxyprogesterone. Results for IQVIA LPD Belgium are not shown as <5 incident events were captured among this population for all outcomes studied. In terms of period prevalence, this was estimated to be ≤4% in most outcomes (**Appendix II – Table 12**).

When stratified by study period, estimates from the post-intervention period were lower than those from the pre-intervention period (**Figure 6** and **Appendix II – Figure 6**). Additional results can be explored in the "ShinyApp".

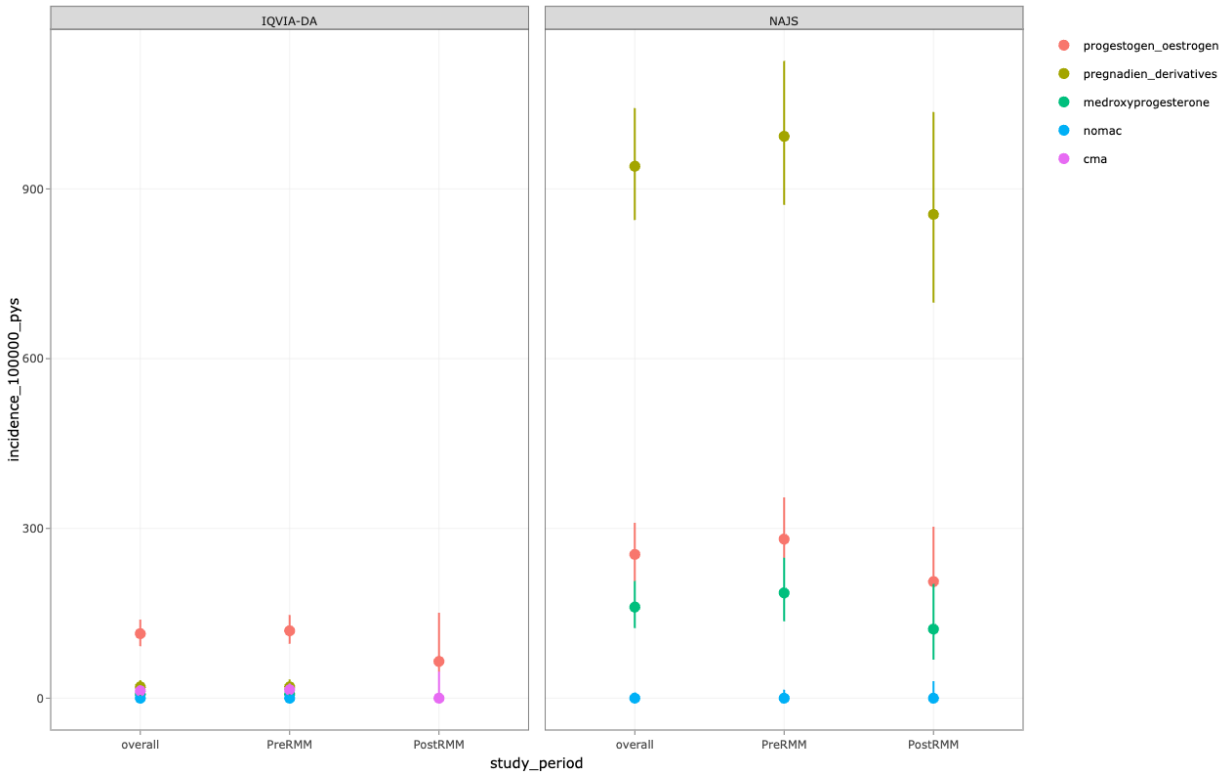

Figure 6. Incidence of drugs of interest among women with a prior history of meningioma, by database and study period.

12.3. Duration and cumulative dose (Objective 2)

12.3.1. Main results

Duration and cumulative dose were described for individuals with a first treatment episode with NOMAC or CMA. Both estimates were assessed at the drug-era level, defined using a 90-day gap to combine individual drug exposures (e.g., prescriptions). For treatment duration, only the first drug era per patient was considered, while all drug eras per patient were considered for cumulative dose. Cumulative dose was not assessed in NAJS. Please see **9.10. Deviations from protocol** for further details.

Average treatment duration for the first treatment episode with NOMAC was approximately 273 days in IQVIA DA Germany, 200 days in IQVIA LPD Belgium, and 138 days in NAJS (**Table 16**). For CMA, these were 193 days in IQVIA DA Germany, 239 days in IQVIA LPD Belgium, and 166 days in NAJS. Average treatment duration for non-HRT use (i.e. women aged 10–49 years) was similar to that reported overall for both ingredients. For HRT use (i.e., women aged ≥50 years), average duration was lower to that reported overall for NOMAC and CMA (**Appendix II – Table 13**).

Cumulative dose substantially differed by database and ingredient, and it is described at drug-era level in **Table 16**, with additional details in **Appendix II – Table 14**. For NOMAC, cumulative dose was 492 mg in IQVIA DA Germany and 615 mg in IQVIA LPD Belgium. For CMA, cumulative dose was 267 mg for IQVIA DA Germany and 28 mg for IQVIA LPD Belgium. Differences by HRT use were observed in some cases (**Appendix II – Table 14**). In IQVIA LPD Belgium, cumulative dose for NOMAC among HRT users was substantially higher than that reported for non-HRT (non-HRT vs. HRT: 450 mg vs. 906.2 mg). Regarding CMA, results by indication were similar in IQVIA LPD Belgium and showed increased cumulative dose for non-HRT in IQVIA DA Germany (non-HRT vs. HRT: 274 mg vs. 184 mg).

Considering both cumulative dose and duration, daily doses for overall results were approximately 2.8 mg for NOMAC in IQVIA DA Germany and 3 mg for IQVIA LPD Belgium. For CMA, this was estimated at approximately 1.4 mg in IQVIA DA Germany and 0.1 mg in IQVIA LPD Belgium. Daily doses were lower than those expected based on authorised products and have been discussed in more detail in **14.2. Limitations of the research methods**. Reasons behind some IQR suggesting quantities of 0 mg have also been addressed in the limitations section.

Cumulative dose at patient-level is described in **Appendix II – Table 15.** On average, women had taken a cumulative dose of NOMAC, expressed as mean (SD), of 701.4 (SD: 987.2) mg in IQVIA DA Germany and 1,025.2 (2,090.2) mg in IQVIA LPD Belgium. For CMA, corresponding figures were 413.2 (858.2) mg and 41.2 (42.2) mg. Patterns by indication were consistent with those described at drug-era level.

12.3.2. Pre- and post-RMM comparison

We used periods of equal duration (i.e. 12 months) to compare pre- and post-intervention periods. Results stratified by time period along with aSMD are reported in **Table 16**. In general, aSMD were suggestive of similar treatment duration before and after RMM implementation. Cases with an aSMD ≥0.2 were seen for treatment duration in IQVIA LPD Belgium, for NOMAC (aSMD = 0.24; pre-RMM vs. post- RMM: 85 vs. 72 days) and CMA (aSMD = 0.33; pre-RMM vs. post- RMM: 117 vs. 71 days). For cumulative dose, aSMD were ≤0.1 across databases and ingredients studied.

Table 16. Treatment duration and cumulative dose of the first treatment episode with NOMAC or CMA, overall and before and after the implementation of RMM.

Estimate[1]	Ingredient	Database	Overall[2]	Pre- RMM[3]	Post-RMM[3]	aSMD
Duration (in days), mean (SD)	NOMAC	IQVIA DA Germany	273.0 (357.1)	131.7 (89.4)	130.2 (86.9)	0.01
		IQVIA LPD Belgium	200.2 (249.7)	75.3 (84.7)	48.8 (72.3)	0.24
		NAJS	138.0 (249.8)	74.5 (75.2)	68.3 (70.02)	0.06
	CMA	IQVIA DA Germany	193.3 (362.2)	64.4 (77.1)	56.6 (70.7)	0.08
		IQVIA LPD Belgium	239.3 (254.2)	117.2 (106.2)	70.9 (91.7)	0.33
		NAJS	169.3 (290.7)	85.4 (81.5)	77.8 (76.9)	0.07
Cumulative dose (in mg), mean (SD)	NOMAC	IQVIA DA Germany	492.4 (681.8)	151.4 (180.4)	125.2 (163.7)	0.11
		IQVIA LPD Belgium	615.2 (1,193.1)	358.6 (507.7)	284.49 (460.6)	0.11
	CMA	IQVIA DA Germany	267.0 (533.3)	115.7 (142.3)	111.4 (137.1)	0.02
		IQVIA LPD Belgium	28.3 (24.6)	16.8 (11.5)	16.50 (10.5)	0.02

[1] Cumulative dose was not assessed in NAJS.
[2] Calculated over the entire study period.
[3] Defined using a 12-month period before and after the intervention (Pre-RMM: October 2021 to September 2022; Post-RMM: February 2023 to January 2024).

12.4. Patient-level characterisation (Objective 3)

In this section we described the characterisation of women initiating treatment with any of the drug classes and progestogens of interest (n= 230,027 in IQVIA DA Germany; n= 35,123 in IQVIA LPD Belgium; n=234,919 in NAJS). For this objective, the drug classes, and progestogens of interest—comprising progestogens and oestrogens in combinations, pregnadien derivatives, NOMAC, CMA, and medroxyprogesterone—were assessed as a single group.

Patients were described based on pre-specified comorbidities and medications, and by means of large-scale characterisation. For conditions, time windows were defined as all prior history to 1 day before index date (i.e., date of first-treatment with any of the drugs or progestogens of interest), 365 to 1 day prior to index date, and at index date. For medications, windows spanned from 365 to 1 day prior to index date, 30 to 1 day prior to index date, and at index date.

The comparison between pre- and post-RMM periods was performed based on conditions (assessed considering all prior history) and can be found in section **12.4.2. Pre- and post-RMM comparison**.

12.4.1. Main results

Pre-specified conditions

Among the population included, meningioma was recorded in 75 (0.03%) women in IQVIA DA Germany, 6 (0.02%) in IQVIA LPD Belgium, and 289 (0.1%) in NAJS. Of those, the number of women diagnosed in the year prior were 24 (0.01%) in IQVIA DA Germany and 175 (0.07%) in NAJS, where 7 were diagnosed at index date. The median years since meningioma were 3.7 [Q25–Q75; 1.0 – 6.0], 1.8 [0.7 – 5.7] in IQVIA LPD Belgium, and 2.4 [0.9 – 4.3] in NAJS.

When considering all prior history, pre-specified conditions related to gynaecological care with higher prevalence across databases were menstrual disorders (33.6% in IQVIA DA Germany; 5.3% in IQVIA LPD Belgium; 20.5% in NAJS) and menopause/perimenopause (7.6% in IQVIA DA Germany; 3.7% in IQVIA LPD Belgium; 6.1% in NAJS). Pre-specified gynaecological disorders were captured in <3% of patients across databases, except for uterine fibroids, which were captured in IQVIA DA Germany and NAJS only (in 4.6% and 6% of patients, respectively). Endometriosis was captured in 2–2.5% of women in IQVIA DA Germany and NAJS, compared to 0.6% in IQVIA LPD Belgium.

Relative to other comorbidities, those most frequently observed when considering all prior observation were asthma and hypertension, followed by obesity (i.e., assessed using diagnostic codes) in IQVIA DA Germany and NAJS (**Table 17**). In NAJS, the proportion of patients with cancer was higher (6.9%) compared to other databases (2% in IQVIA DA Germany; 0.6% in IQVIA LPD Belgium). Diagnostic codes relative to other pre-specified cancer types (i.e., brain cancer, breast cancer, endometrial cancer) were similar across databases, affecting <1.5% of patients.

When assessed in other time windows, results of pre-specified comorbidities were consistent with those reported considering all prior history with lower prevalence estimates.

Table 17. Number (%) of new users of drugs of interest with pre-specified comorbidities, assessed considering all prior history.

Pre-specified conditions	IQVIA DA Germany (n= 230,027)	IQVIA LPD Belgium (n= 35,123)	NAJS (n= 234,919)
Asthma	9,593 (4.2%)	4,539 (12.9%)	16,843 (7.2%)
Autoimmune diseases	5,608 (2.4%)	521 (1.5%)	11,754 (5%)
Neoplasm of the brain	44 (0.02%)	9 (0.03%)	360 (0.15%)
Neoplasm of the breast	814 (0.4%)	79 (0.2%)	3,501 (1.5%)
Cancer (any malignancy)	4,601 (2%)	226 (0.6%)	16,092 (6.9%)
Neoplasm of endometrium	104 (0.1%)	7 (0.02%)	577 (0.3%)
Endometriosis	5,747 (2.5%)	198 (0.6%)	4,571 (2.0%)
Epilepsy	1,253 (0.5%)	313 (0.9%)	3,918 (1.7%)
Hyperlipidaemia	4,891 (2.1%)	1,218 (3.5%)	7,430 (3.2%)
Hypertensive disorder	11,746 (5.1%)	2,659 (7.6%)	36,446 (15.5%)
Meningioma	75 (0.03%)	6 (0.02%)	289 (0.1%)
Menopause/perimenopause	17,518 (7.6%)	1,292 (3.7%)	14,217 (6.1%)
Menstrual disorders	77,263 (33.6%)	1,844 (5.3%)	48,195 (20.5%)
Obesity[1]	14,159 (6.2%)	348 (1.0%)	12,275 (5.2%)
Osteoporosis	1,168 (0.5%)	437 (1.2%)	5,816 (2.5%)
Polycystic ovary syndrome	4,482 (2.0%)	20 (0.1%)	6,642 (2.8%)
Primary ovarian insufficiency	2,060 (1.0%)	0 (0%)	85 (0.04%)
Type 2 diabetes	1965 (0.9%)	663 (1.9%)	9,751 (4.2%)
Type 2 neurofibromatosis	0 (0%)	0 (0%)	0 (0%)
Uterine fibroids	10,679 (4.6%)	0 (0%)	14,062 (6.0%)
Venous thromboembolism	399 (0.2%)	86 (0.2%)	1,011 (0.4%)

[1] Assessed as a condition (measurements were not considered).

Pre-specified medications

Pre-specified medications showed low prevalence (<1%) across databases (**Appendix II – Table 16**). When considering the year prior, pre-specified medications more frequently captured were antidepressants (1.9% in IQVIA DA Germany; 9.9% in IQVIA LPD Belgium; 5.8% in NAJS), antiandrogens (1.9% in IQVIA DA Germany; 1.9% in IQVIA LPD Belgium; 1.0% in NAJS) and metformin (0.4% in IQVIA DA Germany; 1.3% in IQVIA LPD Belgium; 2.0% in NAJS).

Table 18 includes the number of women initiating each of the drug classes or progestogens of interest at index date. Progestogens and oestrogens in combination (excluding NOMAC or CMA) were the most

frequently captured in IQVIA DA Germany (74.2%) and IQVIA LPD Belgium (85.2%), while pregnadien derivatives (excluding NOMAC or CMA) were most frequently recorded in NAJS (62.9%). When compared to other databases, the proportion of women initiating treatment with NOMAC was higher in IQVIA LPD Belgium (7.7% vs. <1.5%), and CMA was higher in IQVIA DA Germany (15.1% vs. 2.5–3%). High-dose products were only captured for NOMAC in IQVIA LPD Belgium (4.1%).

Table 1. Number (%) of new users of drugs of interest, at index date.

Drug classes of interest	IQVIA DA Germany (n= 230,027)	IQVIA LPD Belgium (n= 35,123)	NAJS (n= 234,919)
Progestogens and oestrogens in combination[1]	170,576 (74.2%)	29,914 (85.2%)	59,896 (25.5%)
Pregnadien derivatives[1]	12,948 (5.6%)	647 (1.8%)	147,765 (62.9%)
NOMAC	3,403 (1.5%)	2,703 (7.7%)	866 (0.4%)
- High-dose products	0 (0%)	1,450 (4.1%)	0 (0%)
- Low-dose products	3,403 (1.5%)	1,043 (3.0%)	866 (0.4%)
CMA	34,646 (15.1%)	897 (2.6%)	6,686 (2.8%)
- High-dose products	0 (0%)	0 (0%)	0 (0%)
- Low-dose products	34,626 (15.1%)	897 (2.6%)	6,686 (2.8%)
Medroxyprogesterone	9,455 (4.1%)	1,030 (2.9%)	21,106 (9.0%)

[1] Excluding drug records containing NOMAC or CMA. Products containing medroxyprogesterone were not excluded, and therefore some overlapping between this group and medroxyprogesterone might exist.

Large-scale characteristics:

In large-scale characterisation, all comorbidities and medications recorded within pre-defined time windows among women initiating any of the drug classes and progestogens of interest were described. To facilitate the reporting of the results, only the top 10 conditions and the top 10 medications are described in this report. For simplicity, the results presented in this section include those assessed at index date. Results for all time windows (with and without the top 10 restriction) can be explored in the “Shiny App”.

The top 10 conditions by database (assessed at index date) are described in **Table 19Error! Reference s ource not found.**. In IQVIA DA Germany and NAJS, most frequently recorded conditions were related to gynaecological disorders or physiological states related to pregnancy or menopause. In IQVIA DA Germany, conditions captured in >5% of cases included noninflammatory disorder of the vagina (6%) and dysmenorrhea (5.3%). In NAJS, conditions related with pregnancy in the top 10 included: early state of pregnancy (5.6%), haemorrhagic complication of pregnancy (5.6%), and threatened miscarriage (4.6%). Conditions detected in both IQVIA DA Germany and NAJS were noninflammatory disorder of the vagina and genitourinary tract haemorrhage. Codes related to perimenopause and menopause were seen across all databases, including IQVIA LPD Belgium (5.9%). Other top 10 conditions in IQVIA LPD Belgium were unspecific and unrelated to gynaecological care.

Table 19. Top 10 most recorded conditions among new users of drugs of interest, at index date.

IQVIA DA Germany (n= 230,027)	IQVIA LPD Belgium (n= 35,123)	NAJS (n= 234,919)
Noninflammatory disorder of the vagina: 13,738 (6%)	Menopausal syndrome: 2,079 (5.9%)	Early stage of pregnancy: 13,076 (5.6%)
Dysmenorrhea: 12,125 (5.3%)	Allergic rhinitis: 1,493 (4.2%)	Haemorrhagic complication of pregnancy: 13,076 (5.6%)
Perimenopausal disorder: 8,711 (3.8%)	Essential hypertension: 1,063 (3.0%)	Threatened miscarriage: 10,683 (4.6%)
Lower abdominal pain: 6,047 (2.6%)	Common cold: 954 (2.7%)	Perimenopausal disorder: 10,408 (4.4%)
Cyst of ovary: 5,843 (2.5%)	Disorders of initiating and maintaining sleep: 953 (2.7%)	Inflammatory disease of female genital structure: 9,630 (4.1%)
Genitourinary tract haemorrhage: 5,666 (2.5%)	Hypothyroidism: 830 (2.4%)	Benign neoplasm of ovary: 7304 (3.1%)
Menopausal syndrome: 4,782 (2.1%)	Acute sinusitis: 783 (2.2%)	Female infertility: 6,266 (2.7%)
Acute vaginitis: 3,832 (1.7%)	Migraine: 755 (2.1%)	Cyst of ovary: 5,271 (2.2%)
Acne: 3,783 (1.6%)	Cough: 718 (2.0%)	Disorder of endocrine ovary: 4,870 (2.1%)
Disorder of uterine cervix: 3,083 (1.3%)	Acute pharyngitis: 683 (1.9%)	Genitourinary tract haemorrhage: 4,837 (2.1%)

Results considering all prior observations and the year prior are available in the “Shiny App”. When considering all prior history, most conditions included in the top 10 list were related to symptomatic and acute conditions (e.g., acute upper respiratory tract infection, urinary tract infectious disease). Conditions related to gynaecological care were only captured in IQVIA DA Germany. Conditions captured in the year prior were similar to those reported for all prior history.

The top 10 medications (assessed at ingredient-level) are described in **Table 20**, showing results by database at index date. Most of the medications captured in the top 10 included ingredients used for contraception or for the treatment of gynaecological disorders. Ethinyl estradiol was amongst the most used ingredients (IQVIA DA Germany: 69.7%; IQVIA LPD Belgium: 78.8%; NAJS: 24.7%). Drospirenone, dydrogesterone, and estradiol ranked among the top 10 medications across all databases. In NAJS, these ingredients were observed in a higher proportion of women, particularly for drydrogesterone (58.8% in NAJS, 7–8% in IQVIA databases). CMA was captured in the top 10 for IQVIA DA Germany, while NOMAC was captured in IQVIA LPD Belgium.

Table 20. Top 10 most recorded medications at ingredient-level, at index date.

IQVIA DA Germany (n= 230,027)	IQVIA LPD Belgium (n= 35,123)	NAJS (n= 234,919)
Ethinyl estradiol: 160,285 (69.7%)	Ethinyl estradiol: 27,675 (78.8%)	Dydrogesterone: 138,021 (58.8%)
Levonorgestrel: 68,964 (30.0%)	Desogestrel: 10,676 (30.4%)	Ethinyl estradiol: 58,048 (24.7%)
Dienogest: 66,293 (28.8%)	Levonorgestrel: 7,328 (20.9%)	Drospirenone: 23,463 (10.0%)
Chlormadinone: 34,646 (15.1%)	Drospirenone: 4,963 (14.1%)	Medroxyprogesterone: 21,106 (9.0%)
Estradiol: 32,712 (14.2%)	Estradiol: 4,599 (13.1%)	Gestodene: 20,470 (8.7%)
Desogestrel: 16,532 (7.2%)	Inert ingredients: 3,546 (10.1%)	Folic acid: 17,760 (7.6%)
Dydrogesterone: 15,391 (6.7%)	Gestodene: 2,784 (7.9%)	Estradiol: 13,632 (5.8%)
Drospirenone: 12,628 (5.5%)	Nomegestrol: 2,703 (7.7%)	Ibuprofen: 12,941 (5.5%)
Medroxyprogesterone: 9,455 (4.1%)	Dydrogesterone: 26,38 (7.5%)	Megestrol: 12,587 (5.4%)
Levothyroxine: 7,890 (3.4%)	Dienogest: 2,235 (6.4%)	Diazepam: 11,432 (4.9%)

Results considering the year and month prior to index date are available in the “Shiny App”. The top 10 medications captured within these time windows were mostly not specific to gynaecological care and included commonly used treatments for general health issues, such as pain or infections. Some progestogens and oestrogens were detected among the top 10 medications prior to index date. These were captured in IQVIA DA Germany in ≤3% of patients, except for desogestrel in the year prior (5.5%). Cyproterone acetate was observed in approximately 1–2% of women in the year prior to index date (not shown in the top 10).

12.4.2. Pre- and post-RMM comparison

The proportion of women with a prior history of meningioma initiating treatment before the implementation of RMM was similar to that after, with aSMD ≤0.1 in IQVIA DA Germany (pre-RMM vs. post-RMM: 0.03% vs. 0.05%) and NAJS (0.1% vs. 0.2%). This comparison was not assessed in IQVIA LPD Belgium due to the limited numbers of counts observed (n=6 during the entire study period).

Figure 7 illustrates covariate balance of pre-specified conditions between women initiating drug classes and progestogens of interest (i.e., progestogens and oestrogens combinations, pregnadien derivatives, NOMAC, CMA, or medroxyprogesterone), before and after the intervention, considering all prior history. Overall, most conditions neared the diagonal, indicating comparable cohort characteristics distribution between the 2 groups. Most conditions had an aSMD ≤0.1.

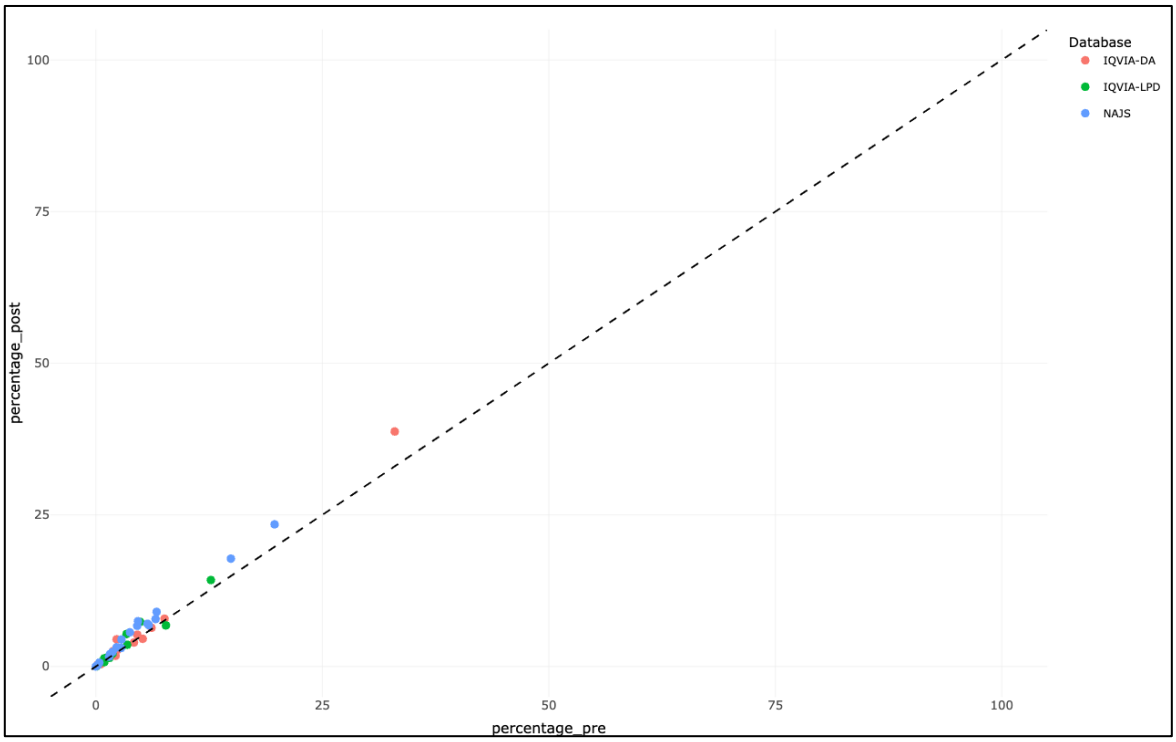

Figure 7. Covariate balance between women initiating any of the drugs and progestogens of interest during the pre- and post-RMM periods in terms of pre-specified conditions.

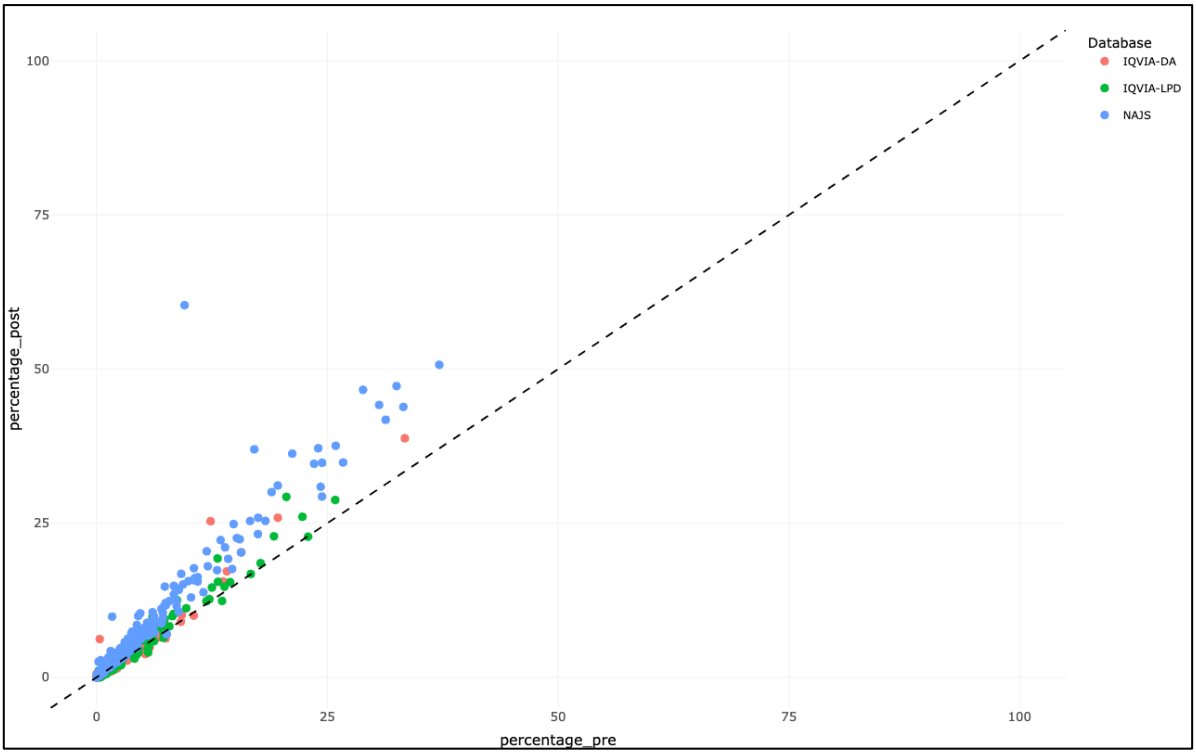

Figure 8. Covariate balance between women initiating any of the drugs and progestogens of interest during the pre- and post-RMM periods in terms of conditions identified through large-scale characterisation.

Figure 8 illustrates covariate balance of conditions identified through large-scale characterisation. Overall, most conditions neared the diagonal, indicating comparable cohort characteristics distribution between the

two groups. However, some covariates were off the diagonal, suggesting a higher prevalence of certain features in women initiating treatment during the post-intervention period, especially in NAJS, where some conditions obtained higher aSMD. The highest aSMD in NAJS were observed for COVID-19 (aSMD=1.26), acute upper respiratory infection (aSMD=0.37), vitamin D deficiency (aSMD=0.36), cough (aSMD=0.34), and accretion on teeth (aSMD=0.34). The number of conditions assessed through large-scale characterisation with an aSMD ≥0.2 was 28, representing only 0.7% of all conditions with sufficient counts for assessment in NAJS. Less than 2 conditions obtained an aSMD ≥0.2 in IQVIA DA Germany (aSMD=0.34 for illness) and IQVIA LPD Belgium (aSMD=0.33 for COVID-19; aSMD=0.2 for cough), representing ≤0.1% of the conditions assessed.

12.5. Line of treatment (Objective 4)

12.5.1. Main results

Records of alternative treatments were retrospectively assessed to determine whether patients newly prescribed with NOMAC or CMA received them as first-line or non-first-line treatments. For NOMAC, most patients received it as a non-first-line treatment in IQVIA DA Germany (first-line vs. no-first-line: 38.9% vs. 61.1%), whereas the opposite pattern was observed in IQVIA LPD Belgium (68.3% vs. 31.7%). In contrast, CMA was predominantly prescribed as a first-line treatment in both databases (IQVIA DA Germany: 58.2% vs. 41.8%; IQVIA LPD Belgium: 58.5% vs. 41.5%). In NAJS, the proportion of women being prescribed first-line and non-first-line treatments was similar for both NOMAC and CMA (**Table 21**).

These patterns were consistent across stratification variables (**Table 21**). Differences between first-line vs. non-first-line treatments were pronounced for HRT use (women ≥50 years) in IQVIA DA Germany for CMA (first-line vs. no-first-use: 72.0% vs. 28.0%) and IQVIA LPD Belgium for NOMAC (76.5% vs. 23.5%).

12.5.2. Pre- and post-RMM comparison

In general, the proportion of women initiating NOMAC or CMA as first-line treatment before and after the implementation of RMM was similar across databases, with aSMD ≤0.2 (**Table 22**).

Table 21. Number of patients (%) prescribed with NOMAC and CMA according to treatment line (first-line vs. non-first line), overall and by indication and dose.

		Line of treatment[1]								
		IQVIA DA Germany			IQVIA LPD Belgium			NAJS		
Strata variable	Strata level	Total	First-line	Non-first-line	Total	First-line	Non-first-line	Total	First-line	Non-first-line
Ingredient: NOMAC										
Overall	-	10,519	4,089 (38.9)	6,430 (61.1)	4,078	2,787 (68.3)	1,291 (31.7)	1,918	911 (47.5)	1,007 (52.5)
Indication	Non-HRT	9,997	3,846 (38.5)	6,151 (61.5)	3,470	2,322 (66.9)	1,148 (33.1)	1,893	898 (47.4)	995 (52.6)
	HRT	522	243 (46.6)	279 (53.5)	608	465 (76.5)	143 (23.5)	25	13 (52.0)	12 (48.0)
Dose	High	0	-	-	2,068	1,508 (72.9)	560 (27.1)	0	-	-
	Low	10,519	4,089 (38.9)	6,430 (61.1)	1,890	1,202 (63.6)	688 (36.4)	1,918	911 (47.5)	1007 (52.5)
Ingredient: CMA										
Overall	-	61,275	35,653 (58.2)	25,622 (41.8)	1,582	925 (58.5)	657 (41.5)	13,512	6,784 (50.2)	6,728 (49.8)
Indication	Non-HRT	31,032	31,032 (56.6)	23,827 (43.4)	914	914 (58.4)	650 (41.6)	13,449	6,743 (50.1)	6,706 (49.9)
	HRT	6,416	4,621 (72.0)	1,795 (28.0)	18	11 (61.1)	7 (38.9)	63	41 (65.1)	22 (34.9)
Dose	High	0	-	-	0	-	-	0	-	-
	Low	61,211	35,633 (58.21)	25,578 (41.8)	1,582	925 (58.5)	657 (41.5)	13,512	6,784 (50.2)	6,728 (49.8)

[1] 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.

Table 22. Number of patients (%) prescribed with NOMAC and CMA as first-line treatment before and after the implementation of RMM

		Line of treatment[1]					
		IQVIA DA Germany		IQVIA LPD Belgium		NAJS	
Ingredient	Stratification[2]	First-line	Non-first-line	First-line	Non-first-line	First-line	Non-first-line
NOMAC	Pre-RMM	32,667 (58.0)	23,668 (42.0)	776 (59.4)	530 (40.6)	5,711 (52.1)	5,244 (47.9)
	Post-RMM	2,532 (61.1)	1,614 (38.9)	123 (52.3)	112 (47.7)	953 (41.3)	1,355 (58.7)
	aSMD[3]	0.06	-	0.14	-	0.22	-
CMA	Pre-RMM	3,721 (39.1)	5,801 (60.9)	2,308 (69.7)	1,003 (30.3)	830 (48.8)	871 (51.2)
	Post-RMM	321 (38.4)	516 (61.6)	397 (61.4)	250 (38.6)	75 (37.5)	125 (62.5)
	aSMD[3]	0.01	-	0.18	-	0.23	-

[1] 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.
[2] Pre-RMM from start date to October 2022, Post-RMM: from February 2023 to study end.
[3] Only calculated for first-line treatments with comparison between pre-RMM and post-RMM values.

12.6. Treatment strategies and meningioma (Objective 5)

12.6.1. Main results

Treatment strategies (i.e., restart, switch, both, and discontinuation) were assessed during the 180 days following the end of treatment, which was defined as the end of the drug era. The most frequently observed strategy was treatment discontinuation, where patients remained untreated in the 180 days after finishing treatment, neither continuing with the original treatment nor switching to an alternative (**Appendix II – Table 17**). For NOMAC, the proportion of women who discontinued was 73.8% for IQVIA DA Germany, 85.3% for IQVIA LPD Belgium, and 57.9% for NAJS. For CMA, corresponding figures (in the same order) were 78.9%, 79.5%, and 58.3%.

Treatment restarts or switches to alternative treatments were observed in 10–15% of women in IQVIA DA Germany and in 15–22% of women in NAJS (**Appendix II – Table 17**). In IQVIA LPD Belgium, restarting treatment was observed in a higher proportion of women compared to switching (restart vs. switching: 9.9% vs. 4.4% for NOMAC; 12.3% vs. 8.1% for CMA). Restarting treatment and subsequently switching to a different one within 180 days was observed in <2% of women across databases for both NOMAC and CMA. Where available, results stratified by ATC groupings were consistent with overall results (**Appendix II – Table 18**).

The occurrence of meningioma was evaluated over two periods: during treatment and in the six months preceding the end of treatment. Cases of meningioma during treatment were either absent or very rare among women included. For NOMAC, no cases were identified in any of the databases studied. In the case of CMA, 8 cases were detected during treatment in IQVIA DA Germany. These cases occurred within the final six months of treatment and occurred during the pre-intervention period. No cases during the post-intervention period were observed.

12.6.2. Pre- and post-RMM comparison

Results stratified by time period along with aSMD are reported in **Table 23**. In most cases, aSMD were ≤0.2 and were suggestive of similar numbers of treatment switches and discontinuations before and after RMM implementation. Cases with higher aSMD were seen for NOMAC for switching in IQVIA DA Germany (aSMD = 0.32; pre-RMM vs. post-RMM: 16.0% vs. 6.2%) in NAJS (aSMD=0.33; 23.6% vs. 11.3%), as well as for treatment discontinuation in IQVIA DA Germany (aSMD = 0.36; 72.6% vs. 87.0%).

Table 23. Number of patients (%) who switched or discontinued treatment 180 days after ending a first treatment with NOMAC or CMA, overall and before and after the implementation of RMM.

Strategy	Ingredient	Database	Overall[1]	Pre- RMM[2]	Post-RMM[2]	aSMD
Switch, N (%)	NOMAC	IQVIA DA Germany	1,530 (14.6%)	1,369 (16.0%)	118 (6.2%)	0.32
		IQVIA LPD Belgium	178 (4.4%)	136 (4.8%)	38 (2.7%)	0.11
		NAJS	417 (21.7%)	364 (23.6%)	47 (11.3%)	0.33
	CMA	IQVIA DA Germany	6,213 (10.1%)	5,557 (10.6%)	592 (6.7%)	0.14
		IQVIA LPD Belgium	128 (8.1%)	96 (8.8%)	24 (4.6%)	0.17
		NAJS	2,051 (15.2%)	1,505 (16.0%)	443 (9.3%)	0.20
Discontinuation, N (%)[2]	NOMAC	IQVIA DA Germany	7,767 (73.8%)	6,215 (72.6%)	1,659 (87.0%)	0.36
		IQVIA LPD Belgium	3,480 (85.3%)	2,437 (86.7%)	1,227 (88.0%)	0.04
		NAJS	1,111 (57.9%)	909 (58.9%)	231 (55.7%)	0.06
	CMA	IQVIA DA Germany	48,367 (78.9%)	41,344 (78.7%)	7,633 (86.4%)	0.20
		IQVIA LPD Belgium	1,257 (79.5%)	880 (81.0%)	450 (85.9%)	0.13
		NAJS	7,880 (58.3%)	5,465 (58.2%)	2,836 (59.8%)	0.03

[1] Calculated over the entire study period.
[2] Pre-RMM from start date to October 2022, Post-RMM: from February 2023 to study end. Treatments ending 180 days before the end of the pre-RMM or post-RMM period were not considered to ensure sufficient time for assessment.
[2] Not treated, neither with the original treatment nor any potential switch.

12.7. Analyses of RMM Effectiveness at population-level (Objective 6)

We analysed the impact of RMM implemented in 2022 on trends of incidence of NOMAC and CMA prescribing at a population-level. For NOMAC, the intervention implemented in 2018 was also considered.

Time series assessed were NOMAC or CMA overall, by dose and by indication (where available). Trends of high-dose products were only assessed for NOMAC in IQVIA LPD Belgium. HRT was only assessed in IQVIA LPD Belgium for NOMAC and IQVIA DA Germany for CMA (see **12.2 Population-level DUS (Objective 1)**).

12.7.1. Model diagnostics

The complete data series for each outcome and database with overall results can be found in **Appendix II** (**Appendix II – Figure 7** to **Appendix II – Figure 9**).

A range of visual displays based on an evaluation of the data and residuals was constructed to assess whether the underlying assumptions were met, including the autocorrelation function (ACF) and partial autocorrelation function (PACF) plots.

For each time series, Poisson and negative binomial models were considered, along with an assessment of whether seasonal adjustment was needed. Point estimates obtained from Poisson and negative binomial models were approximately the same, with the only difference being that standard errors and confidence intervals were inflated in the negative binomial models to account for overdispersion. While adjusting for seasonality had little impact in most cases, its effect was more noticeable in some instances. Relevant analytical choices used for the ITS analyses conducted in this study are detailed in **Table 24** and **Appendix II (Appendix II – Table 19** and **Appendix II – Table 20**).

Regarding the assumption of linearity, the linear model had a smaller AIC than the non-linear and had a non-significant LR test in most cases (p-value <0.05), suggesting no significant deviation from linearity. However, this was not the case for NAJS when assessing the impact of the intervention implemented in 2018 on NOMAC use, as the non-linear model provided a significantly better fit according to the AIC and LHR test for all the time series with sufficient data for assessment (i.e., overall, low-dose products, and non-HRT).

The “Shiny app” allows exploration of all time series studied, as well as ACF and PACF plots, results with and without seasonal adjustment, as well as all diagnostic outputs.

12.7.2. ITS analysis: RMM implemented in 2022

Time series assessed as part of this section spanned from January 2021 to the last month of data used as part of objective 1 (December 2023 in IQVIA DA Germany and IQVIA LPD Belgium; December 2024 in NAJS).

Results for the ITS analyses are presented in **Table 24**, and describe the regression coefficients derived from the model (β_1, β_2, and β_3 in **Equation 1**, respectively). These figures can be interpreted as RR when exponentiated, quantifying the relative changes in rates in NOMAC or CMA prescribing. Step changes (also referred as level changes) indicate the immediate shift in prescribing rates at the time of the intervention compared to the expected rates had the intervention not occurred. Slope changes can be interpreted as the RR corresponding to a unit increase in time (i.e., months). We have also provided an approximate value of the impact of both changes (step and slope) at the last point of available data for each database (i.e., December 2023 in IQVIA databases; December 2024 in NAJS), using the coefficients derived from the model (see **Equation 1**). These values should be interpreted as the impact at that specific point in time and should not be interpreted as the cumulative effect of the intervention.

All figures in this section display the ITS results for the assessed time series, using a consistent set of visual elements: data points represent monthly incidence rates; solid lines depict the fitted pre- and post-intervention trends; and dashed lines indicate the counterfactual scenario—i.e., the projected trend had the intervention not occurred. The grey-shaded area represents the transition period (November 2022 to

January 2023), during which data points were excluded from the model. Where applicable, seasonal adjustments are shown as light grey dashed lines.

NOMAC:

IQVIA DA Germany:

Incidence rates of NOMAC prescribing prior to the intervention showed a downward trend in IQVIA DA Germany. There was a non-significant immediate decrease in incidence rates (RR: 0.907 [95%CI: 0.713 to 1.153]), corresponding to a reduction of -9.4% (95% CI: -28.7 to 15.3). This was followed by a non-significant positive change in slope (RR: 1.014 [0.981 to 1.048]), with rates increasing by 1.4% (-1.9 to 4.8) per month (**Figure 9**). Results for low-dose products and for non-HRT use were similar to those seen for NOMAC overall (**Appendix II – Table 19**).

The trend crossed above the counterfactual line around September 2023. Taking both step and slope changes into consideration, the impact of the intervention on incidence rates in December 2023 was estimated as an increase of approximately 5.7% (95% CI: -24.4 to 47.9).

IQVIA LPD Belgium:

Incidence rates of NOMAC prescribing in prior to the intervention showed a stable trend in IQVIA LPD Belgium. In contrast to other databases, rates of NOMAC prescribing appear to increase following the implementation of restrictions (**Figure 10**). However, there was no statistically significant immediate change in incidence rates after the intervention. RR for the step change was estimated at 1.193 (0.928 to 1.534), corresponding to a 19.3% (-7.3 to 53.4) increase at the time of the intervention. This was followed by a non-significant monthly increase of 1.7% (-1.5 to 5.1) (RR: 1.018 [0.985 to 1.051]).

Trends of high-dose products and HRT use were assessed in this IQVIA LPD Belgium only (**Appendix II – Table 19**). The increase in incidence rates observed was also seen for both low- and high-dose products, with non-significant step or slope changes detected. The step change was estimated at 21.4% (-9.8 to 63.4) for low-dose products and 28.3% (-5.5 to 74.4) for high-dose products. Slope changes were estimated at 1.8% (-1.9 to 5.8) and 0% (-4 to 4.2), respectively (**Appendix II – Figure 10** and **Appendix II – Figure 11**).

The impact of the intervention differed by indication, with no significant step or slope changes detected. Incidence of NOMAC for HRT use showed a step change of 77.9% (-5.4 to 234.5) followed by a decreasing trend with a slope of -3.2% (-10.5 to 4.8). For non-HRT use, the step change was substantially lower and was estimated at 3.3% (-22.3 to 37.3), and in contrast to HRT results, trends after the intervention showed a positive trend with a slope change of 2.9% (-0.8 to 6.8) per month (**Appendix II – Figure 12** and **Appendix II – Figure 13**).

Trends in incidence rates of NOMAC (overall) were above the counterfactual throughout the post-intervention period. Taking both step and slope changes into consideration, the impact of the intervention was estimated as an increase of approximately 44.3% (1.2, 105.9) in December 2023. In stratified results, increases at the end of the time series were more pronounced for non-HRT use compared to HRT (approximately 41.3% [-5.0 to 110.3] vs. 25.1% [-48.3 to 202.5]), and for low-dose products compared to high-dose (approximately 48.3% [-2.8 to 126.2] vs. 28.0% [-17.6 to 99.0]).

NAJS:

Incidence rates of NOMAC prescribing in NAJS showed an upward trend prior to the intervention. The intervention was associated with an immediate decrease in incidence rates (RR 0.546 [0.368 to 0.81]), corresponding to a reduction of -45.4% (-63.2 to -19). The RR for the monthly slope change was non-significant (RR 1.014 [0.987 to 1.041]) and was equivalent to monthly increase of 1.4% (-1.3% to 4.2%). Results for low-dose products and for non-HRT use were similar to those seen for NOMAC overall (**Appendix II – Table 19**).

Trends in incidence rates were below the counterfactual throughout the post-intervention period. Taking both step and slope changes into consideration, the impact of the intervention in December 2024 was estimated as a decrease of -26.2% (-63.6 to 49.7).

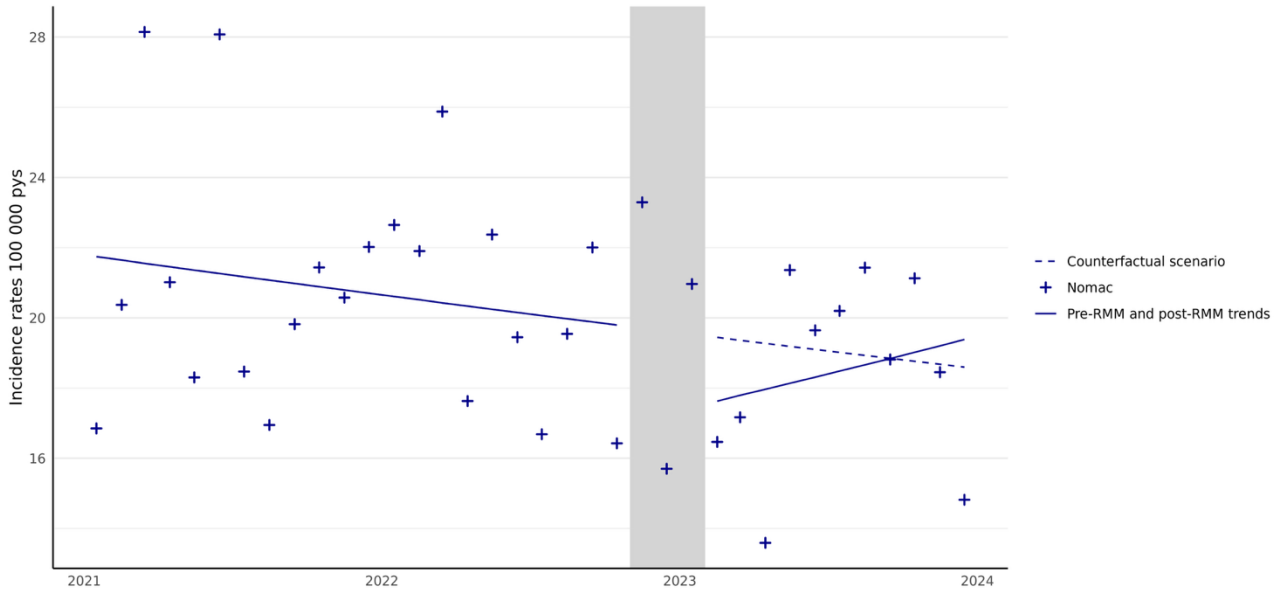

Figure information: Level change = -9.4% (-28.7% to 15.3%), Slope change = 1.4% (-1.9% to 4.8%)

Figure 9. ITS analysis of RMM implemented in 2022 on incidence rates of NOMAC in IQVIA DA Germany.

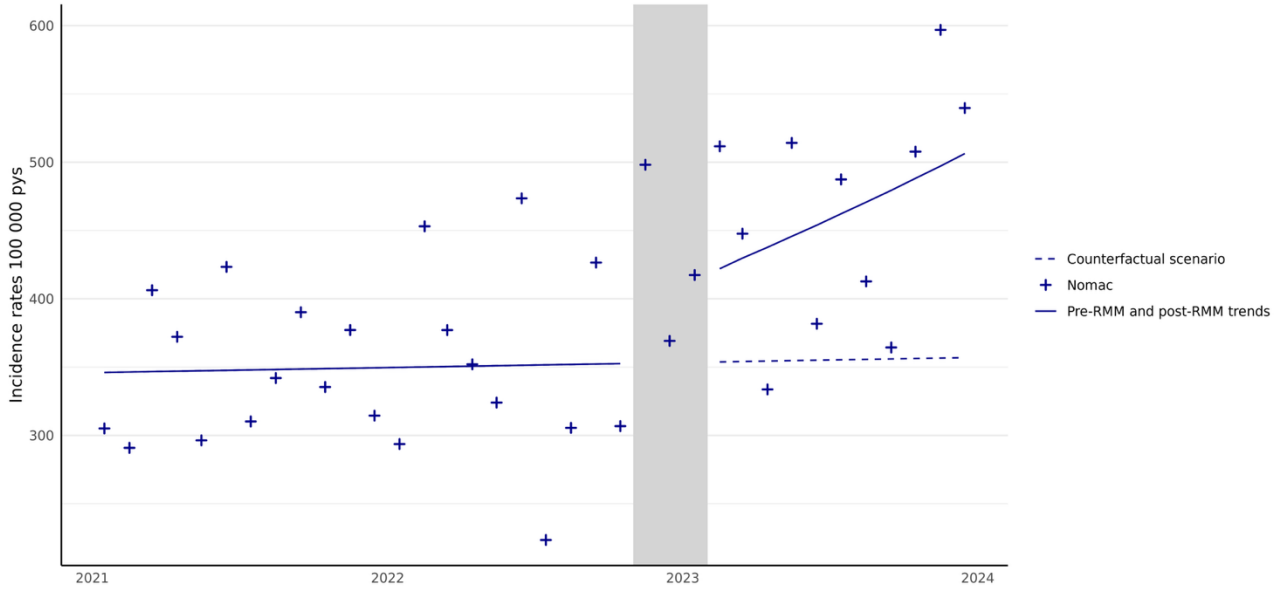

Figure information: Level change = 19.3% (-7.3% to 53.4%), Slope change = 1.7% (-1.5% to 5.1%)

Figure 10. ITS analysis of RMM implemented in 2022 on incidence rates of NOMAC in IQVIA LPD Belgium.

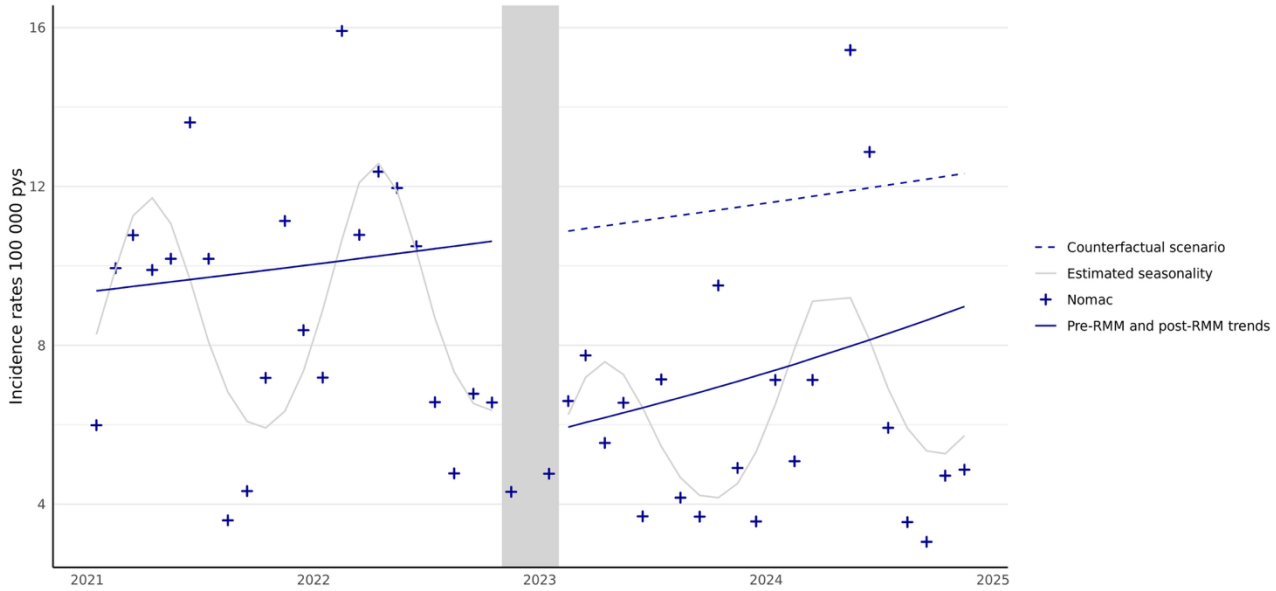

Figure information: Level change = -45.4% (-63.2% to -19%), Slope change = 1.4% (-1.3% to 4.2%)

Figure 11. ITS analysis of RMM implemented in 2022 on incidence rates of NOMAC in NAJS.

CMA:

IQVIA DA Germany:

Incidence rates of CMA prescribing prior to the intervention showed a modest decreasing trend in IQVIA DA Germany. Step and slope changes were not statistically significant, with RRs of 0.910 (0.805 to 1.028) and 1.005 (0.988 to 1.021), respectively. These corresponded to a -9.1% (-19.5 to 2.8) reduction for the step change and a 0.5% (-1.2 to 2.1) for the slope change (**Figure 12**).

HRT use was only assessed in IQVIA DA Germany. The intervention led to a more pronounced negative step change in HRT use compared to non-HRT use. Estimated step and slope changes were -21.4% (-37.8 to -0.5) and 2.1% (-1.1 to 5.5) for HRT, and -7.5% (-18.7 to 5.2) and 0.2% (-1.5 to 2) for non-HRT use (**Appendix II – Figure 14** and **Appendix II – Figure 15**).

The post-intervention trend remained consistently below the counterfactual throughout the post-intervention period. Considering step and slope changes combined, the impact of the intervention was estimated as a decrease of approximately -4.3% (-19.4 to 13.6) in December 2023. When stratified by indication, decreases were estimated as of -0.75% (-26.4 to 33.9) for HRT use and -5.3% (-21.0 to 13.5) for non-HRT use at the end of the time series.

IQVIA LPD Belgium:

Incidence rates of CMA prescribing showed a statistically significant upward trend before the intervention (RR: 1.024 [1.008 to 1.040]). The intervention was associated with an immediate decrease in incidence rates (RR: 0.646 [0.438 to 0.951]), corresponding to a -35.5% (-56.2 to -4.9) reduction. No significant slope change was detected, with a RR of 1.033 (0.984 to 1.085), corresponding to a 3.3% (-1.6 to 8.5) increase per month (**Figure 13**). Results for non-HRT aligned with those seen overall (**Appendix II – Table 20**).

The post-intervention trend remained below the counterfactual throughout the post-intervention period. Considering step and slope changes combined, the impact of the intervention on incidence rates in December 2023 was estimated as a decrease of approximately -7.4% (-43.3 to 51.1).

NAJS:

In contrast to IQVIA LPD Belgium, incidence rates of CMA prescribing prior to the intervention showed a downward trend in NAJS. The intervention was associated with an immediate decrease in incidence rates (RR: 0.751 [0.586 to 0.963]), equivalent to a reduction -24.9% (-41.4 to -3.7). The intervention was also associated with a slope change; however, this was marginally significant (RR: 1.024 [1.01 to 1.04]), corresponding to an estimated 2.4% (0.7 to 4.1) increase per month (**Figure 14**).

The post-intervention trend crossed above the counterfactual around the first quarter of 2024, which had continued the decreasing trend observed during the pre-intervention period. Considering step and slope changes combined, the impact of the intervention on incidence rates was estimated as an increase of 29% (-20.2 to 108.5) in December 2024.

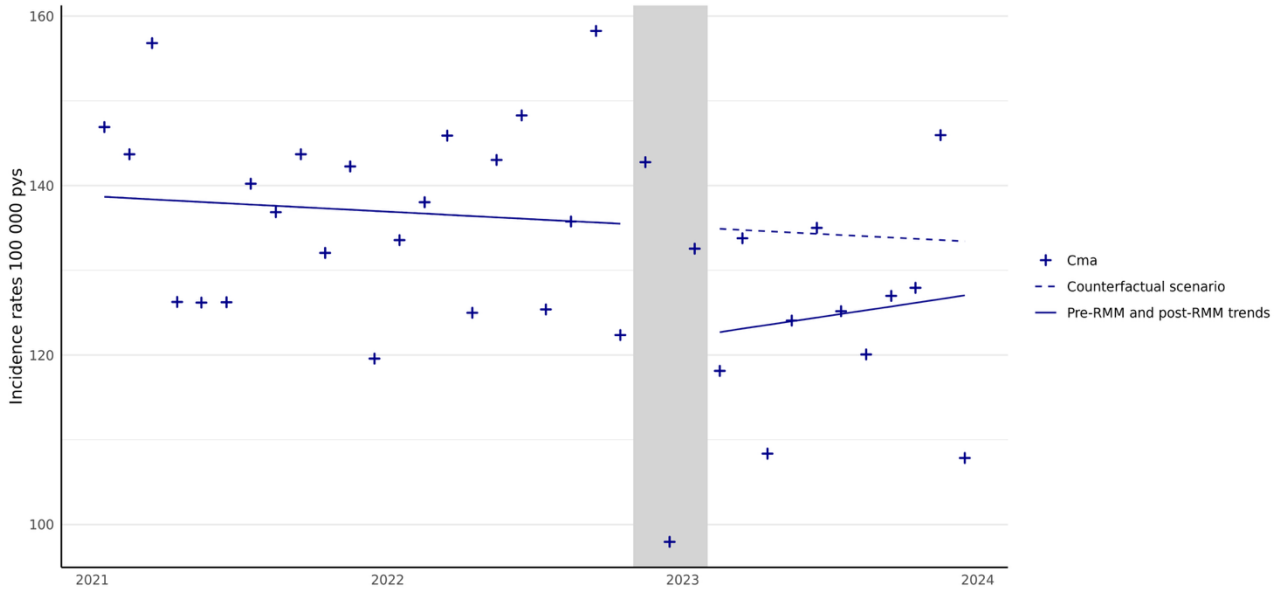

Figure information: Level change = -9.1% (-19.5% to 2.8%), Slope change = 0.5% (-1.2% to 2.1%)

Figure 12. ITS analysis of RMM implemented in 2022 on incidence rates of CMA in IQVIA DA Germany.

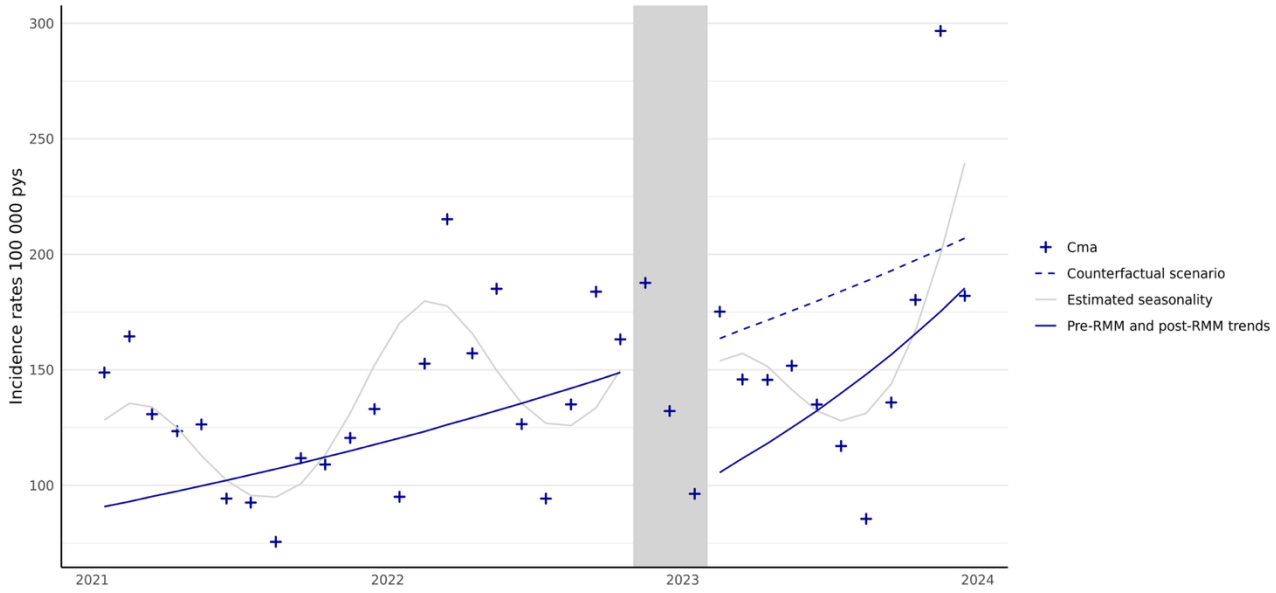

Figure information: Level change = -35.5% (-56.2% to -4.9%), Slope change = 3.3% (-1.6% to 8.5%)

Figure 13. ITS analysis of RMM implemented in 2022 on incidence rates of CMA in IQVIA LPD Belgium.

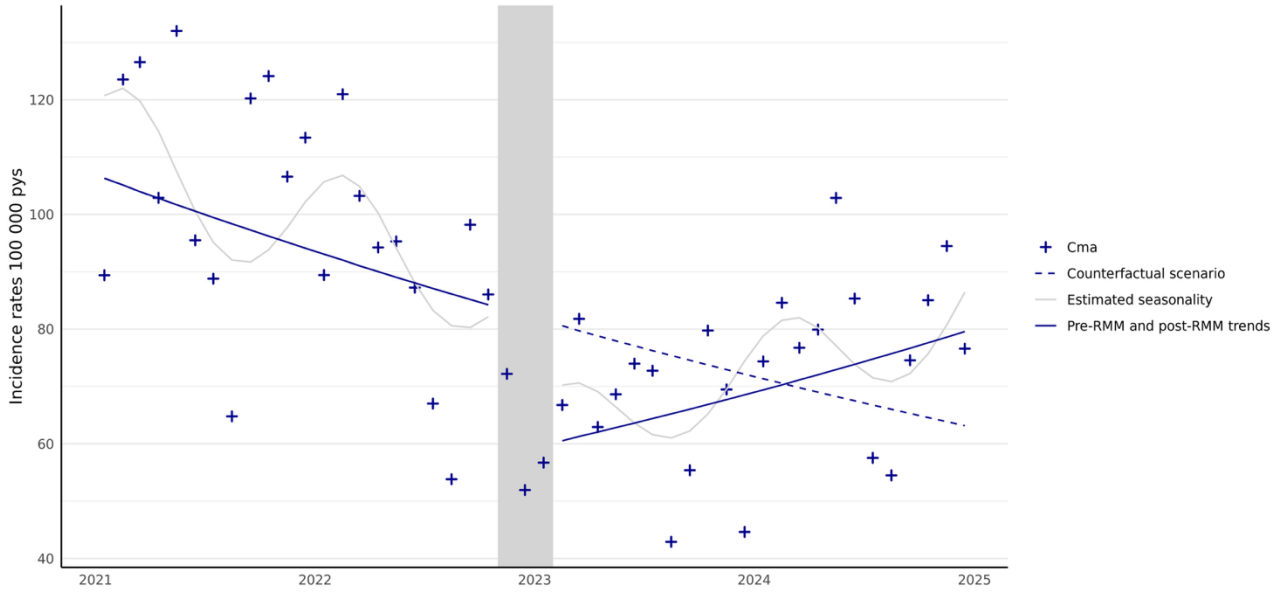

Figure information: Level change = -24.9% (-41.4% to -3.7%), Slope change = 2.4% (0.7% to 4.1%)

Figure 14. ITS analysis of RMM implemented in 2022 on incidence rates of CMA in NAJS.

Table 24. Estimated effects (risk ratio, RR) of the intervention implemented in 2022, by database and ingredient.

Settings		Pre-intervention trend			Step change			Slope change		
Database	Model[1]	Regression coefficient (β_1), (SE)	p-value	RR (95% CI)	Regression coefficient (β_2), (SE)	p-value	RR (95% CI)	Regression coefficient (β_3), (SE)	p-value	RR (95%)
NOMAC										
IQVIA DA Germany	Negative Binomial	–0.004 (0.005)	0.366	0.996 (0.986 to 1.005)	-0.098 (0.123)	0.424	0.907 (0.713 to 1.153)	0.014 (0.017)	0.406	1.014 (0.981 to 1.048)
IQVIA LPD Belgium	Negative Binomial	0.001 (0.006)	0.874	1.001 (0.990 to 1.012)	0.176 (0.128)	0.170	1.193 (0.928 to 1.534)	0.017 (0.017)	0.299	1.018 (0.985 to 1.051)
NAJS	Poisson*	0.006 (0.009)	0.517	1.006 (0.988 to 1.024)	-0.605 (0.201)	0.003	0.546 (0.368 to 0.81)	0.014 (0.014)	0.320	1.014 (0.987 to 1.041)
CMA										
IQVIA DA Germany	Negative Binomial	–0.001 (0.003)	0.672	0.999 (0.994 to 1.004)	-0.095 (0.062)	0.128	0.910 (0.805 to 1.028)	0.005 (0.01)	0.584	1.005 (0.988 to 1.021)
IQVIA LPD Belgium	Poisson*	0.024 (0.008)	0.003	1.024 (1.008 to 1.040)	-0.438 (0.198)	0.024	0.646 (0.438 to 0.951)	0.033 (0.025)	0.191	1.033 (0.984 to 1.085)
NAJS	Negative Binomial*	–0.011 (0.006)	0.073	0.989 (0.977 to 1.001)	-0.286 (0.127)	0.024	0.751 (0.586 to 0.963)	0.024 (0.008)	0.005	1.024 (1.01 to 1.04)

[1] Negative binomial models were used in the presence of overdispersion. *Indicates adjustment for seasonality.

12.7.3. ITS analysis: RMM implemented in 2018

For this analysis, the time series spanned from January 2017 to October 2022, with the transition period (i.e., in grey) occurring between October 2018 and January 2019. Results from the model can be found in **Appendix II – Table 21**. Results for NAJS were not provided as the assumption for linearity did not hold.

IQVIA DA Germany:

Incidence rates of CMA prescribing prior to the intervention showed a decreasing trend in IQVIA DA Germany. A statistically significant step change was found at the time of the intervention, estimated at a RR of 0.714 (95% CI 0.540 to 0.943), corresponding to a reduction of -28.6% (-46 to -5.7). An abrupt decrease in incidence rates was observed 3–4 months after the intervention (i.e., May–August 2019) (**Figure 15**). This was followed by a positive and marginally statistically significant slope change, estimated at a RR of 1.025 (1.009 to 1.042), corresponding to an increase of 2.5% (0.9 to 4.2) per month. Overall results were consistent with those obtained for low-dose products and non-HRT use (**Appendix II – Table 21**).

The post-intervention trend crossed above the counterfactual in early 2020. Taking both step and slope changes into account, the impact of the intervention on incidence rates in October 2022 was estimated as an increase of approximately 121.0% (-12.4 to 457.5).

IQVIA LPD Belgium:

In contrast to IQVIA DA Germany, incidence rates of CMA prescribing prior to the intervention showed a modest upward trend in IQVIA LPD Belgium. Non-significant step and slope changes were observed, with values of 0.926 (0.731 to 1.172) and 0.998 (0.984 to 1.012) for the RRs, which translate to -7.5% (-26.9 to 17.2) and -0.2% (-1.6 to 1.2) reductions, respectively (**Figure 16**).

Negative step changes were observed across stratification variables, with no significant results across doses (high dose: 1.4% [-20.7 to 29.6]; low dose: -10.4 % [-31.7 to 17.6]) or indications (non-HRT: -11.7 % [-30.8 to 12.6]; HRT: -2% [-35.4 to 61.1]). ITS results stratified by dose and indication in IQVIA LPD Belgium are presented in **Appendix II – Figure 16** to **Appendix II – Figure 19**.

For NOMAC (overall), post-intervention trends remained below the counterfactual throughout the available follow-up period. Taking both step and slope changes into account, the impact of the intervention in October 2022 was estimated as an increase of approximately -15.6% (-62.0 to 88.3) in IQVIA LPD Belgium.

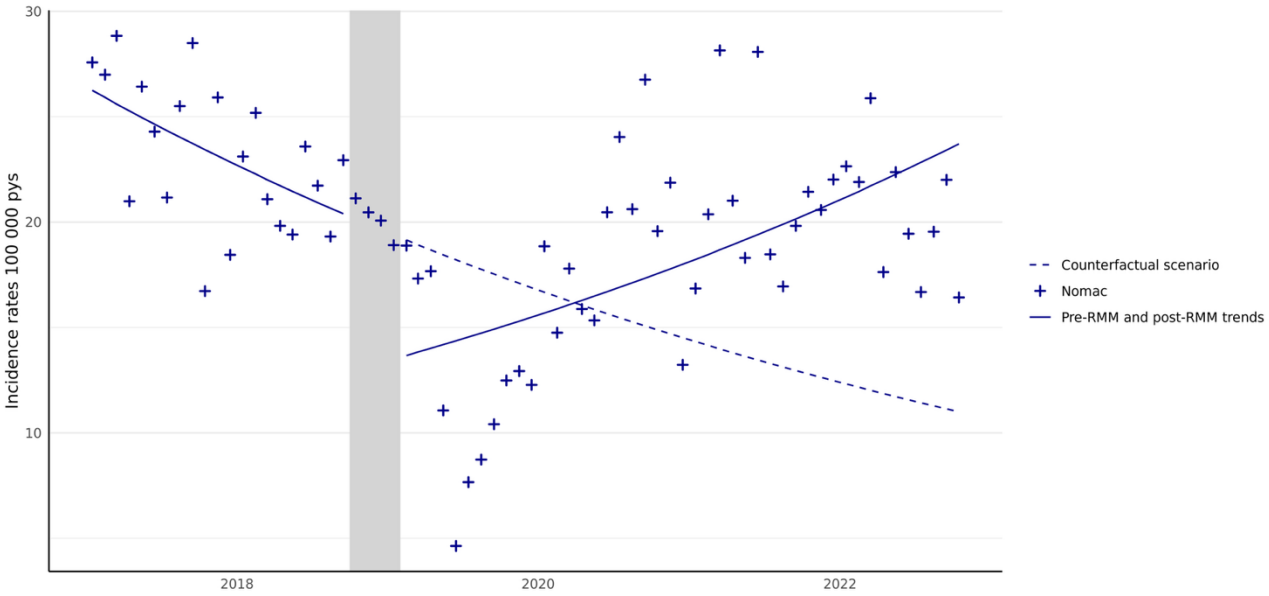

Figure information: Level change = -28.6% (-46% to -5.7%), Slope change = 2.5% (0.9% to 4.2%)

Figure 15. ITS analysis of RMM implemented in 2018 on incidence rates of NOMAC in IQVIA DA Germany.

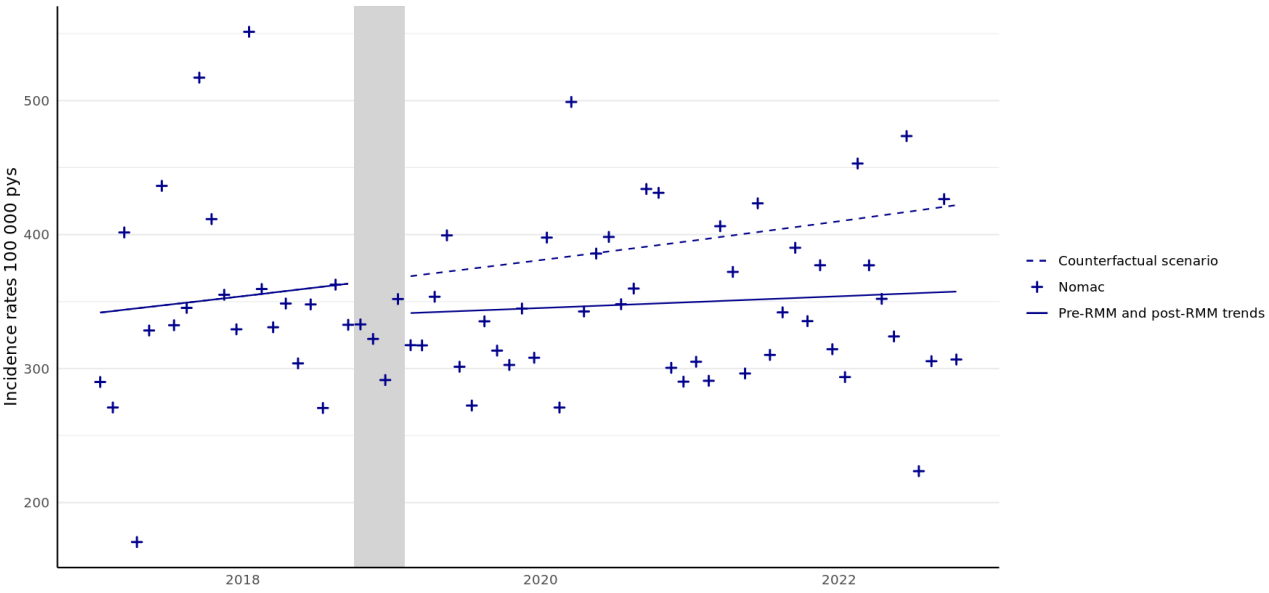

Figure information: Level change = -7.5% (-26.9% to 17.2%), Slope change = -0.2% (-1.6% to 1.2%)

Figure 16. ITS analysis of RMM implemented in 2018 on incidence rates of NOMAC in IQVIA LPD Belgium.

13. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Adverse events/adverse reactions were not 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.

14. DISCUSSION

14.1. Key results

Population-level DUS – Incidence and prevalence (Objective 1):

Incidence per 100,000 PY of NOMAC was 22 (21 to 22) in IQVIA DA Germany, 359 (349 to 369) in IQVIA LPD Belgium, and 13 (12 to 13) in NAJS. For CMA, rates (in the same units and order) were: 162 (161 to 163), 130 (124 to 136), and 96 (95 to 98). In general, incidence rates of NOMAC and CMA were higher among women aged 18–34 years, leading to higher rates for non-HRT than HRT use. The only high dose products observed was for NOMAC in IQVIA LPD Belgium with no high dose CMA. Incident events for high-dose products were only observed for NOMAC in IQVIA LPD Belgium (incidence per 100,000 PY; high-dose vs. low-dose products: 180 [173 to 187] vs. 160 [154 to 167]). Regarding ATC groups, incident records of NOMAC or CMA pertaining to pregnadien derivatives groupings (NOMAC: G03DB04; CMA: G03DB06) were only captured for NOMAC in IQVIA LPD Belgium and CMA in IQVIA DA Germany.

Regarding incidence of other drug classes of interest, progestogens and oestrogens in combination had the highest rates in IQVIA DA Germany and IQVIA LPD Belgium, while pregnadien derivatives obtained the highest rates in NAJS. Incidence of medroxyprogesterone was 41 (41 to 42) in IQVIA DA Germany, 151 (145 to 158) in IQVIA LPD Belgium, and 272 (269 to 274) in NAJS.

Prevalence results aligned with those seen for incidence results, showing similar patterns across outcomes and stratification variables. Less than 2% of women included were exposed to NOMAC, CMA, or medroxyprogesterone across databases. Results stratified by covariates of interest during the entire study period aligned with those seen for incidence results, showing similar patterns across stratification variables.

Regarding the pre- and post-intervention comparison, incidence rates obtained during the pre-intervention period were higher or similar than those obtained during the post-intervention period. This pattern was observed across all drug classes and progestogens of interest in all databases, except for IQVIA LPD Belgium, where increases after the intervention were observed for all drug classes and progestogens studied. Regarding period prevalence, the proportion of women exposed to drugs and progestogens of interest during the post-intervention period was lower than that observed for the pre-intervention period. Stratified analyses of NOMAC and CMA by dose (where available) and ATC groups showed patterns consistent with the overall findings. Changes in incidence or prevalence before and after the intervention obtained as part of Objective 1 should be interpreted with caution, as they do not consider the underlying trends and do not represent a formal analysis of the impact of the RMM.

Patient-level DUS - New users of NOMAC or CMA (Objectives 2, 4, 5):

The study population for objectives 2, 4, and 5, included women newly prescribed with NOMAC (n= 10,519 in IQVIA DA Germany; n= 4,078 in IQVIA LPD Belgium; n=1,918 in NAJS) and with CMA (n= 61,275 in IQVIA DA Germany; n= 1,582 in IQVIA LPD Belgium; n=13,512 in NAJS). Median age at treatment start was approximately 30–37 years for NOMAC and 23–30 years for CMA, with over >80% of women being estimated most likely to be prescribed these medications for non-HRT purposes (i.e., aged 10–49 years).

Average initial treatment duration (in days) for NOMAC was approximately 273 in IQVIA DA Germany, 200 in IQVIA LPD Belgium, and 138 in NAJS. For CMA, figures (in the same units and order) were: 193, 239, and 166. For NOMAC, cumulative dose (assessed at drug-era level) was 492 mg in IQVIA DA Germany and 615 mg in IQVIA LPD Belgium. For CMA, cumulative dose was 267 mg for IQVIA DA Germany and 28 mg for IQVIA LPD Belgium. Cumulative doses recorded in this study were lower than expected, particularly for IQVIA LPD Belgium, and should be interpreted with caution due to inconsistencies in the mapping of certain drug records, which have been discussed in more detail in **14.2. Limitations of the research methods**.

Most women were prescribed NOMAC as a non-first-line treatment in IQVIA DA Germany (first-line vs. no-first-line: 38.9% vs. 61.1%), whereas the opposite pattern was observed in IQVIA LPD Belgium (68.3% vs. 31.7%). CMA was predominantly prescribed as a first-line treatment in both databases (IQVIA DA Germany: 58.2% vs. 41.8%; IQVIA LPD Belgium: 58.5% vs. 41.5%). No differences by line of treatment were observed in NAJS.

The most frequently observed treatment strategy 180 days after the end of treatment was discontinuation. For NOMAC, the proportion of women who discontinued treatment was 73.8% for IQVIA DA Germany, 85.3% for IQVIA LPD Belgium, and 57.9% for NAJS. For CMA, corresponding figures (in the same order) were 78.9%, 79.4%, and 58.3%. Restarting treatment or switching to alternative treatments were observed in 10–15% of women in IQVIA DA Germany and in 15–26% of women in NAJS. In IQVIA LPD Belgium, restarting treatment was more frequent than switching (restart vs. switching: 9.9% vs. 4.4% for NOMAC; 12.3% vs. 8.1% for CMA).

Cases of meningioma during treatment were only observed for CMA in IQVIA DA Germany (n=8). This assessment was based on the occurrence of a diagnostic code during treatment, regardless of whether it marked the first occurrence of the event. These cases occurred within the final six months of treatment, before the implementation of RMM.

Changes in prescribing treatments of NOMAC and CMA before and after the implementation of RMM were assessed using aSMD. For treatment duration and cumulative dose, a 1-year period was used to compare periods of equal duration. In most cases, aSMD were not suggestive of differences in prescribing treatments before and after the implementation of RMM (aSMD $\leq$0.2). However, some modest differences were observed. A shorter treatment duration after the intervention was observed in IQVIA LPD Belgium for NOMAC (aSMD = 0.24; pre-RMM vs. post- RMM: 85 vs. 72 days) and CMA (aSMD = 0.33; pre-RMM vs. post-RMM: 117 vs. 71 days). Regarding treatment strategies, the number of switches among NOMAC users was lower during the post-intervention period in IQVIA DA Germany (aSMD = 0.32, pre-RMM vs. post-RMM: 16.0% vs. 6.2%) and NAJS (aSMD = 0.33, 23.6% vs. 11.3%). The opposite pattern was observed for discontinuation in IQVIA DA Germany (aSMD = 0.36, pre-RMM vs. post-RMM: 72.6% vs. 87.0%).

Patient-level DUS - New users of any of the drug classes and progestogens of interest (Objective 3):

We described the characteristics of women initiating treatment with any of the drug classes and progestogens of interest (n= 230,027 in IQVIA DA Germany; n= 35,123 in IQVIA LPD Belgium; n=234,919 in NAJS). Compared to other databases, the proportion of patients initiating treatment with NOMAC was higher in IQVIA LPD Belgium (7.7% vs. <1.5%), whereas CMA was more common in IQVIA DA Germany (15.1% vs. 2.5–3%). High-dose products were only captured for NOMAC in IQVIA LPD Belgium (4.1%). Progestogens and oestrogens in combination had the highest prevalence at index date in IQVIA DA

Germany (74.2%) and IQVIA LPD Belgium (85.2%), while pregnadien derivatives showed the highest estimates in NAJS (62.9%). Median age at treatment start was 29–35 years, with over >80% of women aged 10–49 years and assumed to be taking these medications for non-HRT purposes.

A total of 370 women exposed to any drug class and progestogens of interest had a prior diagnosis of meningioma (n= 75 in IQVIA DA Germany; n= 6 in IQVIA LPD Belgium; n= 289 in NAJS). The median years [Q25–Q75] since meningioma to treatment start were 3.7 in IQVIA DA Germany, 1.8 [0.7 – 5.7] in IQVIA LPD Belgium, and 2.4 [0.9 – 4.3] in NAJS.

Pre-specified conditions related to gynaecological care with higher prevalence across databases were menstrual disorders (33.6% in IQVIA DA Germany; 5.3% in IQVIA LPD Belgium; 20.5% in NAJS) and menopause/perimenopause (7.6% in IQVIA DA Germany; 3.7% in IQVIA LPD Belgium; 6.1% in NAJS), when considering all prior history. Most pre-specified gynaecological disorders were uncommon, with prevalence <3% in most cases. Pre-specified medications showed low prevalence (≤2%) across databases, except for antidepressants, which were captured among 9.9% of women included in IQVIA LPD Belgium and 5.8% in NAJS. Most frequently recorded conditions and medications identified through large-scale characterisation at index date were related to gynaecological disorders, physiological states related to pregnancy or menopause, and contraception.

The proportion of women with prior history of meningioma did not change before and after the implementation of RMM in IQVIA DA Germany (pre-RMM vs. post-RMM: 0.03% vs. 0.05%) and NAJS (0.1% vs. 0.2%). This comparison was not assessed in IQVIA LPD Belgium due to the limited numbers of counts observed (n=6 during the entire study period). In general, aSMD were suggestive of comparable cohort characteristics between women initiating treatment with any of the drug classes and progestogens of interest before and after the implementation of RMM. Some small differences were seen for conditions identified through large-scale characteristics, particularly in NAJS. However, these were unrelated to gynaecological care and represented <1% of the conditions assessed.

Analyses of RMM Effectiveness at population-level (Objective 6):

The impact of the intervention implemented in 2022 on monthly trends of incidence of NOMAC and CMA prescribing differed across ingredients and databases studied.

The intervention was associated with an immediate decrease in NOMAC prescribing incidence rates in NAJS (45.4% [95% CI -63.2 to -19]). No statistically significant immediate (i.e., step) or trend (i.e., slope) changes were observed in the other databases. In most cases, incidence rates declined at the time of the intervention but subsequently increased. Notably, the immediate change in IQVIA LPD Belgium was in the opposite direction, showing a non-significant increase in incidence rates at the time of the intervention (19.3% [-7.3 to 3.4]). Stratified results for NOMAC (with data across doses in IQVIA LPD Belgium only), showed consistent results with overall findings. For high-dose products, the results were similar to those for low-dose products, with the step and slope changes estimated at 28.3% (-5.5 to 74.4) and 0% (-4 to 4.2), respectively.

Regarding CMA, the intervention was associated with an immediate decrease in incidence rates in both IQVIA LPD Belgium (-35.5% [-56.2 to -4.9]) and NAJS (-24.9% [-41.4 to -3.7]), while a non-significant reduction was observed in IQVIA DA Germany (-9.1% [-19.5 to 2.8]). No significant changes in post-intervention trends were detected, except for a marginally significant positive slope change in NAJS (2.4% [0.7 to 4.1]).

The intervention implemented on 2018 (on high-dose NOMAC only) yield statistically significant results in IQVIA DA Germany. The step change was estimated at -28.6% (-46 to -5.7) and was followed by a positive and marginally statistically significant slope change of 2.5% (0.9 to 4.2). A decrease in incidence rates was observed 3–4 months after the intervention (i.e., May–August 2019) in IQVIA DA Germany. In IQVIA LPD Belgium, non-significant step and slope changes were estimated (-7.5% [-26.9 to 17.2] and -0.2% [-1.6 to

1.2], respectively). Negative step changes were observed across stratification variables, with no significant results across doses. Results for NAJS were not provided as the assumption for linearity did not hold.

14.2. Limitations of the research methods

General limitations:

The study was 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 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 were not captured.

The use of medicines of interest was derived from prescription data, and therefore assumptions about the use and duration of the drug are 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 was not available in the data and was assessed using age as a proxy. Age 50 was used as a threshold to reflect indication, with women aged 50 years or older assumed to take this medication for HRT and younger women assumed to take it for non-HRT reasons. This may have led to misclassification, particularly among women approaching the threshold age. Misclassification might have also occurred 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.(28) In addition, treatment lines were 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.

Recording of medications of interest:

The identification of drug classes using the ATC classification system involves important considerations. Some ATC codes include attributes that are not immediately apparent, such as route of administration, indication, mechanism of action, dosage, and combinations. Therefore, not every ATC code that contains the name of a drug ingredient is necessarily the correct classifier for that drug, as some ingredients appear in multiple ATC codes. As an example, medroxyprogesterone is the ingredient of 9 ATC concepts that have the same name but different attributes, such as different indications. Although recent efforts have improved the hierarchical structure, inconsistencies in the ATC-RxNorm mapping still exist, particularly for combination drugs,(29) and might have resulted in some misclassification of drugs according to ATC groupings.

Drug classes of interest—progestogens and oestrogens in combination, and progestogens that are pregnadien derivatives—were identified using clinical drug forms corresponding to relevant WHO ATC 4th-level codes. For the first group, clinical drug forms are based on combinations (e.g., Estradiol/nomegestrol Oral Tablet), whereas for the second, they are based on single ingredients (e.g., Nomegestrol Oral Tablet). The identification of drug combinations relied on the presence of combination products recorded as single drug entries in the database. Consequently, if a combination was recorded as two separate drug entries, it was not recognised as a true combination in our study, potentially leading to misclassification of the drug group. This might affected objectives where drug classes of interest were included, particularly when treated as separate outcomes (objective 1). This does not affect the overall assessment of NOMAC, CMA, or medroxyprogesterone, as these were assessed at the ingredient level regardless of whether they were administered alone or in combination. Additionally, the approach followed to identify ATC groups of interest could not distinguish all ATC 5th-level codes containing NOMAC or CMA, resulting in broader groups for stratification (see **9.10. Deviations from protocol**). Similarly, we were unable to distinct exclude oncological treatments in the case of medroxyprogesterone use (L02AB02).

The cumulative dose obtained in this study was lower than expected, particularly for CMA in IQVIA LPD Belgium. This is likely to be caused by two reasons. First, some of the concept IDs with ingredients of interest did not have a recorded dose. As a result, they contributed with an amount of 0 mg for cumulative calculations, which led to IQR showing 0 mg for some cases. However, they contributed to the denominator, leading to lower cumulative dose than expected. This issue was observed in some records mapped as branded drug forms (e.g., "Chlormadinone/Ethinyl Estradiol Oral Tablet [Belara]") and clinical drug forms (e.g., "chlormadinone/ethinyl estradiol Oral Tablet"). Based on diagnostic results, this primarily affected IQVIA DA Germany, where approximately 16–18% of individuals had a record of NOMAC or CMA with no dose. Second, current analytical pipelines calculate cumulative dose considering quantity as the number of tablets in each medicinal product.(30) Upon reviewing results, discrepancies were identified in how quantities and box sizes were recorded across products and databases studied, especially for marketed products in IQVIA LPD Belgium (e.g., "Chlormadinone 2 MG/Ethinyl Estradiol 0.03 MG Oral Tablet [Bellina] Box of 3 by Gedeon Richter"). For example, the quantity for products containing CMA in IQVIA LPD Belgium was recorded as the number of blisters per box rather than the actual number of tablets (e.g., 3 in the prior example). This caused the daily dose to be substantially lower, approximately 21 times below expected doses for CMA in IQVIA LPD Belgium (approximate daily dose = 0.11 mg/day). Although drug doses might be inferred from available products (e.g., 2 mg for CMA), the inconsistent recording of quantities and box sizes limited accurate assessment of cumulative dose, as we could not determine the number of tablets taken per patient. Based on the above, estimates for cumulative doses provided in this study are likely not reflective of actual cumulative dose and warrant further investigation. Cumulative dose was not estimated in NAJS due to lower daily doses of drugs were detected during the onboarding process (see **9.10. Deviations from protocol**).

Study period:

Only IQVIA DA Germany could contribute data from the start of the study period (2010) onwards. In IQVIA LPD Belgium and IQVIA DA Germany, the observation period of the patients in these databases were 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 are not considered active. Consequently, the denominators used to calculate the incidence of drugs prescribing in the population present an artefactual decrease whilst the incident users remain, incrementing the incidence and prevalence ratios. The presence of these artefacts affected the amount of follow up available for the study for objectives 1 and 6, with follow up ending in December 2023 (see **9.10. Deviations from protocol**).

Analysis:

The interventions studied were determined based on EU-level restrictions implemented in 2018 (for high-dose NOMAC and objective 6 only) and 2022. We used aSMD to compare patient-level characteristics before and after the intervention. In most cases, no substantial differences were observed before and after the intervention, and where differences were detected, they were generally small in magnitude. Given that SMD values are influenced by both effect size and variability, the high variability observed in the data may have limited our ability to detect meaningful differences between groups.(31)

The impact model for both interventions was hypotheses at protocol-stage as a step and slope change based on the nature of the intervention and the nature of its expected effect on the outcome. We did not explore alternative impact models or design choices to avoid inflating the risk of false positives,(22) as such analyses were not pre-specified in the study protocol. Additional analyses, preferably with additional follow-up data from settings were high-dose products are authorised, will be valuable to assess the long-term impact of the intervention implemented in 2022 and to evaluate its effects under alternative impact

models or study design choices, provided these are specified a priori. It is also important to note that while using monthly data provides more data points, they can introduce great variability, particularly if seasonal or other effects are present. In contrast, using longer time periods might have reduced this variability. However, this was not feasible given the limited number of data points in the post-intervention period.

Restrictions introduced in 2020 on products containing NOMAC in combination with oestradiol were not assessed in this study. This decision was based on the timing of the intervention coinciding with the onset of the coronavirus disease (COVID-19) pandemic, which could have influenced the outcomes and thus introduced a time-varying confounder.(21) Restrictions introduced for NOMAC in 2018 and 2022 were studied as separated interventions. The post-intervention period for the 2018 restrictions covered a longer timeframe, resulting in an unequal number of time points before and after the intervention, which encompassed the pandemic period. In IQVIA DA Germany, a decrease in incidence rates of NOMAC was observed a few months after the intervention (May – August 2019) and could suggest that other simultaneous events may have contributed to observed effects. Restrictions such as those implemented for cyproterone acetate in 2020 due to meningioma risk (32) may have indirectly influenced the outcomes observed. Future studies should consider the inclusion of a control series to account for other unmeasured or unknown concurrent events occurring around the same time as the intervention under study.(33)

14.3. Interpretation

Incidence rates and prevalence of drug classes and progestogens of interest differed by outcome and database. High-dose products were only captured for NOMAC use in IQVIA LPD Belgium, which reflects their availability according to current marketing authorisations. As of 2024, products containing NOMAC at doses of 3.75 or 5 mg were only authorised in six European countries, including Belgium. In other countries (including Germany and Croatia), products with low-dose NOMAC (2.5 mg) were only authorised for contraception in combination with oestradiol.(2) Regarding CMA, high-dose products in Europe are only authorised (but not necessarily marketed) in France for specific gynaecological indications.(4) Therefore, all products captured in this study should correspond to a dose of 2.5 mg for NOMAC (with some exceptions in IQVIA LPD Belgium) and of 2 mg for CMA.

To contextualise findings, we also assessed incidence and prevalence of other relevant drug classes. Prevalence of oral contraceptive use was similar to that reported in prior studies, which were also suggestive of variations across countries/databases.(34, 35) Notably, two key variations were observed across databases studied. First, pregnadien derivatives in NAJS surpassed figures obtained for progestogens and oestrogens in combination and were recorded in 9.4**%** of the women included, compared to ≤1.1% in IQVIA DA Germany and IQVIA LPD Belgium. Second, incidence of all drug classes and progestogens studied increased after the intervention in IQVIA LPD Belgium, when assessed without considering underlying trends. Differences in clinical practices across countries and the over-the-counter availability of some medications—particularly hormonal contraceptives—may explain some of the observed variations. However, the underlying factors contributing to discrepancies in prescribing were not explored in this study and warrant further investigation.

Our findings suggest that women treated with NOMAC or CMA in the included databases typically had an initial treatment duration of less than one year during their first recorded treatment episode, defined using a gap of 90 days between drug records (i.e., prescriptions). Previous studies linking NOMAC or CMA to an increased risk of meningioma have largely attributed this association to prolonged high dose use, usually spanning several years of exposure.(2-4) However, increases in risk were also seen at lower cumulative doses when used over prolonged periods, with doses between 1.2 and 3.6 g of NOMAC associated with a two-fold increase in meningioma risk.(2) While our findings suggest low treatment durations for the first treatment episode, the average cumulative dose per patient in IQVIA LPD Belgium was close to this threshold and should not be understated (mean [SD]: 1,025.2 [2,090.2] mg). Cumulative doses observed in this study were lower than expected and should be interpreted with considerable caution due to

discrepancies in the mapping of some drug records (see **14.2. Limitations of the research methods** for further details). However, these discrepancies were non-differential over time, and therefore, they are not expected to affect the comparison between time periods before and after the intervention.

The highest number of cases of meningioma in women treated with NOMAC have been reported in the context of off-label use (contraception and endometriosis) followed by reports in the authorised treatment of uterine leiomyoma and heavy menstrual bleeding. For CMA, most cases reported refer to use of the product in the endometriosis indication.(9) While indications were not assessed in this study (nor available in the data), our findings suggest that many women initiating treatment with drug classes of interest (which were not limited to NOMAC or CMA) had a prior history or current diagnosis related to menstrual disorders or menopause/perimenopause, with endometriosis and uterine fibroids accounting for a small proportion of cases. In NAJS, approximately 5% of women included had diagnostic codes related to early state of pregnancy, haemorrhagic complication of pregnancy, or threatened miscarriage, which might reflect the use of oral progestogen supplementation, such as dydrogesterone, in women with threatened miscarriage or a history of recurrent miscarriage.(36) Use of hormonal therapies was also recorded prior to the index date (i.e., the date of treatment initiation with the drug classes of interest) in some databases (prevalence ≤3%) and may reflect the use of medications beyond those included in the study.

We did not identify substantial changes in terms of patient characteristics and treatments prescribed following the RMM assessed as part of this study. This may be related to the fact that most NOMAC and CMA exposure observed in the databases would be considered low-dose whilst measures implemented in 2022 mostly targeted high-dose products, stating that such products should be limited to situations where alternative interventions are not appropriate, and that treatment should be confined to the minimum effective dose and shortest duration.(9) The contraindication of use in patients with prior history or current meningioma applied to all products with NOMAC or CMA irrespective of dose and were already in place for NOMAC since 2020.

The low prevalence of meningioma observed in this study is consistent with prior evidence, although most previous studies have been conducted in older populations, which are known to have a higher prevalence of meningiomas.(37-39) In this study, meningioma prior to initiating treatment with any of the drug classes or progestogens of interest (not limited to NOMAC or CMA) was rare. The higher number of cases observed in NAJS (0.1%) compared to IQVIA databases (0.02–0.03%) could be partially explained by the nature of the data, as NAJS includes hospital records, whereas the others are limited to primary care data only. Differences in the granularity of the source data might have also contributed to this discrepancy. Cases of meningioma during treatment with NOMAC or CMA were only captured for eight women in IQVIA DA Germany. These cases occurred within the final six months of CMA treatment and were observed before the implementation of RMM. The low number of meningioma cases observed during treatment may be attributable to the study population, which consisted of women undergoing their first treatment with NOMAC or CMA, most of whom were young (in their 20s or 30s) and were exposed to low-dose products for less than one year. Additionally, the absence of observed meningioma cases following the implementation of the RMM is noteworthy, especially since increased patient monitoring would typically be expected to lead to a higher number of detected cases. However, if cases did occur, they were not observed in the data.

While findings obtained in this study were not suggestive of major differences at-patient level before and after the implementation of RMM, some small differences were observed in IQVIA DA Germany and NAJS. During the post-intervention period, we observed a lower proportion of women using NOMAC switching to alternative treatments compared to before the restrictions. In contrast, a higher proportion of discontinuations were observed after the implementation of restrictions in IQVIA DA Germany. A higher prevalence of certain conditions identified through large-scale characterisation were also seen during the post-intervention period in NAJS. However, they accounted for <1% of the conditions assessed and were not suggestive of significant covariate imbalance. It is important to note that, while all results are available

in the “Shiny App”, we used a threshold of aSMD ≥0.2 to highlight differences before and after the intervention in this report. SMDs can be interpreted as the difference in mean effects between the experimental and comparator groups, divided by the pooled standard deviation of participants’ outcomes. Guiding rules from researchers in the social sciences often interpret an aSMD of 0.2 as a small effect, 0.5 as a moderate effect, and 0.8 as a large effect.(40) Based on these thresholds, the effect sizes of the differences observed in this study were considered small. However, the interpretation of effect sizes is context-dependent and may vary across studies.(31)

Results from ITS analyses varied by database and outcome, suggesting different impact of the RMM at population-level. The intervention was associated with an immediate decrease in incidence rates of NOMAC prescribing in NAJS (45.4% [-63.2 to -19]) and of CMA prescribing in both IQVIA LPD Belgium (-35.5% [-56.2 to -4.9]) and NAJS (-24.9% [-41.4 to -3.7]). In NAJS, significant changes in the slope of CMA prescribing were also observed, with an estimated monthly increase of 2.4% (0.7 to 4.1). Although not statistically significant in most cases, we observed a decline in incidence rates at the time the interventions were implemented (i.e., step change), followed by a positive change in trend (i.e., slope) thereafter. However, this pattern did not apply to NOMAC in IQVIA LPD Belgium, where we estimated a non-significant immediate change in the opposite (positive) direction (19.3% [-7.3 to 53.4]). While increases in incidence rates after the intervention were observed across all outcomes assessed in IQVIA LPD Belgium as part of Objective 1, these changes were not statistically significant for NOMAC after adjusting for underlying trends. The underlying drivers of increases observed in IQVIA LPD Belgium and NAJS were not explored in this study and may warrant further investigation.

The intervention targeting NOMAC in monotherapy, implemented in 2018, showed reductions in prescribing at the time of the intervention, and was followed by an increase in slope thereafter. Step and slope changes were non-significant in IQVIA LPD Belgium but significant in IQVIA DA Germany (step: -28.6% [-46 to -5.7]; slope: 2.5% [0.9 to 4.2]). These findings were unexpected, as the 2018 intervention targeted high dose products only, which were not observed in IQVIA DA Germany (but were present in IQVIA LPD Belgium, where no significant changes were observed). These findings, along with the decrease observed during May–August 2019, raise the possibility that time-varying confounders might have influenced the observed results in IQVIA DA Germany. Other interventions or events occurring around the time of intervention can introduce history bias and threaten the validity of ITS, potentially leading to misattribution of effects to the intervention under study.(33) While we are unaware of any other concurrent events that might have impacted the time series in IQVIA DA Germany, the presence of other confounding factors cannot be excluded and, therefore, results should be interpreted with caution.

It is also important to consider that concurrent events may have influenced the obtained results. For example, EU-level interventions targeting other hormonal therapies, such as RMM related to the use of cyproterone acetate due to meningioma risk were implemented in 2020.(32) Similarly, France implemented restrictions prior to the EU-level measures due to the increased awareness of meningioma risk. A recent study conducted in France reported an 85% reduction in high-dose cyproterone acetate use between August 2018 and December 2021.(41) While we cannot rule out the possibility that some patients switched to alternative medications following these regulatory actions, previous evidence did not observe a shift to a single alternative therapy following these measures. Instead, 34.9% of users switched to other hormonal treatments, with 2.1% and 3.9% being NOMAC and CMA, respectively.(41) Similarly, switches between NOMAC and CMA could have occurred and were not assessed as part of this study.

As previously mentioned, only interventions targeting NOMAC and CMA regardless of dose were those involving the contraindication of use in patients with a prior or current history of meningioma, implemented in 2020 for NOMAC in combination with oestradiol (not assessed in this study) and in 2022 for CMA. The low number of meningioma cases hindered the ability to assess the effect of the intervention at the population-level or to study it as a separate population. Given that most products observed in this study were low-dose, future studies aimed at evaluating this intervention should include data from

countries where high-dose products are marketed and establish distinct timings for low- and high-dose products. The availability of databases in the DARWIN EU® Data Network from settings where high doses of NOMAC and CMA are authorised is described in **14.5. Other information**. In addition, future studies should consider the inclusion of a control series to account for other events occurring around the same time as the intervention to increase the validity of the obtained results.(33)

14.4. Generalisability

This study included data from three databases from three different European countries. While we consider our results to largely reflect the incidence and prevalence of use of the drug classes and progestogens of interest—and to be broadly representative of women prescribed these drug classes—the findings should not be generalised to all of Europe. This is due to potential differences in population characteristics, over-the-counter access to the drugs of interest, and varying national regulatory actions across countries. In addition, data sources had limitations advising caution in interpretation of results, particularly related to cumulative doses.

14.5. Other information

Availability of high-dose products containing NOMAC or CMA in the DARWIN EU® Data Network:

High-dose products containing NOMAC or CMA are authorised in a few countries in Europe, including six countries for NOMAC (France, Italy, Portugal, Belgium, Luxembourg, and Poland) and one country for CMA (France). During the feasibility assessment, the inclusion of the French database Système National des Données de Santé (SNDS) was considered; however, it was not incorporated into the current study due to the lengthy process required to obtain IRB approval. At the time of the feasibility assessment, no databases from Italy, Luxembourg, and Poland were part of the DARWIN EU® Data Network. Although hospital databases with inpatient data from France and Portugal were available, they were not selected for the study due to limited counts for the treatments of interest and the lack of suitability for deriving population-level incidence rates. The process and rationale for database selection are discussed in greater detail in **9.2. Study setting and data sources**.

15. CONCLUSION

The use of NOMAC and CMA was low compared to progestogen-oestrogen combinations and pregnadien derivatives. High-dose products were infrequent and observed only for NOMAC in IQVIA LPD Belgium.

No obvious differences in the prescribing patterns of NOMAC and CMA were observed before and after the implementation of RMM in 2022. However, modest changes were observed regarding treatment duration, switching, and discontinuation in some databases. The characteristics of women initiating treatment with NOMAC, CMA, and other relevant drug classes were also similar across the pre- and post-intervention periods.

Cumulative doses recorded in this study were lower than expected and should be interpreted with caution due to inconsistencies in the mapping of certain drug records. These discrepancies were non-differential over time and are therefore unlikely to affect comparisons between time periods.

The impact of the 2022 intervention on trends in the incidence of NOMAC and CMA prescribing varied across ingredients and databases. In most cases, we observed a decline in incidence rates at the time the intervention was implemented (i.e., step change), followed by a positive change in trend (i.e., slope) thereafter. The intervention was associated with an immediate decrease in NOMAC prescribing in NAJS, and in CMA prescribing in both IQVIA LPD Belgium and NAJS. In NAJS, a significant positive change in the slope of CMA prescribing was also observed. Results for high-dose products (observed in IQVIA LPD Belgium only) were similar to those observed for low-dose products.

The 2018 intervention for NOMAC, assessed in IQVIA databases only, suggested significant reductions in incidence rates at the time of implementation in IQVIA DA Germany, followed by a positive change in slope thereafter. These findings were unexpected, as the 2018 intervention targeted high dose products only, which were not captured in IQVIA DA Germany but were present in IQVIA LPD Belgium, where no significant changes were detected.

In general, no substantial changes in prescribing of NOMAC and CMA following the RMM assessed as part of this study. This may be attributed to the fact that the majority of observed NOMAC and CMA exposures involved low-dose products, whereas the measures introduced in 2022 were predominantly directed at high-dose products. Future studies should prioritise the inclusion of databases from countries were high-dose products are authorised and use appropriate control series to minimise the risk of historical bias.

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17. ANNEXES

Appendix I

Drug classes of interest:

Progestogens

Concept ID[1]	Concept Name
19015533	Nomegestrol
19026733	Chlormadinone
1500211	Medroxyprogesterone

[1] All descendants included.

Progestogens and oestrogens in combination

Concept ID[1]	Concept Name
40893217	Butaperazine / Ethinyl Estradiol / Norethindrone Oral Tablet
43189304	Chlormadinone / Ethinyl Estradiol Delayed Release Oral Tablet
40025106	chlormadinone / ethinyl estradiol Oral Tablet
40133379	chlormadinone / mestranol Oral Tablet
43178398	Desogestrel / Ethinyl Estradiol Delayed Release Oral Tablet
40026728	desogestrel / ethinyl estradiol Oral Tablet
43159816	dienogest / Estradiol Delayed Release Oral Tablet
40181781	dienogest / estradiol Oral Tablet
43805219	dienogest / Ethinyl Estradiol Delayed Release Oral Tablet
40056400	dienogest / ethinyl estradiol Oral Tablet
36026935	drospirenone / estetrol Oral Tablet
43189248	drospirenone / Estradiol Delayed Release Oral Tablet
44785026	drospirenone / estradiol Oral Tablet
40228269	drospirenone / ethinyl estradiol / levomefolate Oral Tablet
36035945	drospirenone / ethinyl estradiol Delayed Release Oral Tablet
43189278	drospirenone / Ethinyl Estradiol Delayed Release Oral Tablet
40057995	drospirenone / ethinyl estradiol Oral Tablet
40042023	estradiol / ethinyl estradiol / levonorgestrel Oral Tablet
41267428	Estradiol / Medroxyprogesterone Extended Release Oral Capsule
40042030	estradiol / medroxyprogesterone Injectable Suspension
41017482	Estradiol / Medroxyprogesterone Oral Capsule
40042032	estradiol / medroxyprogesterone Oral Tablet
43167274	Estradiol / nomegestrol Delayed Release Oral Tablet
21158825	Estradiol / nomegestrol Oral Tablet
43134206	Estradiol / Norethindrone Delayed Release Oral Tablet

40042037	estradiol / norethindrone Oral Tablet
40039800	ethinyl estradiol / ethynodiol Oral Tablet
41174035	Ethinyl Estradiol / ferrous cation / Folic Acid / Norethindrone / pyridoxine Oral Tablet
41111504	Ethinyl Estradiol / ferrous cation / Norethindrone Oral Tablet
43211160	Ethinyl Estradiol / Gestodene Delayed Release Oral Tablet
40039760	ethinyl estradiol / gestodene Oral Tablet
36026967	ethinyl estradiol / levonorgestrel Chewable Tablet
43145189	Ethinyl Estradiol / Levonorgestrel Delayed Release Oral Tablet
43859607	Ethinyl Estradiol / Levonorgestrel Oral Lozenge
40039762	ethinyl estradiol / levonorgestrel Oral Tablet
40039774	ethinyl estradiol / lynestrenol Oral Capsule
40039775	ethinyl estradiol / lynestrenol Oral Tablet
40986435	Ethinyl Estradiol / Megestrol Oral Tablet
40039777	ethinyl estradiol / norethindrone Chewable Tablet
43526711	ethinyl estradiol / norethindrone Oral Capsule
40039778	ethinyl estradiol / norethindrone Oral Tablet
40039807	ethinyl estradiol / norgestimate Oral Tablet
43156395	Ethinyl Estradiol / Norgestrel Delayed Release Oral Tablet
40039793	ethinyl estradiol / norgestrel Oral Tablet
40059963	ethynodiol / mestranol Oral Tablet
40955139	Lynestrenol / Mestranol Oral Tablet
40062921	mestranol / norethindrone Oral Tablet
40924037	17-alpha-Hydroxyprogesterone / Estradiol Injectable Solution
40042027	17-alpha-hydroxyprogesterone / estradiol Injectable Suspension
35830364	17-alpha-hydroxyprogesterone / estradiol Injection
41267429	17-alpha-Hydroxyprogesterone / Estradiol Oral Solution
40830591	17-alpha-Hydroxyprogesterone / Estradiol Prefilled Syringe
41174212	Carbachol / Ergocalciferol / Estrone / Neostigmine / Procaine / Progesterone Injectable Solution
43134116	Dydrogesterone / Estradiol Delayed Release Oral Tablet
36269491	Dydrogesterone / Estradiol Extended Release Oral Capsule
36261782	Dydrogesterone / Estradiol Oral Capsule
40033424	dydrogesterone / estradiol Oral Tablet
40955278	Dydrogesterone / Ethinyl Estradiol Oral Tablet
40042019	estradiol / estriol / levonorgestrel Oral Tablet
40042020	estradiol / estriol / norethindrone Oral Tablet
43679562	Estradiol / Levonorgestrel Delayed Release Oral Tablet
21148852	Estradiol / Levonorgestrel Oral Tablet
40042036	estradiol / norethindrone Injectable Solution

40042056	estradiol / norgestimate Oral Tablet
21129093	Estradiol / Norgestrel Oral Tablet
40042042	estradiol / progesterone Injectable Solution
40042043	estradiol / progesterone Injectable Suspension
1356326	estradiol / progesterone Oral Capsule
21099778	Estriol / Norethindrone Oral Tablet
40037955	estrogens, conjugated (USP) / estrogens, esterified (USP) / medroxyprogesterone Oral Tablet
36880832	Estrogens, Conjugated (USP) / Medrogestone Delayed Release Oral Tablet
40037957	estrogens, conjugated (USP) / medrogestone Oral Tablet
36893485	Estrogens, Conjugated (USP) / Medroxyprogesterone Delayed Release Oral Tablet
42482220	Estrogens, Conjugated (USP) / Medroxyprogesterone Extended Release Oral Tablet
44094665	Estrogens, Conjugated (USP) / Medroxyprogesterone Oral Capsule
40037958	estrogens, conjugated (USP) / medroxyprogesterone Oral Tablet
40037966	estrogens, conjugated (USP) / norgestrel Oral Tablet
40038638	estrone / progesterone Injectable Solution
40038639	estrone / progesterone Injectable Suspension
36880831	Estrone / Progesterone Prefilled Syringe
40039471	ethinyl estradiol / ethisterone Oral Tablet
40062928	mestranol / norethynodrel Oral Tablet

[1] All descendants included.

Pregnadien derivates

Concept ID[1]	Concept Name
40075790	promegestone Oral Tablet
40058693	nomegestrol Oral Tablet
40066018	megestrol Oral Tablet
40066015	megestrol Oral Suspension
21023165	Megestrol Oral Capsule
40116980	Megestrol Acetate Oral Tablet
40126726	Megestrol Acetate Oral Suspension
40065265	medrogestone Oral Tablet
40033432	dydrogesterone Oral Tablet
43178242	Dydrogesterone Delayed Release Oral Tablet
45775362	dienogest Oral Tablet
35136860	dienogest Disintegrating Oral Tablet
35745301	dienogest Delayed Release Oral Tablet
40054930	demegestone Oral Tablet
40025118	chlormadinone Oral Tablet

42944746	Chlormadinone Extended Release Oral Tablet

[1] All descendants included, excluding 40037957 and 36880832.

Covariates for stratification

NOMAC: High-dose products

Concept ID	Concept Name
43029313	Estradiol 1.5 MG / nomegestrol 3.75 MG Oral Tablet
36894168	nomegestrol 3.75 MG
43136017	nomegestrol 3.75 MG [LUTENYL]
43146930	nomegestrol 3.75 MG Oral Tablet
43158124	nomegestrol 3.75 MG Oral Tablet [LUTENYL]
43158125	nomegestrol 3.75 MG Oral Tablet [LUTENYL] Box of 14
43158126	nomegestrol 3.75 MG Oral Tablet [LUTENYL] Box of 14 by TEVA
43029312	nomegestrol 3.75 MG Oral Tablet [LUTENYL] Box of 14 by Theramex HQ
43169007	nomegestrol 3.75 MG Oral Tablet Box of 14
19015535	nomegestrol 5 MG
43146927	nomegestrol 5 MG [LUTENYL]
36264180	nomegestrol 5 MG [Nogest]
43146928	nomegestrol 5 MG [NOMEGESTROL ARROW]
43212872	nomegestrol 5 MG [NOMEGESTROL BIOGARAN]
43190982	nomegestrol 5 MG [NOMEGESTROL EG]
43190983	nomegestrol 5 MG [NOMEGESTROL MYLAN]
43136010	nomegestrol 5 MG [NOMEGESTROL RATIOPHARM]
43158122	nomegestrol 5 MG [NOMEGESTROL SANDOZ]
36276925	nomegestrol 5 MG [Nomegestrol Stragen]
43212873	nomegestrol 5 MG [NOMEGESTROL TEVA]
43180093	nomegestrol 5 MG [NOMEGESTROL ZENTIVA]
19063240	nomegestrol 5 MG Oral Tablet
43136011	nomegestrol 5 MG Oral Tablet [LUTENYL]
43190985	nomegestrol 5 MG Oral Tablet [LUTENYL] Box of 10
43136012	nomegestrol 5 MG Oral Tablet [LUTENYL] Box of 10 by TEVA
43029311	nomegestrol 5 MG Oral Tablet [LUTENYL] Box of 10 by Theramex HQ
36257622	nomegestrol 5 MG Oral Tablet [LUTENYL] Box of 30
36276617	nomegestrol 5 MG Oral Tablet [LUTENYL] Box of 30 by TEVA
42656688	nomegestrol 5 MG Oral Tablet [LUTENYL] Box of 30 by Theramex
36265279	nomegestrol 5 MG Oral Tablet [LUTENYL] Box of 90
36258849	nomegestrol 5 MG Oral Tablet [LUTENYL] Box of 90 by TEVA
42656689	nomegestrol 5 MG Oral Tablet [LUTENYL] Box of 90 by Theramex
36262705	nomegestrol 5 MG Oral Tablet [Nogest]

36260143	nomegestrol 5 MG Oral Tablet [Nogest] Box of 30
42656686	nomegestrol 5 MG Oral Tablet [Nogest] Box of 30 by Ceres
36266488	nomegestrol 5 MG Oral Tablet [Nogest] Box of 30 by Mithra
36267862	nomegestrol 5 MG Oral Tablet [Nogest] Box of 90
42656687	nomegestrol 5 MG Oral Tablet [Nogest] Box of 90 by Ceres
36266577	nomegestrol 5 MG Oral Tablet [Nogest] Box of 90 by Mithra
43190986	nomegestrol 5 MG Oral Tablet [NOMEGESTROL ARROW]
43158123	nomegestrol 5 MG Oral Tablet [NOMEGESTROL ARROW] Box of 10
43190987	nomegestrol 5 MG Oral Tablet [NOMEGESTROL ARROW] Box of 10 by Arrow
43190988	nomegestrol 5 MG Oral Tablet [NOMEGESTROL BIOGARAN]
43136013	nomegestrol 5 MG Oral Tablet [NOMEGESTROL BIOGARAN] Box of 10
43146929	nomegestrol 5 MG Oral Tablet [NOMEGESTROL BIOGARAN] Box of 10 by Biogaran
43180094	nomegestrol 5 MG Oral Tablet [NOMEGESTROL EG]
43190989	nomegestrol 5 MG Oral Tablet [NOMEGESTROL EG] Box of 10
43180095	nomegestrol 5 MG Oral Tablet [NOMEGESTROL EG] Box of 10 by Eurogenerics
43136014	nomegestrol 5 MG Oral Tablet [NOMEGESTROL MYLAN]
43212874	nomegestrol 5 MG Oral Tablet [NOMEGESTROL MYLAN] Box of 10
43212875	nomegestrol 5 MG Oral Tablet [NOMEGESTROL MYLAN] Box of 10 by Mylan
43180096	nomegestrol 5 MG Oral Tablet [NOMEGESTROL RATIOPHARM]
43202041	nomegestrol 5 MG Oral Tablet [NOMEGESTROL RATIOPHARM] Box of 10
43212876	nomegestrol 5 MG Oral Tablet [NOMEGESTROL RATIOPHARM] Box of 10 by TEVA
43212877	nomegestrol 5 MG Oral Tablet [NOMEGESTROL SANDOZ]
43212878	nomegestrol 5 MG Oral Tablet [NOMEGESTROL SANDOZ] Box of 10
43202042	nomegestrol 5 MG Oral Tablet [NOMEGESTROL SANDOZ] Box of 10 by Sandoz
36267861	nomegestrol 5 MG Oral Tablet [Nomegestrol Stragen]
36257621	nomegestrol 5 MG Oral Tablet [Nomegestrol Stragen] Box of 10
36786403	nomegestrol 5 MG Oral Tablet [Nomegestrol Stragen] Box of 10 by Bepharbel
36266272	nomegestrol 5 MG Oral Tablet [Nomegestrol Stragen] Box of 10 by Stragen
43190990	nomegestrol 5 MG Oral Tablet [NOMEGESTROL TEVA]
43212879	nomegestrol 5 MG Oral Tablet [NOMEGESTROL TEVA] Box of 10
43136015	nomegestrol 5 MG Oral Tablet [NOMEGESTROL TEVA] Box of 10 by TEVA
43202043	nomegestrol 5 MG Oral Tablet [NOMEGESTROL ZENTIVA]
43180097	nomegestrol 5 MG Oral Tablet [NOMEGESTROL ZENTIVA] Box of 10
43136016	nomegestrol 5 MG Oral Tablet [NOMEGESTROL ZENTIVA] Box of 10 by Sanofi
43190984	nomegestrol 5 MG Oral Tablet Box of 10
43029310	nomegestrol 5 MG Oral Tablet Box of 10 by Arrow
42683408	nomegestrol 5 MG Oral Tablet Box of 10 by Bepharbel
43029308	nomegestrol 5 MG Oral Tablet Box of 10 by Biogaran

43029307	nomegestrol 5 MG Oral Tablet Box of 10 by Eurogenerics
43029306	nomegestrol 5 MG Oral Tablet Box of 10 by Mylan
43029309	nomegestrol 5 MG Oral Tablet Box of 10 by Sandoz
43029305	nomegestrol 5 MG Oral Tablet Box of 10 by Zentiva
36272374	nomegestrol 5 MG Oral Tablet Box of 30
36267291	nomegestrol 5 MG Oral Tablet Box of 90
43180089	nomegestrol Oral Tablet [LUTENYL]
36269587	nomegestrol Oral Tablet [Nogest]
43180090	nomegestrol Oral Tablet [NOMEGESTROL ARROW]
43212871	nomegestrol Oral Tablet [NOMEGESTROL BIOGARAN]
43180091	nomegestrol Oral Tablet [NOMEGESTROL EG]
43202038	nomegestrol Oral Tablet [NOMEGESTROL MYLAN]
43169006	nomegestrol Oral Tablet [NOMEGESTROL SANDOZ]
36277221	nomegestrol Oral Tablet [Nomegestrol Stragen]

NOMAC: Low-dose products

Concept ID	Concept Name
1832962	24 (Estradiol 1.5 MG / nomegestrol 2.5 MG Oral Tablet) / 4 (inert ingredients 0 MG Oral Tablet) Pack [Zoely] box
1832966	24 (Estradiol 1.5 MG / nomegestrol 2.5 MG Oral Tablet) / 4 (inert ingredients 0 MG Oral Tablet) Pack [Zoely] box
43211087	Estradiol / nomegestrol Delayed Release Oral Tablet [Zoely]
21139027	Estradiol / nomegestrol Oral Tablet [Zoely]
41235146	Estradiol 1.31 MG / nomegestrol 2.14 MG [Zoely]
41148787	Estradiol 1.31 MG / nomegestrol 2.14 MG Oral Tablet
41252190	Estradiol 1.31 MG / nomegestrol 2.14 MG Oral Tablet [Zoely]
41127409	Estradiol 1.31 MG / nomegestrol 2.14 MG Oral Tablet [Zoely] Box of 28
44160090	Estradiol 1.31 MG / nomegestrol 2.14 MG Oral Tablet [Zoely] Box of 28 by Merck
41283082	Estradiol 1.31 MG / nomegestrol 2.14 MG Oral Tablet [Zoely] Box of 84
44167647	Estradiol 1.31 MG / nomegestrol 2.14 MG Oral Tablet [Zoely] Box of 84 by Merck
41273102	Estradiol 1.31 MG / nomegestrol 2.14 MG Oral Tablet Box of 28
40836451	Estradiol 1.31 MG / nomegestrol 2.14 MG Oral Tablet Box of 84
41204207	Estradiol 1.5 MG / nomegestrol 2.19 MG [NAEMIS]
41023230	Estradiol 1.5 MG / nomegestrol 2.19 MG Oral Tablet
41064573	Estradiol 1.5 MG / nomegestrol 2.19 MG Oral Tablet [NAEMIS]
41158886	Estradiol 1.5 MG / nomegestrol 2.19 MG Oral Tablet [NAEMIS] Box of 24
41136393	Estradiol 1.5 MG / nomegestrol 2.19 MG Oral Tablet [NAEMIS] Box of 24 by TEVA
40824651	Estradiol 1.5 MG / nomegestrol 2.19 MG Oral Tablet [NAEMIS] Box of 72
41117308	Estradiol 1.5 MG / nomegestrol 2.19 MG Oral Tablet Box of 24
40898631	Estradiol 1.5 MG / nomegestrol 2.19 MG Oral Tablet Box of 72

21060527	Estradiol 1.5 MG / nomegestrol 2.5 MG [Zoely]
43167275	Estradiol 1.5 MG / nomegestrol 2.5 MG Delayed Release Oral Tablet
43156331	Estradiol 1.5 MG / nomegestrol 2.5 MG Delayed Release Oral Tablet [Zoely]
43200280	Estradiol 1.5 MG / nomegestrol 2.5 MG Delayed Release Oral Tablet [Zoely] Box of 24
43145148	Estradiol 1.5 MG / nomegestrol 2.5 MG Delayed Release Oral Tablet [Zoely] Box of 24 by TEVA
43178339	Estradiol 1.5 MG / nomegestrol 2.5 MG Delayed Release Oral Tablet [Zoely] Box of 72
43211090	Estradiol 1.5 MG / nomegestrol 2.5 MG Delayed Release Oral Tablet [Zoely] Box of 72 by TEVA
35754778	Estradiol 1.5 MG / nomegestrol 2.5 MG Delayed Release Oral Tablet [Zoely] Box of 84
35753402	Estradiol 1.5 MG / nomegestrol 2.5 MG Delayed Release Oral Tablet [Zoely] Box of 84 by Merck
35757584	Estradiol 1.5 MG / nomegestrol 2.5 MG Delayed Release Oral Tablet [Zoely] by Merck
36274031	Estradiol 1.5 MG / nomegestrol 2.5 MG Delayed Release Oral Tablet [Zoely] by TEVA
43211088	Estradiol 1.5 MG / nomegestrol 2.5 MG Delayed Release Oral Tablet Box of 24
43211089	Estradiol 1.5 MG / nomegestrol 2.5 MG Delayed Release Oral Tablet Box of 72
35745772	Estradiol 1.5 MG / nomegestrol 2.5 MG Delayed Release Oral Tablet Box of 84
21168636	Estradiol 1.5 MG / nomegestrol 2.5 MG Oral Tablet
21139028	Estradiol 1.5 MG / nomegestrol 2.5 MG Oral Tablet [Zoely]
2919390	estradiol 1.5 MG / nomegestrol 2.5 MG Oral Tablet [Zoely] Box of 3
21139029	Estradiol 1.5 MG / nomegestrol 2.5 MG Oral Tablet [Zoely] Box of 84
21050714	Estradiol 1.5 MG / nomegestrol 2.5 MG Oral Tablet [Zoely] Box of 84 by Merck
36063446	estradiol 1.5 MG / nomegestrol 2.5 MG Oral Tablet [Zoely] Box of 84 by Theramex HQ
21089906	Estradiol 1.5 MG / nomegestrol 2.5 MG Oral Tablet [Zoely] by Merck
36260923	Estradiol 1.5 MG / nomegestrol 2.5 MG Oral Tablet [Zoely] by TEVA
36063447	estradiol 1.5 MG / nomegestrol 2.5 MG Oral Tablet [Zoely] by Theramex HQ
2919391	estradiol 1.5 MG / nomegestrol 2.5 MG Oral Tablet Box of 3
21080206	Estradiol 1.5 MG / nomegestrol 2.5 MG Oral Tablet Box of 84
41201610	nomegestrol 2.14 MG
41044847	nomegestrol 2.19 MG
21021738	nomegestrol 2.5 MG
41300299	Estradiol / nomegestrol Oral Tablet [NAEMIS]

CMA: High-dose products

Concept ID	Concept Name
36882346	Chlormadinone 10 MG
43201389	Chlormadinone 10 MG [CHLORMADINONE MYLAN]
43135359	Chlormadinone 10 MG [CHLORMADINONE SANDOZ]
43168393	Chlormadinone 10 MG [CHLORMADINONE TEVA]
43212195	Chlormadinone 10 MG [LUTERAN]
36888639	Chlormadinone 10 MG Oral Tablet

43146244	Chlormadinone 10 MG Oral Tablet [CHLORMADINONE MYLAN]
43201390	Chlormadinone 10 MG Oral Tablet [CHLORMADINONE MYLAN] Box of 12
43179443	Chlormadinone 10 MG Oral Tablet [CHLORMADINONE MYLAN] Box of 12 by Mylan
43179444	Chlormadinone 10 MG Oral Tablet [CHLORMADINONE SANDOZ]
43201391	Chlormadinone 10 MG Oral Tablet [CHLORMADINONE SANDOZ] Box of 12
43179445	Chlormadinone 10 MG Oral Tablet [CHLORMADINONE SANDOZ] Box of 12 by Sandoz
43201392	Chlormadinone 10 MG Oral Tablet [CHLORMADINONE TEVA]
43190329	Chlormadinone 10 MG Oral Tablet [CHLORMADINONE TEVA] Box of 12
43168394	Chlormadinone 10 MG Oral Tablet [CHLORMADINONE TEVA] Box of 12 by TEVA
43157502	Chlormadinone 10 MG Oral Tablet [LUTERAN]
43179446	Chlormadinone 10 MG Oral Tablet [LUTERAN] Box of 12
43190330	Chlormadinone 10 MG Oral Tablet [LUTERAN] Box of 12 by Sanofi
43157501	Chlormadinone 10 MG Oral Tablet Box of 12
43031051	Chlormadinone 10 MG Oral Tablet Box of 12 by Mylan
43031053	Chlormadinone 10 MG Oral Tablet Box of 12 by Sandoz
43031052	Chlormadinone 10 MG Oral Tablet Box of 12 by TEVA
19026736	chlormadinone 5 MG
43190327	Chlormadinone 5 MG [CHLORMADINONE MYLAN]
43212191	Chlormadinone 5 MG [CHLORMADINONE SANDOZ]
43146240	Chlormadinone 5 MG [CHLORMADINONE TEVA]
43168392	Chlormadinone 5 MG [LUTERAN]
19060223	chlormadinone 5 MG Oral Tablet
43157498	Chlormadinone 5 MG Oral Tablet [CHLORMADINONE MYLAN]
43146241	Chlormadinone 5 MG Oral Tablet [CHLORMADINONE MYLAN] Box of 10
43212193	Chlormadinone 5 MG Oral Tablet [CHLORMADINONE MYLAN] Box of 10 by Mylan
43179442	Chlormadinone 5 MG Oral Tablet [CHLORMADINONE SANDOZ]
43190328	Chlormadinone 5 MG Oral Tablet [CHLORMADINONE SANDOZ] Box of 10
43212194	Chlormadinone 5 MG Oral Tablet [CHLORMADINONE SANDOZ] Box of 10 by Sandoz
43157499	Chlormadinone 5 MG Oral Tablet [CHLORMADINONE TEVA]
43146243	Chlormadinone 5 MG Oral Tablet [CHLORMADINONE TEVA] Box of 10
43135356	Chlormadinone 5 MG Oral Tablet [CHLORMADINONE TEVA] Box of 10 by TEVA
43135357	Chlormadinone 5 MG Oral Tablet [LUTERAN]
43135358	Chlormadinone 5 MG Oral Tablet [LUTERAN] Box of 10
43157500	Chlormadinone 5 MG Oral Tablet [LUTERAN] Box of 10 by Sanofi
43212192	Chlormadinone 5 MG Oral Tablet Box of 10
43031048	Chlormadinone 5 MG Oral Tablet Box of 10 by Mylan
43031050	Chlormadinone 5 MG Oral Tablet Box of 10 by Sandoz
43031049	Chlormadinone 5 MG Oral Tablet Box of 10 by TEVA

43135352	Chlormadinone Oral Tablet [CHLORMADINONE MYLAN]
43201386	Chlormadinone Oral Tablet [CHLORMADINONE SANDOZ]
43190325	Chlormadinone Oral Tablet [CHLORMADINONE TEVA]
43212189	Chlormadinone Oral Tablet [LUTERAN]

CMA: Low-dose products

Concept ID	Concept Name
44179720	Chlormadinone / Ethinyl Estradiol Delayed Release Oral Tablet [Angiletta]
40988818	Chlormadinone / Ethinyl Estradiol Delayed Release Oral Tablet [Balanca]
43134255	Chlormadinone / Ethinyl Estradiol Delayed Release Oral Tablet [Belara]
43156393	Chlormadinone / Ethinyl Estradiol Delayed Release Oral Tablet [BELARA]
36785561	Chlormadinone / Ethinyl Estradiol Delayed Release Oral Tablet [Bellina]
44160882	Chlormadinone / Ethinyl Estradiol Delayed Release Oral Tablet [Bellissima]
40926262	Chlormadinone / Ethinyl Estradiol Delayed Release Oral Tablet [Bonita Al]
41269706	Chlormadinone / Ethinyl Estradiol Delayed Release Oral Tablet [Chariva]
40926261	Chlormadinone / Ethinyl Estradiol Delayed Release Oral Tablet [Chloee]
41082535	Chlormadinone / Ethinyl Estradiol Delayed Release Oral Tablet [Enriqa]
40957525	Chlormadinone / Ethinyl Estradiol Delayed Release Oral Tablet [Helen]
40895290	Chlormadinone / Ethinyl Estradiol Delayed Release Oral Tablet [Lisette]
44172252	Chlormadinone / Ethinyl Estradiol Delayed Release Oral Tablet [Madinance]
40926260	Chlormadinone / Ethinyl Estradiol Delayed Release Oral Tablet [Madinette 30]
40988816	Chlormadinone / Ethinyl Estradiol Delayed Release Oral Tablet [Minette]
41238777	Chlormadinone / Ethinyl Estradiol Delayed Release Oral Tablet [Mona Hexal]
41300719	Chlormadinone / Ethinyl Estradiol Delayed Release Oral Tablet [Pink Luna]
41082534	Chlormadinone / Ethinyl Estradiol Delayed Release Oral Tablet [Solera]
43618415	Chlormadinone / Ethinyl Estradiol Oral Tablet [Angiletta]
43726351	Chlormadinone / Ethinyl Estradiol Oral Tablet [Balanca]
43744405	Chlormadinone / Ethinyl Estradiol Oral Tablet [Belara]
43708412	Chlormadinone / Ethinyl Estradiol Oral Tablet [BELARA]
36259447	Chlormadinone / Ethinyl Estradiol Oral Tablet [Bellina]
43690551	Chlormadinone / Ethinyl Estradiol Oral Tablet [Bellissima]
43816340	Chlormadinone / Ethinyl Estradiol Oral Tablet [Bonita Al]
43654573	Chlormadinone / Ethinyl Estradiol Oral Tablet [Chariva]
43600401	Chlormadinone / Ethinyl Estradiol Oral Tablet [Chloee]
43600399	Chlormadinone / Ethinyl Estradiol Oral Tablet [Enriqa]
41113764	Chlormadinone / Ethinyl Estradiol Oral Tablet [Helen]
43816342	Chlormadinone / Ethinyl Estradiol Oral Tablet [Lisette]
43780363	Chlormadinone / Ethinyl Estradiol Oral Tablet [Madinance]

43654571	Chlormadinone / Ethinyl Estradiol Oral Tablet [Madinette 30]
43780364	Chlormadinone / Ethinyl Estradiol Oral Tablet [Minette]
43600400	Chlormadinone / Ethinyl Estradiol Oral Tablet [Mona Hexal]
41300720	Chlormadinone / Ethinyl Estradiol Oral Tablet [Neo Eunomin]
43834562	Chlormadinone / Ethinyl Estradiol Oral Tablet [Pink Luna]
43744404	Chlormadinone / Ethinyl Estradiol Oral Tablet [Solera]
40832903	Chlormadinone / Mestranol Oral Tablet [Eunomin]
40926259	Chlormadinone / Mestranol Oral Tablet [Gestamestrol]
41019751	Chlormadinone / Mestranol Oral Tablet [Ovosiston]
40889838	Chlormadinone 0.714 MG
40954344	Chlormadinone 0.714 MG / Mestranol 0.075 MG [Eunomin]
41086908	Chlormadinone 0.714 MG / Mestranol 0.075 MG Oral Tablet
40941921	Chlormadinone 0.714 MG / Mestranol 0.075 MG Oral Tablet [Eunomin]
41004253	Chlormadinone 0.714 MG / Mestranol 0.075 MG Oral Tablet [Eunomin] Box of 168
40941920	Chlormadinone 0.714 MG / Mestranol 0.075 MG Oral Tablet [Eunomin] Box of 84
41118203	Chlormadinone 0.714 MG / Mestranol 0.075 MG Oral Tablet Box of 168
41305096	Chlormadinone 0.714 MG / Mestranol 0.075 MG Oral Tablet Box of 84
43780362	Chlormadinone 1 MG
41266468	Chlormadinone 1 MG / Ethinyl Estradiol 0.05 MG [Neo Eunomin]
43852521	Chlormadinone 1 MG / Ethinyl Estradiol 0.05 MG Oral Tablet
41316317	Chlormadinone 1 MG / Ethinyl Estradiol 0.05 MG Oral Tablet [Neo Eunomin]
41285034	Chlormadinone 1 MG / Ethinyl Estradiol 0.05 MG Oral Tablet [Neo Eunomin] Box of 132
41066530	Chlormadinone 1 MG / Ethinyl Estradiol 0.05 MG Oral Tablet [Neo Eunomin] Box of 22
40918367	Chlormadinone 1 MG / Ethinyl Estradiol 0.05 MG Oral Tablet [Neo Eunomin] Box of 22 by Gedeon Richter
40879613	Chlormadinone 1 MG / Ethinyl Estradiol 0.05 MG Oral Tablet [Neo Eunomin] Box of 66
41324225	Chlormadinone 1 MG / Ethinyl Estradiol 0.05 MG Oral Tablet [Neo Eunomin] Box of 66 by Gedeon Richter
43744406	Chlormadinone 1 MG / Ethinyl Estradiol 0.05 MG Oral Tablet [Neo Eunomin] by Gedeon Richter
41118204	Chlormadinone 1 MG / Ethinyl Estradiol 0.05 MG Oral Tablet Box of 132
41305097	Chlormadinone 1 MG / Ethinyl Estradiol 0.05 MG Oral Tablet Box of 22
41024174	Chlormadinone 1 MG / Ethinyl Estradiol 0.05 MG Oral Tablet Box of 66
41266466	Chlormadinone 1 MG / Mestranol 0.1 MG [Eunomin]
41086907	Chlormadinone 1 MG / Mestranol 0.1 MG Oral Tablet
41066518	Chlormadinone 1 MG / Mestranol 0.1 MG Oral Tablet [Eunomin]
41129373	Chlormadinone 1 MG / Mestranol 0.1 MG Oral Tablet [Eunomin] Box of 126
41316309	Chlormadinone 1 MG / Mestranol 0.1 MG Oral Tablet [Eunomin] Box of 21
40879602	Chlormadinone 1 MG / Mestranol 0.1 MG Oral Tablet [Eunomin] Box of 63
41180770	Chlormadinone 1 MG / Mestranol 0.1 MG Oral Tablet Box of 126
41180771	Chlormadinone 1 MG / Mestranol 0.1 MG Oral Tablet Box of 21

40930669	Chlormadinone 1 MG / Mestranol 0.1 MG Oral Tablet Box of 63
40827279	Chlormadinone 1.5 MG
40860834	Chlormadinone 1.5 MG / Ethinyl Estradiol 0.0225 MG [BELARA]
40923079	Chlormadinone 1.5 MG / Ethinyl Estradiol 0.0225 MG [Bellissima]
41016556	Chlormadinone 1.5 MG / Ethinyl Estradiol 0.0225 MG [Chariva]
40993176	Chlormadinone 1.5 MG / Ethinyl Estradiol 0.0225 MG Oral Tablet
40972923	Chlormadinone 1.5 MG / Ethinyl Estradiol 0.0225 MG Oral Tablet [BELARA]
41191980	Chlormadinone 1.5 MG / Ethinyl Estradiol 0.0225 MG Oral Tablet [BELARA] Box of 112
41035342	Chlormadinone 1.5 MG / Ethinyl Estradiol 0.0225 MG Oral Tablet [BELARA] Box of 168
41004262	Chlormadinone 1.5 MG / Ethinyl Estradiol 0.0225 MG Oral Tablet [BELARA] Box of 28
41253983	Chlormadinone 1.5 MG / Ethinyl Estradiol 0.0225 MG Oral Tablet [BELARA] Box of 84
41098047	Chlormadinone 1.5 MG / Ethinyl Estradiol 0.0225 MG Oral Tablet [Bellissima]
41004261	Chlormadinone 1.5 MG / Ethinyl Estradiol 0.0225 MG Oral Tablet [Bellissima] Box of 168
41191979	Chlormadinone 1.5 MG / Ethinyl Estradiol 0.0225 MG Oral Tablet [Bellissima] Box of 28
40848457	Chlormadinone 1.5 MG / Ethinyl Estradiol 0.0225 MG Oral Tablet [Bellissima] Box of 84
41066532	Chlormadinone 1.5 MG / Ethinyl Estradiol 0.0225 MG Oral Tablet [Chariva]
41004260	Chlormadinone 1.5 MG / Ethinyl Estradiol 0.0225 MG Oral Tablet [Chariva] Box of 168
40910634	Chlormadinone 1.5 MG / Ethinyl Estradiol 0.0225 MG Oral Tablet [Chariva] Box of 28
41285035	Chlormadinone 1.5 MG / Ethinyl Estradiol 0.0225 MG Oral Tablet [Chariva] Box of 84
40930672	Chlormadinone 1.5 MG / Ethinyl Estradiol 0.0225 MG Oral Tablet Box of 112
40899520	Chlormadinone 1.5 MG / Ethinyl Estradiol 0.0225 MG Oral Tablet Box of 168
40899521	Chlormadinone 1.5 MG / Ethinyl Estradiol 0.0225 MG Oral Tablet Box of 28
41118205	Chlormadinone 1.5 MG / Ethinyl Estradiol 0.0225 MG Oral Tablet Box of 84
40860833	Chlormadinone 1.5 MG / Ethinyl Estradiol 0.05 MG [Neo Eunomin]
41086910	Chlormadinone 1.5 MG / Ethinyl Estradiol 0.05 MG Oral Tablet
41316319	Chlormadinone 1.5 MG / Ethinyl Estradiol 0.05 MG Oral Tablet [Neo Eunomin]
41066531	Chlormadinone 1.5 MG / Ethinyl Estradiol 0.05 MG Oral Tablet [Neo Eunomin] Box of 132
41230997	Chlormadinone 1.5 MG / Ethinyl Estradiol 0.05 MG Oral Tablet [Neo Eunomin] Box of 132 by Gruenenthal
40910633	Chlormadinone 1.5 MG / Ethinyl Estradiol 0.05 MG Oral Tablet [Neo Eunomin] Box of 22
40918369	Chlormadinone 1.5 MG / Ethinyl Estradiol 0.05 MG Oral Tablet [Neo Eunomin] Box of 22 by Gruenenthal
41316318	Chlormadinone 1.5 MG / Ethinyl Estradiol 0.05 MG Oral Tablet [Neo Eunomin] Box of 66
41261732	Chlormadinone 1.5 MG / Ethinyl Estradiol 0.05 MG Oral Tablet [Neo Eunomin] Box of 66 by Gruenenthal
41305098	Chlormadinone 1.5 MG / Ethinyl Estradiol 0.05 MG Oral Tablet Box of 132
40837312	Chlormadinone 1.5 MG / Ethinyl Estradiol 0.05 MG Oral Tablet Box of 22
40993175	Chlormadinone 1.5 MG / Ethinyl Estradiol 0.05 MG Oral Tablet Box of 66
19026737	chlormadinone 2 MG
41204654	Chlormadinone 2 MG / Ethinyl Estradiol 0.02 MG [Menova]
40868453	Chlormadinone 2 MG / Ethinyl Estradiol 0.02 MG Oral Tablet

40910632	Chlormadinone 2 MG / Ethinyl Estradiol 0.02 MG Oral Tablet [Menova]
41160848	Chlormadinone 2 MG / Ethinyl Estradiol 0.02 MG Oral Tablet [Menova] Box of 30
40918368	Chlormadinone 2 MG / Ethinyl Estradiol 0.02 MG Oral Tablet [Menova] Box of 30 by Mylan
40993174	Chlormadinone 2 MG / Ethinyl Estradiol 0.02 MG Oral Tablet Box of 30
43654574	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG [Angiletta]
43690553	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG [Balanca]
41047878	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG [Beatrice]
43178396	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG [BELARA]
43834564	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG [Belara]
36261703	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG [Bellina]
43708416	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG [Bellissima]
41266467	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG [Bilmon]
43744407	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG [Bonita Al]
41016555	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG [Chantal]
43780365	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG [Chariva]
43708414	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG [Chloee]
43852523	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG [Enriqa]
40954345	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG [Eufem]
40985478	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG [Helen]
43762271	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG [Labibiane]
43672705	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG [Lisa]
43852524	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG [Lisette]
43726352	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG [Madinance]
43690552	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG [Madinette 30]
43762270	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG [Minette]
43726353	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG [Mona Hexal]
43708413	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG [Pink Luna]
43618418	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG [Solera]
41016554	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG [Verana Ratiopharm]
43134256	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet
44173843	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Angiletta]
44177616	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Angiletta] Box of 21
44175331	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Angiletta] Box of 21 by Puren
44181329	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Angiletta] Box of 63
44186575	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Angiletta] Box of 63 by Puren
41129381	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Balanca]
40848455	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Balanca] Box of 126
44186574	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Balanca] Box of 126 by Gedeon

41292890	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Balanca] Box of 126 by
44177615	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Balanca] Box of 21
44179086	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Balanca] Box of 21 by Gedeon
44171607	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Balanca] Box of 21 by
41066526	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Balanca] Box of 63
41230993	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Balanca] Box of 63 by Gedeon
41074509	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Balanca] Box of 63 by
40910630	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Beatrice]
44177614	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Beatrice] Box of 126
44171606	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Beatrice] Box of 126 by Pfizer
41066525	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Beatrice] Box of 63
41324223	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Beatrice] Box of 63 by Pfizer
43167335	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [BELARA]
43167336	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Belara]
40972917	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [BELARA] Box of 126
44167838	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [BELARA] Box of 126 by Eurim-
41230992	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [BELARA] Box of 126 by Gerke
44171604	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [BELARA] Box of 126 by
44171603	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [BELARA] Box of 126 by Mtk
41012051	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [BELARA] Box of 126 by Orifarm
43134259	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Belara] Box of 21
43145196	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [BELARA] Box of 21
43145197	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [BELARA] Box of 21 by Gedeon
43145198	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Belara] Box of 21 by Gedeon
40825060	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [BELARA] Box of 21 by
43145199	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Belara] Box of 63
43200344	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [BELARA] Box of 63
40856167	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [BELARA] Box of 63 by Cc
40980710	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [BELARA] Box of 63 by Emra-Med
44179085	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [BELARA] Box of 63 by Eurim-
43156394	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Belara] Box of 63 by Gedeon
43134258	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [BELARA] Box of 63 by Gedeon
41292889	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [BELARA] Box of 63 by Gerke
41137316	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [BELARA] Box of 63 by
44171605	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [BELARA] Box of 63 by Mtk
41160844	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [BELARA] Box of 84
40949697	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [BELARA] Box of 84 by Cc
36785557	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Bellina]

36785552	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Bellina] Box of 13
36785551	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Bellina] Box of 13 by Gedeon
36785556	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Bellina] Box of 3
36785555	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Bellina] Box of 3 by Gedeon
36785554	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Bellina] Box of 6
36785553	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Bellina] Box of 6 by Gedeon
44170123	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Bellissima]
44188913	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Bellissima] Box of 126
44186573	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Bellissima] Box of 126 by Meda
44166372	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Bellissima] Box of 21
44175330	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Bellissima] Box of 21 by Meda
44188914	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Bellissima] Box of 63
44160282	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Bellissima] Box of 63 by Meda
41129378	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Bilmon]
41253979	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Bilmon] Box of 126
41074507	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Bilmon] Box of 126 by 1 A
41160843	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Bilmon] Box of 21
41012050	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Bilmon] Box of 21 by 1 A
41066524	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Bonita Al]
44188912	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Bonita Al] Box of 126
44164075	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Bonita Al] Box of 126 by Aliud
41316315	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Bonita Al] Box of 21
40887507	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Bonita Al] Box of 21 by Aliud
41285033	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Bonita Al] Box of 63
41012049	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Bonita Al] Box of 63 by Aliud
41285032	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Chantal]
41223015	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Chantal] Box of 21
40848454	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Chariva]
41066523	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Chariva] Box of 126
41285031	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Chariva] Box of 21
41261726	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Chariva] Box of 21 by
40972916	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Chariva] Box of 63
40941925	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Chloee]
41004257	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Chloee] Box of 126
41324221	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Chloee] Box of 126 by Sanofi
40910628	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Chloee] Box of 21
41168518	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Chloee] Box of 21 by Sanofi
41098044	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Enriqa]

40879609	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Enriqa] Box of 21
41324220	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Enriqa] Box of 21 by Jenapharm
44177613	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Enriqa] Box of 63
44167837	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Enriqa] Box of 63 by Jenapharm
40879608	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Eufem]
44166370	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Eufem] Box of 126
44164074	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Eufem] Box of 126 by Novartis
41223012	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Eufem] Box of 21
41168516	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Eufem] Box of 21 by Novartis
44166371	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Eufem] Box of 63
44175329	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Eufem] Box of 63 by Novartis
41129376	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Helen]
41191972	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Helen] Box of 126
36785546	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Helen] Box of 13
36785545	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Helen] Box of 13 by Mithra
36785550	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Helen] Box of 3
36785549	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Helen] Box of 3 by Mithra
36785548	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Helen] Box of 6
36785547	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Helen] Box of 6 by Mithra
40941924	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Helen] Box of 63
40941923	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Labibiane]
41191971	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Labibiane] Box of 126
40949695	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Labibiane] Box of 126 by TEVA
41285030	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Labibiane] Box of 21
41004256	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Labibiane] Box of 63
40972915	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Lisette]
44170122	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Lisette] Box of 126
44167836	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Lisette] Box of 126 by Mylan
41160841	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Lisette] Box of 21
41074506	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Lisette] Box of 21 by Mylan
41066521	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Lisette] Box of 63
41230990	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Lisette] Box of 63 by Mylan
44185063	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Madinance]
44166369	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Madinance] Box of 21
44167835	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Madinance] Box of 21 by Acis
41004255	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Madinette 30]
41285028	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Madinette 30] Box of 126
41043136	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Madinette 30] Box of 126 by

41191969	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Madinette 30] Box of 21
44171602	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Madinette 30] Box of 21 by
41253977	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Madinette 30] Box of 63
41137314	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Madinette 30] Box of 63 by
41160839	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Madinette 30] Box of 84
41066520	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Minette]
40848453	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Minette] Box of 126
40910624	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Minette] Box of 21
44170121	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Minette] Box of 63
40879605	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Mona Hexal]
41285027	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Mona Hexal] Box of 21
41261724	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Mona Hexal] Box of 21 by
40910623	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Pink Luna]
41191968	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Pink Luna] Box of 63
41261723	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Pink Luna] Box of 63 by Stada
40910622	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Solera]
44162552	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Solera] Box of 126
44160281	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Solera] Box of 126 by Hormosan
41098042	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Solera] Box of 21
41168513	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Solera] Box of 21 by Hormosan
40910621	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Solera] Box of 63
40918363	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Solera] Box of 63 by Hormosan
41191966	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Verana Ratiopharm]
41098041	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Verana Ratiopharm] Box of 126
41105916	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Verana Ratiopharm] Box of 126
41129374	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Verana Ratiopharm] Box of 21
41012048	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Verana Ratiopharm] Box of 21
41253976	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Verana Ratiopharm] Box of 84
40918362	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet [Verana Ratiopharm] Box of 84
40930671	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet Box of 126
44171608	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet Box of 126 by Aristo
41043138	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet Box of 126 by Steiner Berlin
36785558	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet Box of 13
43134257	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet Box of 21
40980709	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet Box of 21 by Aristo
36785560	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet Box of 3
36785559	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet Box of 6
43145195	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet Box of 63

44179087	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet Box of 63 by Aristo
40887506	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet Box of 63 by Steiner Berlin
41149671	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Delayed Release Oral Tablet Box of 84
19107239	chlormadinone 2 MG / ethinyl estradiol 0.03 MG Oral Tablet
43744408	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Angiletta]
41035341	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Angiletta] Box of 126
41261730	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Angiletta] Box of 126 by Puren
41223019	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Angiletta] Box of 21
41261731	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Angiletta] Box of 21 by Puren
41129383	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Angiletta] Box of 63
41292895	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Angiletta] Box of 63 by Puren
43708419	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Angiletta] by Actavis
43690555	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Balanca]
41253982	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Balanca] Box of 126
41137320	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Balanca] Box of 126 by Gedeon Richter
40856169	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Balanca] Box of 126 by Gruenenthal
41066529	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Balanca] Box of 21
40856174	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Balanca] Box of 21 by Gedeon Richter
41137321	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Balanca] Box of 21 by Gruenenthal
41129380	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Balanca] Box of 63
40856170	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Balanca] Box of 63 by Gedeon Richter
40918365	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Balanca] Box of 63 by Gruenenthal
43600403	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Balanca] by Gedeon Richter
41160847	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Beatrice]
41160846	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Beatrice] Box of 126
41199924	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Beatrice] Box of 126 by Pfizer
41223018	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Beatrice] Box of 21
40918366	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Beatrice] Box of 21 by Pfizer
41129379	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Beatrice] Box of 63
40980711	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Beatrice] Box of 63 by Pfizer
43618422	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Belara]
43582366	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [BELARA]
41129382	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [BELARA] Box of 126
41137319	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [BELARA] Box of 126 by Cc
41043143	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [BELARA] Box of 126 by Eurim-Pharm
40949696	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [BELARA] Box of 126 by Gerke
41168523	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [BELARA] Box of 126 by Kohlpharma
41105920	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [BELARA] Box of 126 by Mtk

41324222	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [BELARA] Box of 126 by Orifarm Leverkus
40848456	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [BELARA] Box of 21
41292894	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [BELARA] Box of 21 by Cc
40856168	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [BELARA] Box of 21 by Gedeon Richter
41168520	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [BELARA] Box of 21 by Gruenenthal
41035340	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [BELARA] Box of 63
41199922	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [BELARA] Box of 63 by Cc
41261727	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [BELARA] Box of 63 by Emra-Med
41012052	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [BELARA] Box of 63 by Eurim-Pharm
41261729	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [BELARA] Box of 63 by Gedeon Richter
41074508	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [BELARA] Box of 63 by Gerke
41168519	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [BELARA] Box of 63 by Gruenenthal
41230996	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [BELARA] Box of 63 by Kohlpharma
40856173	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [BELARA] Box of 63 by Mtk
41316316	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [BELARA] Box of 84
40918364	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [BELARA] Box of 84 by Cc
43654577	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Belara] by Gedeon Richter
43654578	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [BELARA] by Gedeon Richter
36265736	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Bellina]
36265735	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Bellina] Box of 13
36261121	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Bellina] Box of 13 by Gedeon Richter
36270822	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Bellina] Box of 3
36271249	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Bellina] Box of 3 by Gedeon Richter
36273382	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Bellina] Box of 6
36257113	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Bellina] Box of 6 by Gedeon Richter
43618423	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Bellissima]
41035339	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Bellissima] Box of 126
40887510	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Bellissima] Box of 126 by Meda
41223017	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Bellissima] Box of 21
41199923	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Bellissima] Box of 21 by Meda
40972922	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Bellissima] Box of 63
41168522	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Bellissima] Box of 63 by Meda
43816346	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Bellissima] by Meda
40972921	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Bilmon]
40910629	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Bilmon] Box of 126
40823811	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Bilmon] Box of 126 by 1 A
40941926	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Bilmon] Box of 21
41199921	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Bilmon] Box of 21 by 1 A

41191978	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Bilmon] Box of 63
40949699	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Bilmon] Box of 63 by 1 A
43654575	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Bilmon] by 1 A
43636539	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Bonita Al]
41066528	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Bonita Al] Box of 126
40887509	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Bonita Al] Box of 126 by Aliud
41035337	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Bonita Al] Box of 21
41292888	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Bonita Al] Box of 21 by Aliud
41129377	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Bonita Al] Box of 63
41043141	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Bonita Al] Box of 63 by Aliud
43600402	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Bonita Al] by Aliud
41316314	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Chantal]
41191974	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Chantal] Box of 21
43744410	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Chariva]
41035336	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Chariva] Box of 126
41223014	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Chariva] Box of 21
41292887	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Chariva] Box of 21 by Gruenenthal
41223013	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Chariva] Box of 63
43726357	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Chariva] by Gedeon Richter
43834565	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Chloee]
41035335	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Chloee] Box of 126
41168517	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Chloee] Box of 126 by Sanofi
41316313	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Chloee] Box of 21
41230991	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Chloee] Box of 21 by Sanofi
40910631	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Chloee] Box of 63
40887508	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Chloee] Box of 63 by Sanofi
43744409	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Chloee] by Zentiva
43726354	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Enriqa]
41098046	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Enriqa] Box of 126
40856172	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Enriqa] Box of 126 by Jenapharm
41316312	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Enriqa] Box of 21
41261725	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Enriqa] Box of 21 by Jenapharm
40972920	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Enriqa] Box of 63
41105919	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Enriqa] Box of 63 by Jenapharm
43816343	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Enriqa] by Jenapharm
40941928	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Eufem]
41191976	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Eufem] Box of 126
41324224	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Eufem] Box of 126 by Novartis

41066522	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Eufem] Box of 21
41168515	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Eufem] Box of 21 by Novartis
41191977	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Eufem] Box of 63
40949698	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Eufem] Box of 63 by Novartis
41191973	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Helen]
41160842	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Helen] Box of 126
36275969	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Helen] Box of 13
42683360	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Helen] Box of 13 by Ceres
36273999	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Helen] Box of 13 by Mithra
36270823	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Helen] Box of 3
42683362	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Helen] Box of 3 by Ceres
36263402	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Helen] Box of 3 by Mithra
36268332	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Helen] Box of 6
42683361	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Helen] Box of 6 by Ceres
36266110	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Helen] Box of 6 by Mithra
40879607	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Helen] Box of 63
43690557	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Labibiane]
41316311	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Labibiane] Box of 126
41043140	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Labibiane] Box of 126 by TEVA
40910627	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Labibiane] Box of 21
40941922	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Labibiane] Box of 63
43654579	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Labibiane] by TEVA
43798323	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Lisa]
43726356	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Lisa] by Meda
43672708	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Lisette]
41098045	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Lisette] Box of 126
41074510	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Lisette] Box of 126 by Mylan
40879606	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Lisette] Box of 21
41043137	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Lisette] Box of 21 by Mylan
41160840	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Lisette] Box of 63
41137315	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Lisette] Box of 63 by Mylan
43708418	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Lisette] by Mylan
43618420	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Madinance]
41253981	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Madinance] Box of 126
40856171	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Madinance] Box of 126 by Acis
40879610	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Madinance] Box of 21
40980712	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Madinance] Box of 21 by Acis
40941927	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Madinance] Box of 63

41261728	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Madinance] Box of 63 by Acis
43852525	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Madinance] by Acis
43636538	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Madinette 30]
40822173	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Madinette 30] Box of 126
40980708	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Madinette 30] Box of 126 by Mibe
41160845	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Madinette 30] Box of 21
41230995	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Madinette 30] Box of 21 by Mibe
41285029	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Madinette 30] Box of 63
41168514	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Madinette 30] Box of 63 by Mibe
40910625	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Madinette 30] Box of 84
43690554	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Madinette 30] by Mibe
43816344	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Minette]
41098043	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Minette] Box of 126
41066519	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Minette] Box of 21
40972919	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Minette] Box of 63
43672707	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Minette] by Dr. Kade
43852526	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Mona Hexal]
41223016	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Mona Hexal] Box of 126
41168521	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Mona Hexal] Box of 126 by Novartis
41035334	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Mona Hexal] Box of 21
41105917	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Mona Hexal] Box of 21 by Novartis
41004259	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Mona Hexal] Box of 63
41292892	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Mona Hexal] Box of 63 by Novartis
43726355	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Mona Hexal] by Hexal
43672706	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Pink Luna]
41066527	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Pink Luna] Box of 126
41043142	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Pink Luna] Box of 126 by Stada
41004258	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Pink Luna] Box of 21
41292891	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Pink Luna] Box of 21 by Stada
41191967	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Pink Luna] Box of 63
41324219	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Pink Luna] Box of 63 by Stada
43582365	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Pink Luna] by Stada
43654576	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Solera]
41035338	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Solera] Box of 126
41230994	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Solera] Box of 126 by Hormosan
41035333	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Solera] Box of 21
41043135	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Solera] Box of 21 by Hormosan
41004254	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Solera] Box of 63

40856166	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Solera] Box of 63 by Hormosan
43816345	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Solera] by Hormosan
41253980	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Verana Ratiopharm]
40879604	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Verana Ratiopharm] Box of 126
40918361	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Verana Ratiopharm] Box of 126 by Ratiopharm
41285026	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Verana Ratiopharm] Box of 21
41324218	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Verana Ratiopharm] Box of 21 by Ratiopharm
40972918	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Verana Ratiopharm] Box of 63
41105918	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Verana Ratiopharm] Box of 63 by Ratiopharm
41191965	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Verana Ratiopharm] Box of 84
41137313	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet [Verana Ratiopharm] Box of 84 by Ratiopharm
40993173	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet Box of 126
41292893	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet Box of 126 by Aristo
41292886	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet Box of 126 by Steiner Berlin
36275086	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet Box of 13
41086909	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet Box of 21
41199920	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet Box of 21 by Aristo
41137318	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet Box of 21 by Steiner Berlin
36269971	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet Box of 3
36264893	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet Box of 6
41212153	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet Box of 63
41137317	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet Box of 63 by Aristo
41043139	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet Box of 63 by Steiner Berlin
41243100	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet Box of 84
43672709	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet by Aristo
43618419	Chlormadinone 2 MG / Ethinyl Estradiol 0.03 MG Oral Tablet by Gedeon Richter
43852522	Chlormadinone 2 MG / Ethinyl Estradiol 0.05 MG [Neo Eunomin]
19106342	chlormadinone 2 MG / ethinyl estradiol 0.05 MG Oral Tablet
43582363	Chlormadinone 2 MG / Ethinyl Estradiol 0.05 MG Oral Tablet [Neo Eunomin]
43672704	Chlormadinone 2 MG / Ethinyl Estradiol 0.05 MG Oral Tablet [Neo Eunomin] by Gedeon Richter
41079252	Chlormadinone 2 MG / Mestranol 0.05 MG [Esticia]
41297507	Chlormadinone 2 MG / Mestranol 0.05 MG [Gestamestrol]
40821238	Chlormadinone 2 MG / Mestranol 0.05 MG Oral Tablet [Esticia]
41160838	Chlormadinone 2 MG / Mestranol 0.05 MG Oral Tablet [Esticia] Box of 126
40980707	Chlormadinone 2 MG / Mestranol 0.05 MG Oral Tablet [Esticia] Box of 126 by Almirall
40910620	Chlormadinone 2 MG / Mestranol 0.05 MG Oral Tablet [Esticia] Box of 21
41012047	Chlormadinone 2 MG / Mestranol 0.05 MG Oral Tablet [Esticia] Box of 21 by Almirall
41253975	Chlormadinone 2 MG / Mestranol 0.05 MG Oral Tablet [Esticia] Box of 63

41043134	Chlormadinone 2 MG / Mestranol 0.05 MG Oral Tablet [Esticia] Box of 63 by Almirall
41316310	Chlormadinone 2 MG / Mestranol 0.05 MG Oral Tablet [Gestamestrol]
40879603	Chlormadinone 2 MG / Mestranol 0.05 MG Oral Tablet [Gestamestrol] Box of 21
40918360	Chlormadinone 2 MG / Mestranol 0.05 MG Oral Tablet [Gestamestrol] Box of 21 by Almirall
41160837	Chlormadinone 2 MG / Mestranol 0.05 MG Oral Tablet [Gestamestrol] Box of 63
40856165	Chlormadinone 2 MG / Mestranol 0.05 MG Oral Tablet [Gestamestrol] Box of 63 by Almirall
41180772	Chlormadinone 2 MG / Mestranol 0.05 MG Oral Tablet Box of 126
41243099	Chlormadinone 2 MG / Mestranol 0.05 MG Oral Tablet Box of 21
40930670	Chlormadinone 2 MG / Mestranol 0.05 MG Oral Tablet Box of 63
41110654	Chlormadinone 2 MG / Mestranol 0.08 MG [Ovosiston]
41316308	Chlormadinone 2 MG / Mestranol 0.08 MG Oral Tablet [Ovosiston]
41316307	Chlormadinone 2 MG / Mestranol 0.08 MG Oral Tablet [Ovosiston] Box of 126
41253974	Chlormadinone 2 MG / Mestranol 0.08 MG Oral Tablet [Ovosiston] Box of 21
41004252	Chlormadinone 2 MG / Mestranol 0.08 MG Oral Tablet [Ovosiston] Box of 63
40899519	Chlormadinone 2 MG / Mestranol 0.08 MG Oral Tablet Box of 126
41305095	Chlormadinone 2 MG / Mestranol 0.08 MG Oral Tablet Box of 21
40930668	Chlormadinone 2 MG / Mestranol 0.08 MG Oral Tablet Box of 63
40985479	Chlormadinone 2 MG [Chlormadinon Jenapharm]
43190326	Chlormadinone 2 MG [CHLORMADINONE TEVA]
41266469	Chlormadinone 2 MG [Gestafortin]
43135353	Chlormadinone 2 MG [LUTERAN]
19060222	chlormadinone 2 MG Oral Tablet
41004263	Chlormadinone 2 MG Oral Tablet [Chlormadinon Jenapharm]
41129384	Chlormadinone 2 MG Oral Tablet [Chlormadinon Jenapharm] Box of 100
44182836	Chlormadinone 2 MG Oral Tablet [Chlormadinon Jenapharm] Box of 100 by Jenapharm
41191983	Chlormadinone 2 MG Oral Tablet [Chlormadinon Jenapharm] Box of 12
44167839	Chlormadinone 2 MG Oral Tablet [Chlormadinon Jenapharm] Box of 12 by Jenapharm
41035344	Chlormadinone 2 MG Oral Tablet [Chlormadinon Jenapharm] Box of 14
44175332	Chlormadinone 2 MG Oral Tablet [Chlormadinon Jenapharm] Box of 14 by Jenapharm
40848458	Chlormadinone 2 MG Oral Tablet [Chlormadinon Jenapharm] Box of 20
44171609	Chlormadinone 2 MG Oral Tablet [Chlormadinon Jenapharm] Box of 20 by Jenapharm
40910636	Chlormadinone 2 MG Oral Tablet [Chlormadinon Jenapharm] Box of 36
44186576	Chlormadinone 2 MG Oral Tablet [Chlormadinon Jenapharm] Box of 36 by Jenapharm
41160849	Chlormadinone 2 MG Oral Tablet [Chlormadinon Jenapharm] Box of 60
44179088	Chlormadinone 2 MG Oral Tablet [Chlormadinon Jenapharm] Box of 60 by Jenapharm
43135355	Chlormadinone 2 MG Oral Tablet [CHLORMADINONE TEVA]
43201387	Chlormadinone 2 MG Oral Tablet [CHLORMADINONE TEVA] Box of 10
43157497	Chlormadinone 2 MG Oral Tablet [CHLORMADINONE TEVA] Box of 10 by TEVA

41223020	Chlormadinone 2 MG Oral Tablet [Gestafortin]
41191982	Chlormadinone 2 MG Oral Tablet [Gestafortin] Box of 14
40918371	Chlormadinone 2 MG Oral Tablet [Gestafortin] Box of 14 by Mylan
41253984	Chlormadinone 2 MG Oral Tablet [Gestafortin] Box of 20
41012053	Chlormadinone 2 MG Oral Tablet [Gestafortin] Box of 20 by Mylan
40910635	Chlormadinone 2 MG Oral Tablet [Gestafortin] Box of 24
41074511	Chlormadinone 2 MG Oral Tablet [Gestafortin] Box of 24 by Mylan
41035343	Chlormadinone 2 MG Oral Tablet [Gestafortin] Box of 42
41043144	Chlormadinone 2 MG Oral Tablet [Gestafortin] Box of 42 by Mylan
41191981	Chlormadinone 2 MG Oral Tablet [Gestafortin] Box of 84
40918370	Chlormadinone 2 MG Oral Tablet [Gestafortin] Box of 84 by Mylan
43179439	Chlormadinone 2 MG Oral Tablet [LUTERAN]
43201388	Chlormadinone 2 MG Oral Tablet [LUTERAN] Box of 10
43168391	Chlormadinone 2 MG Oral Tablet [LUTERAN] Box of 10 by Sanofi
43135354	Chlormadinone 2 MG Oral Tablet Box of 10
41180773	Chlormadinone 2 MG Oral Tablet Box of 100
40949700	Chlormadinone 2 MG Oral Tablet Box of 100 by Jenapharm
40930674	Chlormadinone 2 MG Oral Tablet Box of 12
41230998	Chlormadinone 2 MG Oral Tablet Box of 12 by Jenapharm
41086911	Chlormadinone 2 MG Oral Tablet Box of 14
41105921	Chlormadinone 2 MG Oral Tablet Box of 14 by Jenapharm
40930673	Chlormadinone 2 MG Oral Tablet Box of 20
41324226	Chlormadinone 2 MG Oral Tablet Box of 20 by Jenapharm
40868454	Chlormadinone 2 MG Oral Tablet Box of 24
40899523	Chlormadinone 2 MG Oral Tablet Box of 36
41199926	Chlormadinone 2 MG Oral Tablet Box of 36 by Jenapharm
40993177	Chlormadinone 2 MG Oral Tablet Box of 42
40837313	Chlormadinone 2 MG Oral Tablet Box of 60
41199925	Chlormadinone 2 MG Oral Tablet Box of 60 by Jenapharm
40899522	Chlormadinone 2 MG Oral Tablet Box of 84
43690549	Chlormadinone 2 MG Oral Tablet by Jenapharm
41014384	Chlormadinone 3 MG
40860832	Chlormadinone 3 MG / Mestranol 0.1 MG [Gestamestrol]
41086906	Chlormadinone 3 MG / Mestranol 0.1 MG Oral Tablet
40879601	Chlormadinone 3 MG / Mestranol 0.1 MG Oral Tablet [Gestamestrol]
41035332	Chlormadinone 3 MG / Mestranol 0.1 MG Oral Tablet [Gestamestrol] Box of 21
41316306	Chlormadinone 3 MG / Mestranol 0.1 MG Oral Tablet [Gestamestrol] Box of 63
40961932	Chlormadinone 3 MG / Mestranol 0.1 MG Oral Tablet Box of 21

41118202	Chlormadinone 3 MG / Mestranol 0.1 MG Oral Tablet Box of 63
19093201	chlormadinone acetate 2 MG
19107629	chlormadinone acetate 2 MG / mestranol 0.05 MG Oral Tablet
1503191	chlormadinone acetate 2 MG / mestranol 0.08 MG Oral Tablet
41019752	Chlormadinone Oral Tablet [Chlormadinon Jenapharm]

NOMAC: G03AA14 & G03FB12

Concept ID[1]	Concept Name
21158825	Estradiol / nomegestrol Oral Tablet
43167274	Estradiol / nomegestrol Delayed Release Oral Tablet

[1] All descendants included

NOMAC: G03DB04

Concept ID[1]	Concept Name
40058693	Nomegestrol Oral Tablet

[1] All descendants included

CMA: G03AA15, G03AB07 & G03FB03

Concept ID[1]	Concept Name
43189304	Chlormadinone / Ethinyl Estradiol Delayed Release Oral Tablet
40025106	chlormadinone / ethinyl estradiol Oral Tablet

[1] All descendants included

CMA: G03DB06

Concept ID[1]	Concept Name
40025118	Chlormadinone Oral Tablet
42944746	Chlormadinone Extended Release Oral Tablet

[1] All descendants included

Pre-specified conditions and medications

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
4091617	Malignant neoplasm of cerebral arachnoid mater
4178974	Malignant neoplasm of cerebral meninges
4181482	Malignant neoplasm of spinal meninges
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
4100554	Secretory meningioma
4098902	Spinal meningioma
4277603	Transitional meningioma
4175395	Xanthomatous meningioma

Pre-specified medications (not previously detailed):

Concept Name	Included Concept IDs[1]	Excluded Concept IDs
Antiandrogens	970250, 1356461, 996416, 19010792,	
Antidepressants	21604686 (N06A)	
Biphosphonates	21604148	
Clonidine	21600398	
Gonadotropin Releasing Hormone	19058410, 21602719, 19010868	
Metformin	1503297	

Pre-specified comorbidities (not previously detailed):

Concept Name	Included Concept IDs[1]	Excluded Concept IDs
Asthma	317009	
Autoimmune diseases	434621	
Cancer (any malignancy)	4189640, 443392, 141232	4155297, 433435
Endometriosis	433527	
Epilepsy	380378	
Hyperlipidaemia	432867	
Hypertensive disorder	201313, 4228419, 4317265, 442604,	4071202, 4118910, 321080
Menopause/Perimenopause	4054881, 4010333, 4296346, 4141640,	4128330
Menstrual disorders	39081, 4242733, 442274, 4302555,	
Neoplasm of the brain	4028542, 4135326, 42513839, 42513840,	432851, 440059, 44502806, 4189640,
Neoplasm of the breast	4112853, 4310721, 4313043, 4310988	432851, 440059, 42536723, 44502235,
Neurofibromatosis type 2	380975	
Obesity	433736, 4215968	
Osteoporosis	40480160, 80502	
Polycystic ovary syndrome	40443308, 36683296	

Primary ovarian insufficiency	4279913	4129547
Type 2 diabetes	201826, 443731, 376065, 443733, 443732	
Uterine fibroids	197236	
Venous thromboembolism	440417, 4133004	

[1] All descendants included except for those excluded.

Appendix II

Appendix II – Table 1. Study attrition of individuals included in Objective 1

	IQVIA DA Germany	IQVIA LPD Belgium	NAJS
Starting population	45,156,504	1,094,334	4,853,340
Birth date available	45,156,504	1,094,334	4,853,340
Sex available	45,128,169	1,094,334	4,853,340
Satisfied age criteria during the study period based on year of birth	43,307,003	1,027,578	4,485,794
Individuals with observation time available during the study period[1]	36,870,425	1,004,772	4,354,272
Satisfied age criteria during the study period	36,870,425	1,004,694	4,354,272
Prior history requirement fulfilled during the study period	17,039,838	648,220	4,301,338
Individuals with sex "Female"	9,704,732	348,525	2,205,014
Individuals with observation time available after applying age and prior observation	9,560,010	343,270	2,204,945

[1] Study period spanned from study start (or data availability start, if later) to end of data availability. In IQVIA DA Germany and IQVIA LPD Belgium, follow up for objective 1 ended on 31st December 2023.

Appendix II – Table 2. Study attrition of individuals included in the subgroup analysis for Objective 1 (prior history of meningioma)

	IQVIA DA Germany	IQVIA LPD Belgium	NAJS
Starting population[1]	33,302	200	12,711
Birth date available	33,302	200	12,711
Sex available	33,273	200	12,711
Satisfied age criteria during the study period based on year of birth	33,263	200	12,677
Individuals with observation time available during the study period[2]	31,276	200	12,339
Satisfied age criteria during the study period	31,276	200	12,339
Prior history requirement fulfilled during the study period	23,857	162	12,308
Individuals with sex "Female"	18,468	127	8,683
Individuals with observation time available after applying age and prior observation	18,467	127	8,682

[1] Individuals with a recorded diagnosis of meningioma.
[2] Study period spanned from study start (or data availability start, if later) to end of data availability.

Appendix II – Table 3. Study attrition of new users of drug classes and progestogens of interest (Objective 3)

	IQVIA DA Germany	IQVIA LPD Belgium	NAJS
Initial qualifying events	6,150,646	217,149	1,948,082
Collapse records separated by 90 or less days	2,145,828	148,475	954,622
Require first event	1,042,112	75,034	399,458
Require prior observation of 365 days	318,232	34,245	319,816
Require cohort start date during the study period[1]	230,635	33,787	251,421
Require female	230,034	33,639	234,925
Require age ≥10	230,027	33,631	234,919

[1] Study period spanned from study start (or data availability start, if later) to end of data availability.

Appendix II – Table 4. Baseline characteristics of new users of drug classes and progestogens of interest, overall and stratified by study period (Objective 3)

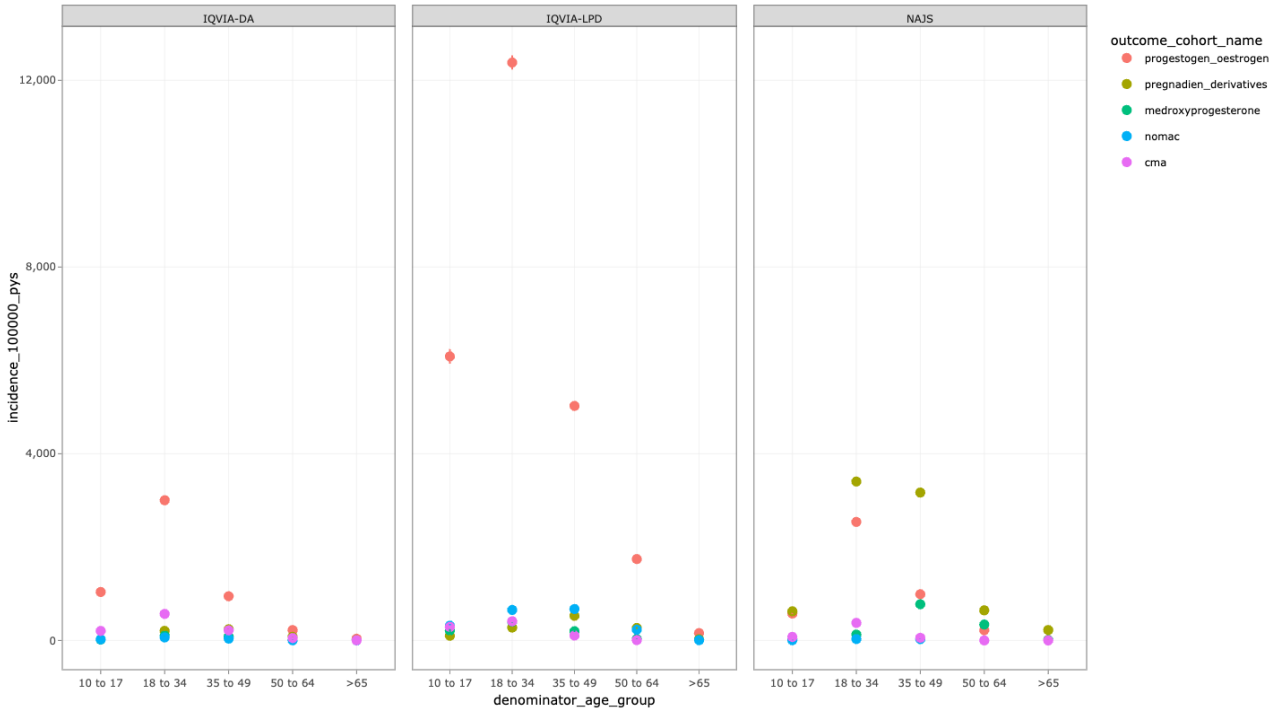
			IQVIA DA Germany			IQVIA LPD Belgium			NAJS		
			Overall	Pre-RMM	Post-RMM	Overall	Pre-RMM	Post-RMM	Overall	Pre-RMM	Post-RMM
Subjects	-	N	230,027	206,549	20,232	35,123	29,449	4,787	234,919	185,070	43,828
Age	-	Median [Q25 - Q75]	31 [21 - 42]	31 [21 - 42]	32 [22 - 43]	29 [19 - 41]	29 [20 - 41]	27 [18 - 41]	35 [25 - 45]	34 [25 - 45]	36 [25 - 47]
		Mean (SD)	32.80 (13.1)	32.8 (13.1)	33.0 (13.1)	31.5 (13.5)	31.6 (13.4)	30.6 (14.2)	36.0 (13.80)	35.7 (13.6)	36.7 (14.6)
		Range	10 to 99	11 to 95	11.0 to 99.0	10 to 91	10 to 91	11 to 87	10 to 98	10 to 98	10 to 98
Age group	10 to 17	N (%)	24,978 (10.9%)	22,283 (10.8%)	2,316 (11.4%)	5,889 (16.8%)	4,724 (16.0%)	1,001 (20.9%)	13,017 (5.5%)	9,644 (5.2%)	2,980 (6.8%)
	18 to 34	N (%)	111,440 (48.4%)	100,781 (48.8%)	9,190 (45.4%)	15,890 (45.2%)	13,399 (45.5%)	2,092 (43.7%)	104,226 (44.4%)	84,073 (45.4%)	17,708 (40.4%)
	35 to 49	N (%)	64,811 (28.2%)	57,711 (27.9%)	6,115 (30.2%)	9,005 (25.6%)	7,733 (26.3%)	1,063 (22.2%)	84,572 (36.0%)	66,199 (35.8%)	16,135 (36.8%)
	50 to 64	N (%)	25,420 (11.1%)	22,639 (11.0%)	2,390 (11.8%)	3,930 (11.2%)	3,262 (11.1%)	566 (11.8%)	23,860 (10.2%)	18,309 (9.9%)	4,892 (11.2%)
	> 65	N (%)	3,378 (1.5%)	3,135 (1.5%)	221 (1.1%)	409 (1.2%)	331 (1.1%)	65 (1.40%)	9,244 (3.9%)	6,845 (3.7%)	2,113 (4.8%)
Indication	Non-HRT	N (%)	201,229 (87.5%)	180,775 (87.5%)	17,621 (87.1%)	30,784 (87.6%)	25,856 (87.8%)	4,156 (86.8%)	201,815 (85.9%)	159,916 (86.4%)	36,823 (84.0%)
	HRT	N (%)	28,798 (12.5%)	25,774 (12.5%)	2,611 (12.9%)	4,339 (12.4%)	3,593 (12.2%)	631 (13.2%)	33,104 (14.1%)	25,154 (13.6%)	7,005 (16.0%)

[1] Study period spanned from study start (or data availability start, if later) to end of data availability. In IQVIA DA Germany and IQVIA LPD Belgium, follow up ended on 31st December 2023. Pre-RMM: from start date to October 2022, Post-RMM: from February 2023 to study end. Women initiating treatment during the transition period (November 2022 to January 2023) were not included in results stratified by study period.

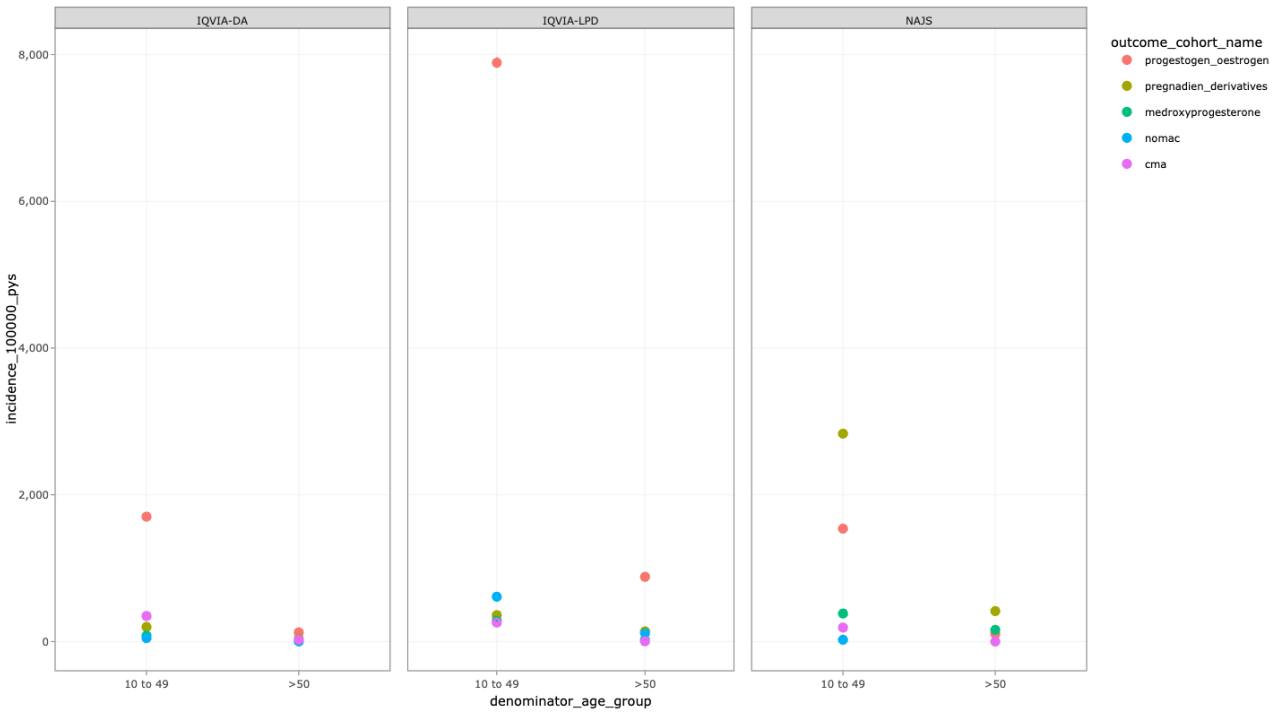
Appendix II – Table 5. Incidence rates of drug classes or progestogens of interest for the entire study period by database.

Outcome	Database name[1]	Number of events[2]	Person-years (PY)	Incidence per 100,000 PY (95% CI)[3]
Progestogens and oestrogens in combination	IQVIA DA Germany	390,018	50,660,998	770 (767 to 772)
	IQVIA LPD Belgium	51,198	1,260,576	4,061 (4,026 to 4,097)
	NAJS	124,351	15,275,728	814 (810 to 819)
Pregnadien derivatives	IQVIA DA Germany	56,592	52,392,863	108 (107 to 109)
	IQVIA LPD Belgium	3,502	1,405,630	249 (241 to 258)
	NAJS	247,961	15,347,543	1,616 (1,609 to 1,622)
NOMAC	IQVIA DA Germany	11,334	52,440,943	22 (21 to 22)
	IQVIA LPD Belgium	5,036	1,401,508	359 (349 to 369)
	NAJS	2,018	15,666,357	13 (12 to 13)
CMA	IQVIA DA Germany	84,619	52,218,787	162 (161 to 163)
	IQVIA LPD Belgium	1,836	1,408,788	130 (124 to 136)
	NAJS	15,065	15,636,273	96 (95 to 98)
Medroxyprogesterone	IQVIA DA Germany	21,643	52,403,735	41 (41 to 42)
	IQVIA LPD Belgium	2,133	1,407,985	151 (145 to 158)
	NAJS	42,428	15,613,825	272 (269 to 274)

[1] Study period spanned from study start (or data availability start, if later) to end of data availability. In IQVIA DA Germany and IQVIA LPD Belgium, follow up ended on 31st December 2023.
[2] Events correspond to prescriptions of drugs of interest. Incident events were defined using a washout of 365 days.
[3] Incidence estimates are rounded to the nearest whole number.



Appendix II – Figure 1. Incidence rates of drugs of interest for the entire study period by database, stratified by age groups.

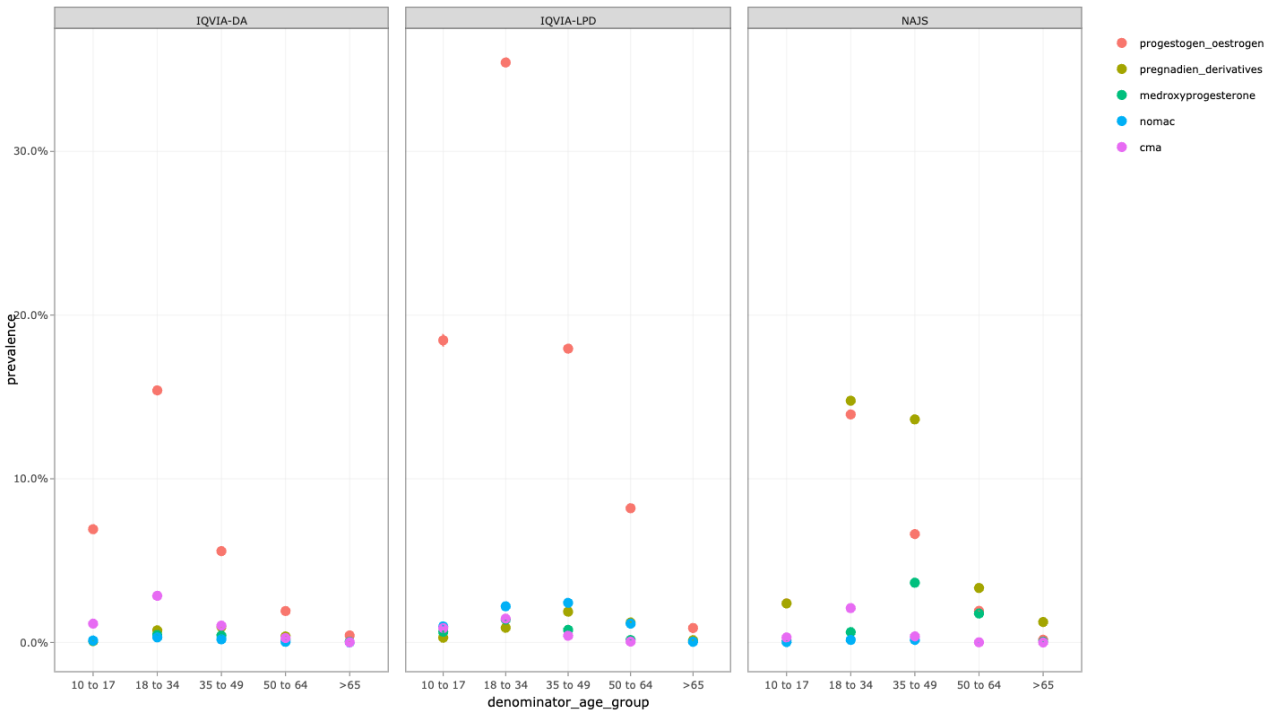


Appendix II – Figure 2. Incidence rates of drugs of interest for the entire study period by database, stratified by indication (assessed using age as a proxy; non-HRT: 10-49 years; HRT: ³ 50 years).

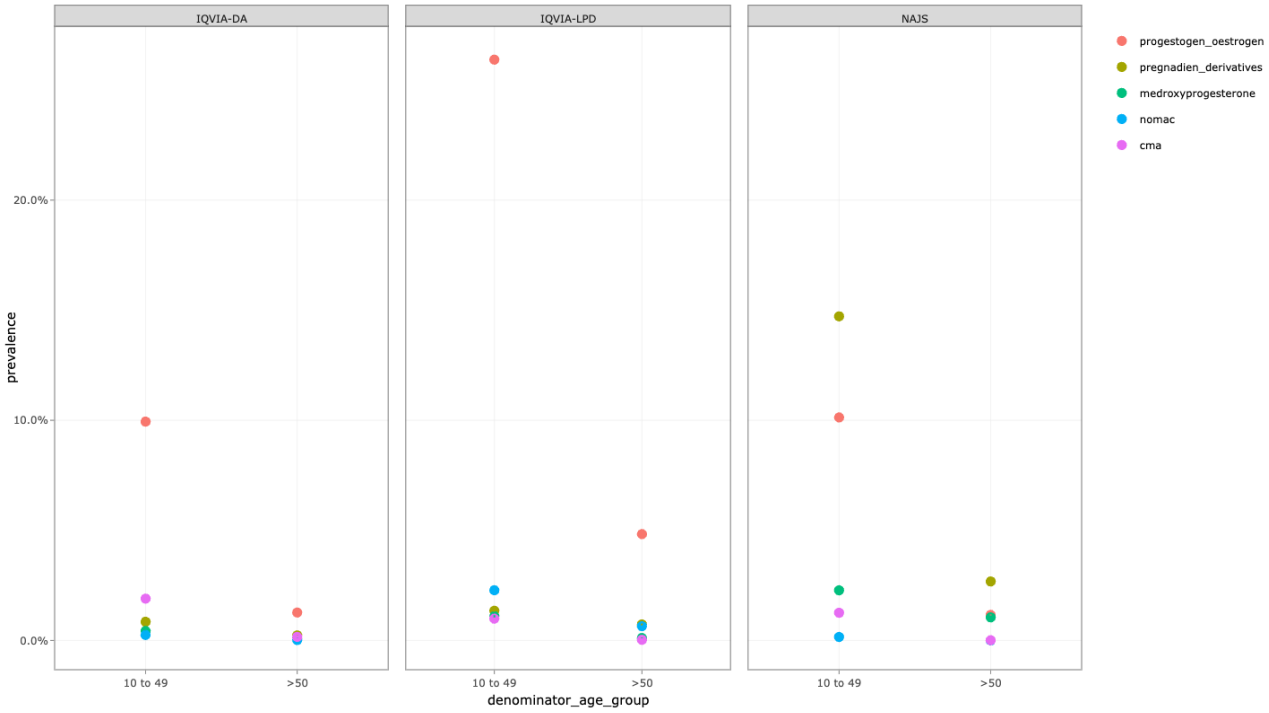
Appendix II – Table 6. Prevalence of drug classes and progestogens of interest for the entire study period by database.

Outcome	Database name[1]	N population	N cases	Prevalence (95% CI)
Progestogens and oestrogens in combination	IQVIA DA Germany	9,560,010	542,388	5.7 (5.7 to 5.7)
	IQVIA LPD Belgium	343,270	57,110	16.6 (16.5 to 16.8)
	NAJS	2,204,945	133,693	6.1 (6 to 6.1)
Pregnadien derivatives	IQVIA DA Germany	9,560,010	52,937	0.6 (0.6 to 0.6)
	IQVIA LPD Belgium	343,270	3,634	1.1 (1.0 to 1.1)
	NAJS	2,204,945	206,555	9.4 (9.3 to 9.4)
NOMAC	IQVIA DA Germany	9,560,010	13,073	0.14 (0.1 to 0.14)
	IQVIA LPD Belgium	343,270	5,235	1.5 (1.5 to 1.6)
	NAJS	2,204,945	1,926	0.1 (0.1 to 0.1)
CMA	IQVIA DA Germany	9,560,010	101,532	1.1 (1.1 to 1.1)
	IQVIA LPD Belgium	343,270	1,929	0.6 (0.6 to 0.6)
	NAJS	2,204,945	15,369	0.7 (0.7 to 0.7)
Medroxyprogesterone	IQVIA DA Germany	9,560,010	25,600	0.3 (0.3 to 0.3)
	IQVIA LPD Belgium	343,270	2,266	0.7 (0.7 to 0.7)
	NAJS	2,204,945	38,336	1.7 (1.7 to 1.8)

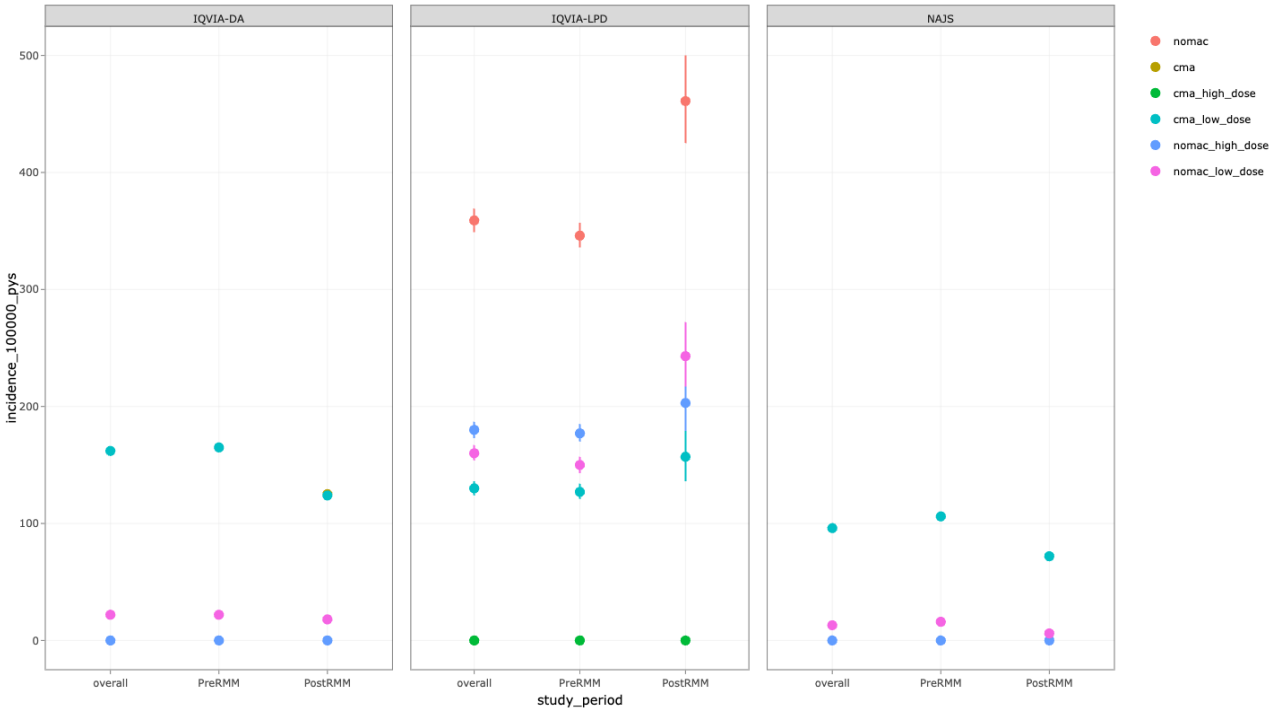
[1] Study period spanned from study start (or data availability start, if later) to end of data availability. In IQVIA DA Germany and IQVIA LPD Belgium, follow up ended on 31st December 2



Appendix II – Figure 3. Prevalence of drugs of interest by database, stratified by age groups.



Appendix II – Figure 4. Prevalence of drugs of interest by database, stratified by indication (assessed using age as a proxy; non-HRT: 10-49 years; HRT: ³ 50 years).



Appendix II – Figure 5. Incidence of NOMAC and CMA, stratified by dose and study period.

Appendix II – Table 7. Incidence rates of drug classes of interest during the pre-intervention period, by database.

Outcome	Database name	Number of events	Person-years (PY)	Incidence per 100,000 PY (95% CI)[3]
Progestogens and oestrogens in combination	IQVIA DA Germany	365,172	46,876,249	779 (776 to 782)
	IQVIA LPD Belgium	40,582	1,021,991	3,971 (3,932 to 4,010)
	NAJS	96,533	11,075,126	872 (866 to 877)
Pregnadien derivates	IQVIA DA Germany	50,669	48,495,197	104 (104 to 105)
	IQVIA LPD Belgium	2,792	1,140,430	245 (236 to 254)
	NAJS	182,581	11,134,685	1,640 (1,632 to 1,647)
NOMAC	IQVIA DA Germany	10,598	48,537,172	22 (21 to 22)
	IQVIA LPD Belgium	3,979	1,137,042	350 (339 to 361)
	NAJS	1,771	11,368,094	16 (15 to 16)
CMA	IQVIA DA Germany	79,768	48,326,783	165 (164 to 166)
	IQVIA LPD Belgium	1,464	1,142,940	128 (122 to 135)
	NAJS	12,016	11,345,790	106 (104 to 108)
Medroxyprogesterone	IQVIA DA Germany	20,070	48,501,234	41 (41 to 42)
	IQVIA LPD Belgium	1,700	1,142,301	149 (142 to 156)
	NAJS	31,737	11,328,875	280 (277 to 283)

Appendix II – Table 8. Incidence rates of drug classes of interest during the post-intervention period, by database.

	Database name	Number of events	Person-years (PY)	Incidence per 100,000 PY (95% CI)[3]
Progestogens and oestrogens in combination	IQVIA DA Germany	33,861	4,330,407	782 (774 to 790)
	IQVIA LPD Belgium	9,734	220,009	4,424 (4,337 to 4,513)
	NAJS	24,661	3,719,572	663 (655 to 671)
Pregnadien derivates	IQVIA DA Germany	8,330	4,474,044	186 (182 to 190)
	IQVIA LPD Belgium	712	243,726	292 (271 to 314)
	NAJS	57,754	3,730,005	1,548 (1,536 to 1,561)
NOMAC	IQVIA DA Germany	1,001	4,481,871	22 (21 to 24)
	IQVIA LPD Belgium	1,122	242,989	462 (435 to 490)
	NAJS	228	3,805,544	6 (5 to 7)
CMA	IQVIA DA Germany	6,300	4,468,159	141 (138 to 145)
	IQVIA LPD Belgium	365	244,412	149 (134 to 165)
	NAJS	2,750	3,798,771	72 (70 to 75)
Medroxyprogesterone	IQVIA DA Germany	2,186	4,480,202	49 (47 to 51)
	IQVIA LPD Belgium	421	244,290	172 (156 to 190)
	NAJS	9,420	3,793,749	248 (243 to 253)

Appendix II – Table 9. Prevalence of drug classes of interest during the pre-intervention period, by database.

Outcome	Database name[1]	N population	N cases	Prevalence (95% CI)
Progestogens and oestrogens in combination	IQVIA DA Germany	9,139,296	518,204	5.7 (5.7 to 5.7)
	IQVIA LPD Belgium	324,477	50,101	15.4 (15.3 to 15.6)
	NAJS	2,136,571	114,350	5.3 (5.3 to 5.4)
Pregnadien derivates	IQVIA DA Germany	9,139,296	47,649	0.5 (0.5 to 0.5)
	IQVIA LPD Belgium	324,477	3,064	0.9 (0.9 to 1.0)
	NAJS	2,136,571	163,046	7.6 (7.6 to 7.7)
NOMAC	IQVIA DA Germany	9,139,296	12,290	0.1 (0.1 to 0.1)
	IQVIA LPD Belgium	324,477	4,445	1.4 (1.3 to 1.4)
	NAJS	2,136,571	1,709	0.1 (0.1 to 0.1)
CMA	IQVIA DA Germany	9,139,296	97,260	1.1 (1.1 to 1.1)
	IQVIA LPD Belgium	324,477	1,654	0.5 (0.5 to 0.5)
	NAJS	2,136,571	12,792	0.6 (0.6 to 0.6)
Medroxyprogesterone	IQVIA DA Germany	9,139,296	24,159	0.3 (0.3 to 0.3)
	IQVIA LPD Belgium	324,477	1,922	0.6 (0.6 to 0.6)
	NAJS	2,136,571	29,831	1.4 (1.4 to 1.4)

Appendix II – Table 10. Prevalence of drug classes of interest during the post-intervention period, by database.

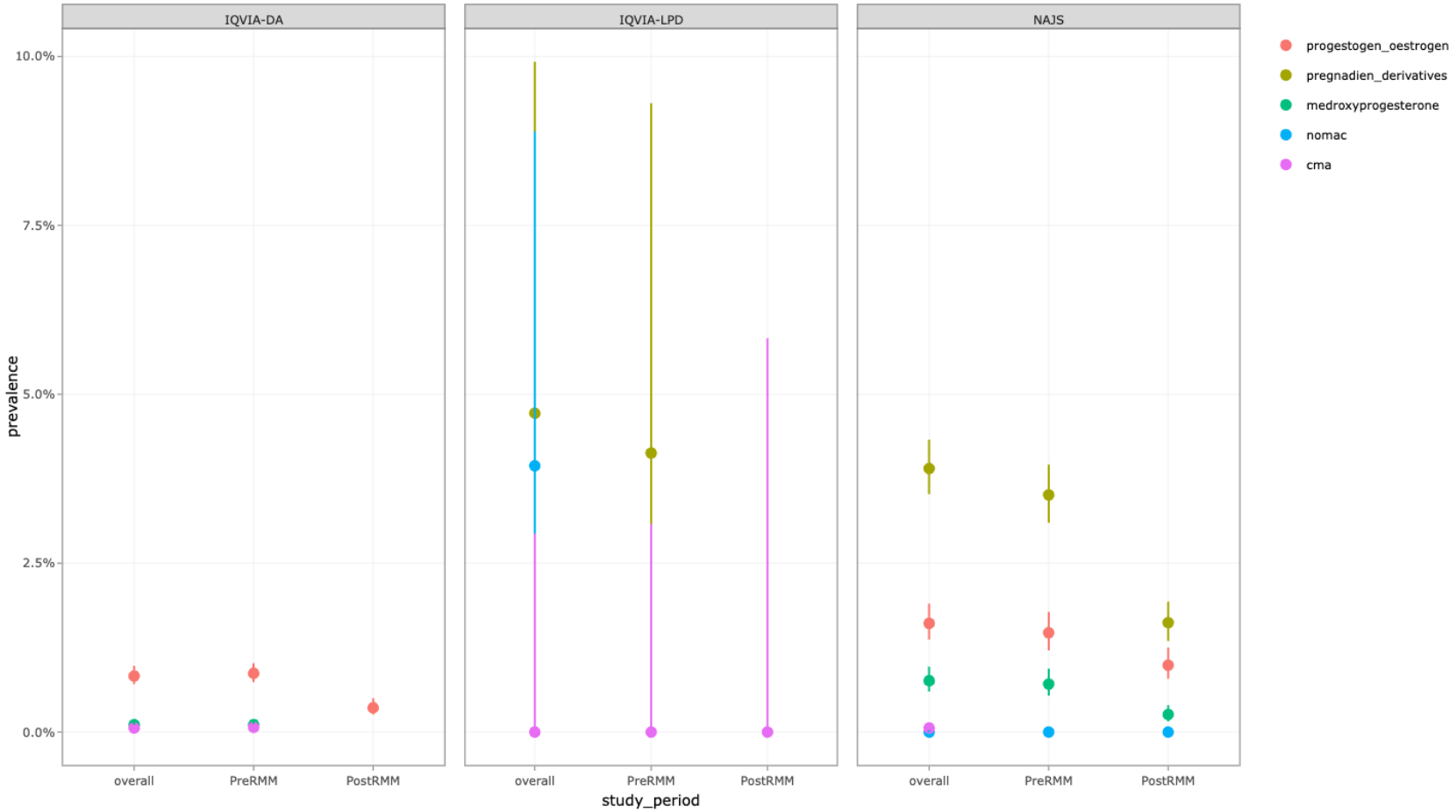
Outcome	Database name[1]	N population	N cases	Prevalence (95% CI)
Progestogens and oestrogens in combination	IQVIA DA Germany	4,134,816	130,323	3.1 (3.1 to 3.2)
	IQVIA LPD Belgium	173,167	19,471	11.2 (11.1 to 11.4)
	NAJS	2,037,820	55,841	2.7 (2.7 to 2.8)
Pregnadien derivates	IQVIA DA Germany	4,134,816	12,023	0.3 (0.3 to 0.3)
	IQVIA LPD Belgium	173,167	1,203	0.7 (0.7 to 0.7)
	NAJS	2,037,820	66,189	3.2 (3.2 to 3.3)
NOMAC	IQVIA DA Germany	4,134,816	2,584	0.1 (0.1 to 0.1)
	IQVIA LPD Belgium	173,167	1,796	1.0 (1.0 to 1.1)
	NAJS	2,037,820	418	0.0 (0.0 to 0.0)
CMA	IQVIA DA Germany	4,134,816	14,876	0.4 (0.4 to 0.4)
	IQVIA LPD Belgium	173,167	651	0.4 (0.4 to 0.4)
	NAJS	2,037,820	5,079	0.2 (0.2 to 0.3)
Medroxyprogesterone	IQVIA DA Germany	4,134,816	4,457	0.1 (0.1 to 0.1)
	IQVIA LPD Belgium	173,167	776	0.4 (0.4 to 0.5)
	NAJS	2,037,820	10,683	0.5 (0.5 to 0.5)

Appendix II – Table 11. Incidence rates of drug classes of interest for the sub-group analysis (prior history of meningioma), by database.

Outcome	Database name[1]	Number of events[2]	Person-years (PY)	Incidence per 100,000 PY (95% CI)[3]
Progestogens and oestrogens in combination	IQVIA DA Germany	101	89,770	113 (92 to 137)
	IQVIA LPD Belgium	<5	524	-
	NAJS	97	38,182	254 (206 to 310)
Pregnadien derivates	IQVIA DA Germany	20	90,228	22 (14 to 34)
	IQVIA LPD Belgium	5	514	973 (316 to 2,271)
	NAJS	358	38,080	940 (845 to 1,043)
NOMAC	IQVIA DA Germany	0	90,266	0 (0 to 4)
	IQVIA LPD Belgium	<5	516	-
	NAJS	0	38,551	0 (0 to 10)
CMA	IQVIA DA Germany	12	90,246	13 (7 to 23)
	IQVIA LPD Belgium	0	530	0 (0 to 696)
	NAJS	<5	38,543	-
Medroxyprogesterone	IQVIA DA Germany	8	90,208	9 (4 to 17)
	IQVIA LPD Belgium	0	530	0 (0 to 696)
	NAJS	62	38,454	161 (124 to 207)

Appendix II – Table 12. Prevalence of drug classes of interest for the sub-group analysis (prior history of meningioma), by database.

Outcome	Database name	N population	N cases	Prevalence (95% CI)
Progestogens and oestrogens in combination	IQVIA DA Germany	19,424	161	0.8 (0.7 to 1.0)
	IQVIA LPD Belgium	126	<5	-
	NAJS	8,682	140	1.6 (1.4 to 1.9)
Pregnadien derivates	IQVIA DA Germany	19,424	22	0.1 (0.1 to 0.2)
	IQVIA LPD Belgium	126	6	4.8 (2.2 to 10.0)
	NAJS	8,682	339	3.9 (3.5 to 4.3)
NOMAC	IQVIA DA Germany	19,424	<5	-
	IQVIA LPD Belgium	126	5	4.0 (1.7 to 8.9)
	NAJS	8,682	0	0.0 (0.0 to 0.0)
CMA	IQVIA DA Germany	19,424	13	0.1 (0.0 to 0.1)
	IQVIA LPD Belgium	126	0	0.0 (0.0 to 3.0)
	NAJS	8,682	5	0.1 (0.0 to 0.1)
Medroxyprogesterone	IQVIA DA Germany	19,424	24	0.1 (0.1 to 0.2)
	IQVIA LPD Belgium	126	0	0.0 (0.0 to 3.0)
	NAJS	8,682	66	0.8 (0.6 to 1.0)



Appendix II – Figure 6. Prevalence of drug classes of interest for the sub-group analysis (prior history of meningioma), by database and study period.

Appendix II – Table 13. Treatment duration of first treatment with NOMAC or CMA (in days), overall and stratified by indication.

Ingredient	Strata variable	Strata level	Estimate name	IQVIA DA Germany	IQVIA LPD Belgium	NAJS
NOMAC	Overall	-	Mean (SD)	273.0 (357.1)	200.2 (249.7)	138.0 (249.8)
			Median (Q25 - Q75)	126.0 (84.0 - 311.0)	90.0 (84.0 - 287.8)	45 (30 - 135)
	Indication	Non-HRT	Mean (SD)	274.0 (359.5)	205.0 (258.6)	138.9 (251.2)
			Median (Q25 - Q75)	126.0 (84.0 - 313.0)	90.0 (84.0 - 307.8)	48 (30 - 135)
		HRT	Mean (SD)	254.1 (307.1)	172.8 (189.6)	64.2 (59.6)
			Median (Q25 - Q75)	84.0 (84.0 - 293.5)	90.0 (84.0 - 212.0)	30 (30 - 82)
CMA	Overall	-	Mean (SD)	193.3 (362.2)	239.3 (254.2)	169.3 (290.7)
			Median (Q25 - Q75)	63.0 (18.0 - 168.0)	183.5 (63.0 - 273.0)	61 (30 - 165)
	Indication	Non-HRT	Mean (SD)	207.1 (373.1)	239.6 (254.9)	169.8 (291.2)
			Median (Q25 - Q75)	63.0 (18.0 - 199.0)	183.50 (63.0 -273.0)	62 (30 - 166)
		HRT	Mean (SD)	75.1 (217.5)	217.2 (180.0)	55.6 (103.9)
			Median (Q25 - Q75)	18.0 (12.0 - 60.0)	199.5 (72.8 - 273.0)	30 (30 - 30)

Appendix II – Table 14. Cumulative dose of NOMAC and CMA (in mg), estimated at drug-era level, overall and stratified by indication.

Ingredient	Strata variable	Strata level	Estimate name	IQVIA DA Germany	IQVIA LPD Belgium
NOMAC	Overall	-	Mean (SD)	492.4 (681.8)	615.2 (1,193.1)
			Median (Q25 - Q75)	179.8 (179.8 - 539.3)	150.0 (0.0 - 805.0)
	Indication	Non-HRT	Mean (SD)	496.6 (691.4)	551.8 (1,182.2)
			Median (Q25 - Q75)	179.8 (179.8 - 539.3)	0.0 (0.0 - 450.0)
		HRT	Mean (SD)	437.0 (535.8)	906.2 (1,200.3)
			Median (Q25 - Q75)	179.8 (179.8 - 539.3)	450.0 (318.8 - 900.0)
CMA	Overall	-	Mean (SD)	267.0 (533.3)	28.3 (24.6)
			Median (Q25 - Q75)	96.0 (0.0 - 252.0)	26.0 (12.0 - 32.0)
	Indication	Non-HRT	Mean (SD)	274.2 (539.7)	28.3 (24.6)
			Median (Q25 - Q75)	120.0 (0.0 - 252.0)	26.0 (12.0 - 32.0)
		HRT	Mean (SD)	183.9 (442.7)	26.6 (20.1)
			Median (Q25 - Q75)	72.0 (24.0 - 168.0)	26.0 (12.0 - 29.0)

Appendix II – Table 15. Cumulative dose of NOMAC and CMA (in mg) at patient-level, overall and stratified by indication.

Ingredient	Strata variable	Strata level	Estimate name	IQVIA DA Germany	IQVIA LPD Belgium
NOMAC	Overall	-	Mean (SD)	701.4 (987.2)	1049.6 (2145.3)
			Median (Q25 - Q75)	359.5 (179.8, 883.8)	150 (0, 900)
	Indication	Non-HRT	Mean (SD)	692.8 (974.6)	921.4 (2069.2)
			Median (Q25 - Q75)	359.5 (179.8, 719)	0 (0, 900)
		HRT	Mean (SD)	635.2 (717.4)	1407.4 (1989)
			Median (Q25 - Q75)	359.5 (179.8, 898.8)	750 (450, 1800)
CMA	Overall	-	Mean (SD)	431.2 (858.2)	43.7 (42.7)
			Median (Q25 - Q75)	126 (24, 378)	26 (12, 58)
	Indication	Non-HRT	Mean (SD)	444.2 (865.4)	43.7 (42.7)
			Median (Q25 - Q75)	126 (24, 420)	26 (12, 56)
		HRT	Mean (SD)	251.1 (630.6)	33.3 (26.3)
			Median (Q25 - Q75)	72 (24, 200)	26 (12, 44)

Appendix II – Table 16. Number (%) of new users of drug classes of interest with pre-specified medications, assessed in the year prior to index date.

Drug classes of classes of interest	IQVIA DA Germany	IQVIA LPD Belgium	NAJS
Antiandrogens	4333 (1.9 %)	621 (1.8 %)	2438 (1 %)
Antidepressants	4476 (1.9 %)	3374 (10 %)	13602 (5.8 %)
Biophosphonates	69 (0.03 %)	30 (0.09 %)	843 (0.4 %)
Clonidine	13 (0.01 %)	38 (0.1 %)	0 (0 %)
CMA	0 (0 %)	0 (0 %)	0 (0 %)
High-dose CMA	0 (0 %)	0 (0 %)	0 (0 %)
Low-dose CMA	0 (0 %)	0 (0 %)	0 (0 %)
Gonadotropin Releasing Hormone antagonists	298 (0.1 %)	0 (0 %)	0 (0 %)
Medroxyprogesterone	0 (0 %)	0 (0 %)	0 (0 %)
Metformin	813 (0.4 %)	438 (1.3 %)	4611 (2 %)
NOMAC	0 (0 %)	0 (0 %)	0 (0 %)
High-dose NOMAC	0 (0 %)	0 (0 %)	0 (0 %)
Low-dose NOMAC	0 (0 %)	0 (0 %)	0 (0 %)
Pregnadien derivatives[1]	0 (0 %)	0 (0 %)	0 (0 %)
Progestogens and oestrogens in combination[1]	0 (0 %)	0 (0 %)	0 (0 %)

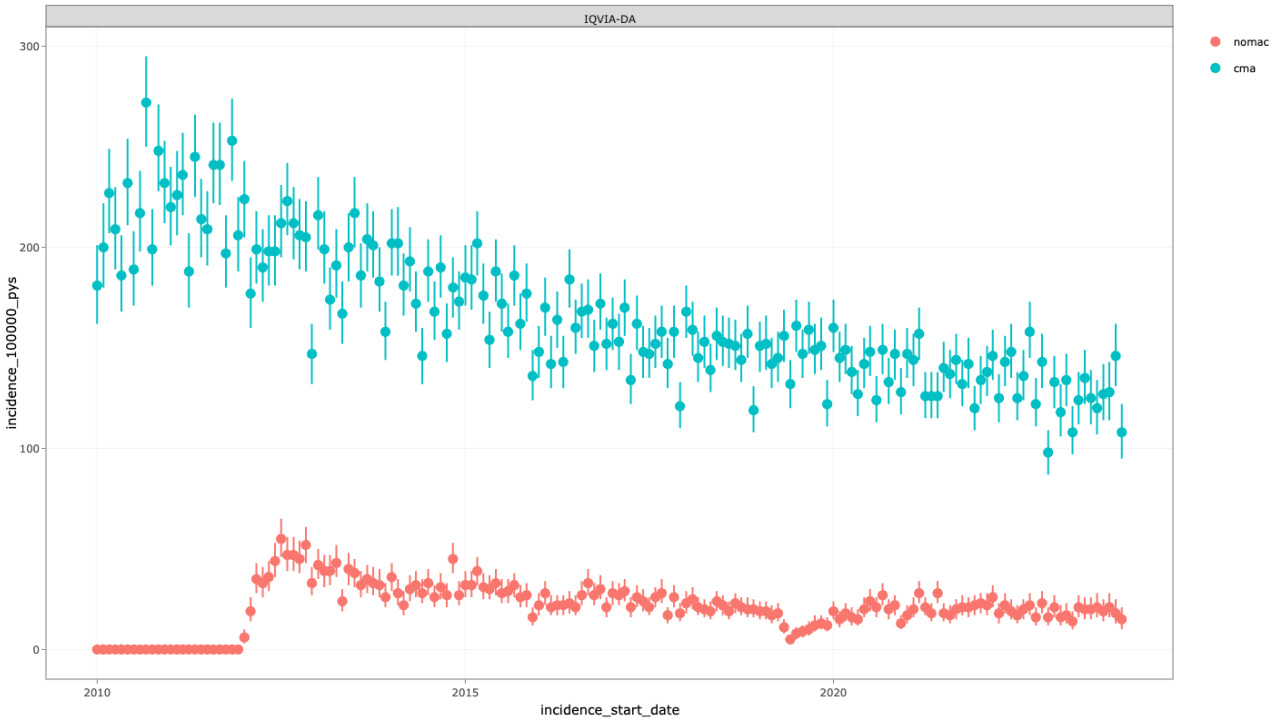
Appendix II – Table 17. Number of patients (%) following different treatment strategies 180 days after ending a first treatment with NOMAC or CMA.

Ingredient	Treatment strategy	IQVIA DA Germany	IQVIA LPD Belgium	NAJS
NOMAC[1]	Restart	1,151 (10.9%)	404 (9.9%)	352 (18.4%)
	Switch	1,530 (14.6%)	178 (4.4%)	417 (21.7%)
	Restart and switch	71 (0.7%)	16 (0.4%)	38 (2.0%)
	Discontinuation[3]	7,767 (73.8%)	3,480 (85.3%)	1,111 (57.9%)
CMA[2]	Restart	6,436 (10.5%)	195 (12.3%)	3,454 (25.6%)
	Switch	6,213 (10.1%)	128 (8.1%)	2,051 (15.2%)
	Restart and switch	259 (0.4%)	<5	127 (0.9%)
	Discontinuation[3]	48,367 (78.9%)	1,257 (79.5%)	7,880 (58.3%)

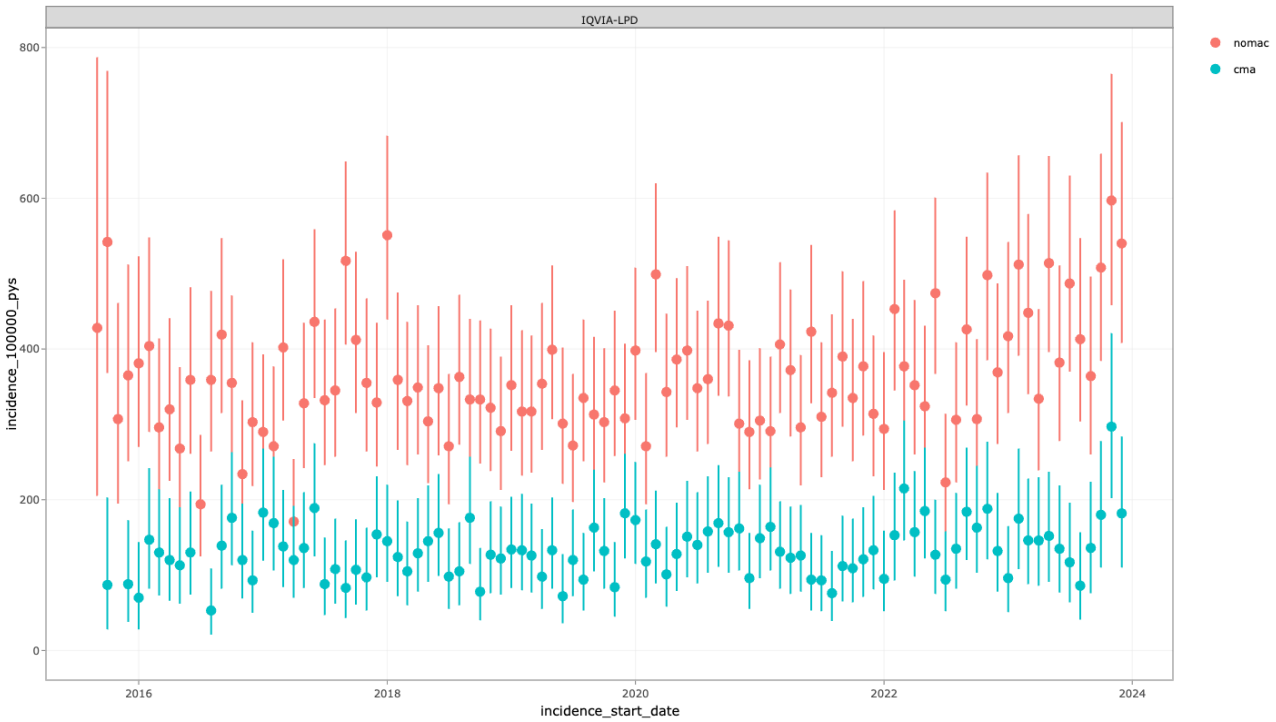
[1] Number of patients included: n= 10,519 in IQVIA DA Germany; n= 4,078 in IQVIA LPD Belgium; n=1,918 in NAJS.
[2] Number of patients included: n= 61,275 in IQVIA DA Germany; n= 1,582 in IQVIA LPD Belgium; n=13,512 in NAJS.
[3] Not treated, neither with the original treatment nor any potential switch.

Appendix II – Table 18. Number of patients (%) following different treatment strategies 180 days after ending a first treatment with NOMAC or CMA, stratified by ATC groups.

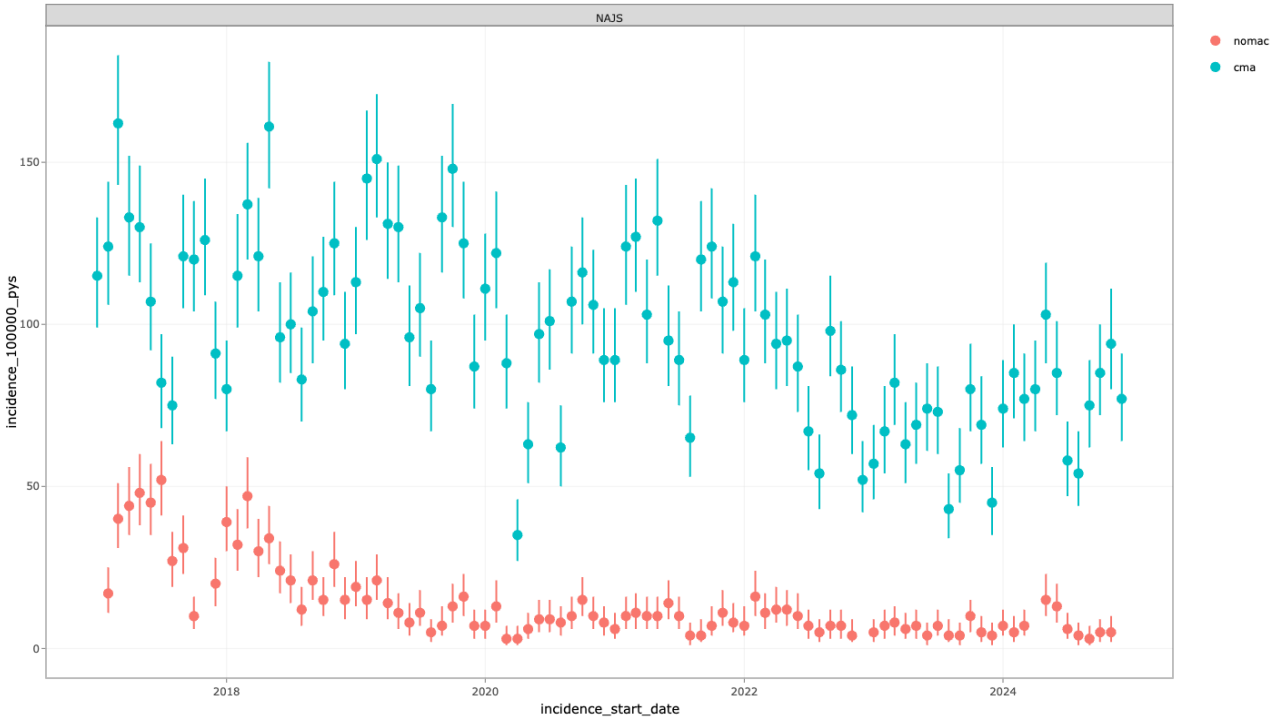
Ingredient	Treatment strategy	IQVIA DA Germany	IQVIA LPD Belgium	NAJS
NOMAC: G03AA14, G03FB12	Restart	1151 (10.9)	176 (8.7)	352 (18.4)
	Switch	1530 (14.5)	96 (4.8)	417 (21.7)
	Restart and switch	71 (0.7)	7 (0.3)	38 (2)
	Discontinuation	7767 (73.8)	1737 (86.2)	1111 (57.9)
NOMAC: G03DB04	Restart	0 (0)	245 (12.4)	0 (0)
	Switch	0 (0)	74 (3.7)	0 (0)
	Restart and switch	0 (0)	6 (0.3)	0 (0)
	Discontinuation	0 (0)	1656 (83.6)	0 (0)
CMA: G03AA15, G03AB07, G03FB03	Restart	5332 (15.1)	191 (12.6)	3454 (25.6)
	Switch	4254 (12)	123 (8.1)	2051 (15.2)
	Restart and switch	174 (0.5)	<5	127 (0.9)
	Discontinuation	25553 (72.4)	1193 (79)	7880 (58.3)
CMA: G03DB06	Restart	1207 (4.2)	0 (0)	0 (0)
	Switch	2221 (7.8)	0 (0)	0 (0)
	Restart and switch	83 (0.3)	0 (0)	0 (0)
	Discontinuation	24942 (87.7)	0 (0)	0 (0)



Appendix II - Figure 7. Incidence of NOMAC and CMA prescribing in IQVIA DA Germany (2010–2023).



Appendix II - Figure 8. Incidence of NOMAC and CMA prescribing in IQVIA LPD Belgium (2015–2023).



Appendix II - Figure 9. Incidence of NOMAC and CMA prescribing in NAJS (2017–2024).

Appendix II – Table 19. Estimated effects (risk ratio, RR) of the intervention implemented in 2022 for NOMAC, by database and covariates of interest.

Settings			Step change			Slope change		
Database	Strata name	Regression model[1]	Regression coefficient (β_2), (SE)	p-value	RR (95%)	Regression coefficient (β_3), (SE)	p-value	RR (95%)
IQVIA DA Germany	Low dose	Negative binomial*	-0.166 (0.136)	0.221	0.847 (0.649 to 1.106)	0.023 (0.018)	0.213	1.022 (0.987 to 1.060)
	Non-HRT	Negative binomial*	-0.247 (0.138)	0.074	0.781 (0.596 to 1.024)	0.026 (0.019)	0.157	1.027 (0.99 to 1.065)
IQVIA LPD Belgium	High dose	Poisson	0.249 (0.156)	0.111	1.283 (0.945 to 1.744)	0.0002 (0.021)	0.992	1 (0.960 to 1.042)
	Low dose	Poisson	0.194 (0.152)	0.201	1.214 (0.902 to 1.634)	0.018 (0.0193)	0.344	1.018 (0.981 to 1.058)
	HRT	Poisson*	0.576 (0.322)	0.074	1.779 (0.946 to 3.345)	-0.032 (0.040)	0.425	0.969 (0.895 to 1.048)
	Non-HRT	Negative binomial	0.032 (0.145)	0.823	1.033 (0.777 to 1.373)	0.029 (0.019)	0.131	1.029 (0.992 to 1.068)
NAJS	Low dose	Poisson*	-0.605 (0.201)	0.003	0.546 (0.368 to 0.81)	0.014 (0.014)	0.320	1.014 (0.987 to 1.042)
	Non-HRT	Poisson*	-0.568 (0.203)	0.005	0.567 (0.381 to 0.844)	0.014 (0.014)	0.304	1.014 (0.987 to 1.042)

[1] Negative binomial models were used in the presence of overdispersion. *Indicates adjustment for seasonality.
All regression coefficients and model results can be explored in the "Shiny App".

Appendix II – Table 20. Estimated effects (risk ratio, RR) of the intervention implemented in 2022 for CMA, by database and covariates of interest.

Settings			Step change			Slope change		
Database	Strata name	Regression model[1]	Regression coefficient (β_2), (SE)	p-value	RR (95% CI)	Regression coefficient (β_3), (SE)	p-value	RR (95%)
IQVIA DA Germany	Low dose	Negative binomial	-0.093 (0.063)	0.141	0.912 (0.806 to 1.031)	0.004 (0.008)	0.670	1.004 (0.987 to 1.020)
	Non-HRT	Negative binomial	-0.078 (0.066)	0.232	0.925 (0.813 to 1.052)	0.002 (0.009)	0.806	1.002 (0.985 to 1.020)
	HRT	Poisson*	-0.240 (0.12)	0.045	0.786 (0.622 to 0.995)	0.021 (0.016)	0.195	1.021 (0.989 to 1.055)
IQVIA LPD Belgium	Low dose	Poisson*	-0.438 (0.198)	0.027	0.646 (0.438 to 0.951)	0.033 (0.03)	0.191	1.033 (0.984 to 1.085)
	Non-HRT	Poisson*	-0.485 (0.200)	0.0152	0.616 (0.417 to 0.911)	0.0363 (0.0252)	0.150	1.037 (0.987 to 1.090)
NAJS	Low dose	Negative binomial*	-0.286 (0.127)	0.024	0.751 (0.586 to 0.963)	0.024 (0.008)	0.005	1.024 (1.007 to 1.041)
	Non-HRT	Negative binomial*	-0.291 (0.128)	0.023	0.748 (0.582 to 0.960)	0.024 (0.008)	0.005	1.024 (1.007 to 1.041)

[1] Negative binomial models were used in the presence of overdispersion. *Indicates adjustment for seasonality.
All regression coefficients and model results can be explored in the "Shiny App".

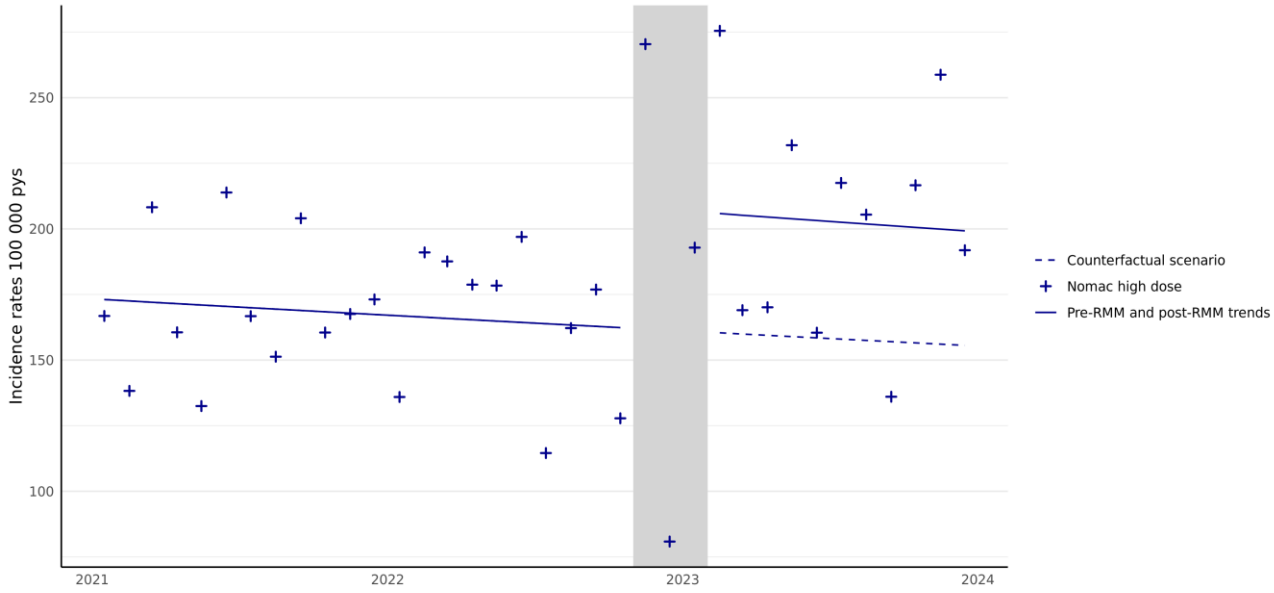


Figure information: Level change = 28.3% (-5.5% to 74.4%), Slope change = 0% (-4% to 4.2%)

Appendix II – Figure 10. ITS analysis of RMM implemented in 2022 on incidence rates of high-dose NOMAC in IQVIA LPD Belgium.

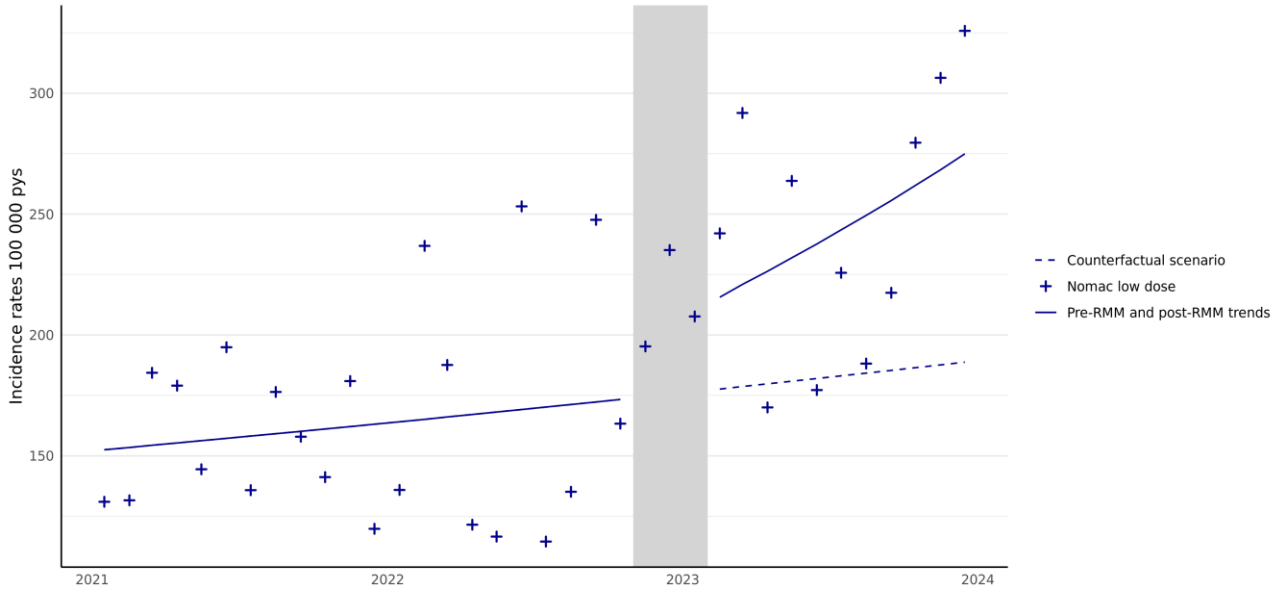


Figure information: Level change = 21.4% (-9.8% to 63.4%), Slope change = 1.8% (-1.9% to 5.8%)

Appendix II – Figure 11. ITS analysis of RMM implemented in 2022 on incidence rates of low-dose NOMAC in IQVIA LPD Belgium.

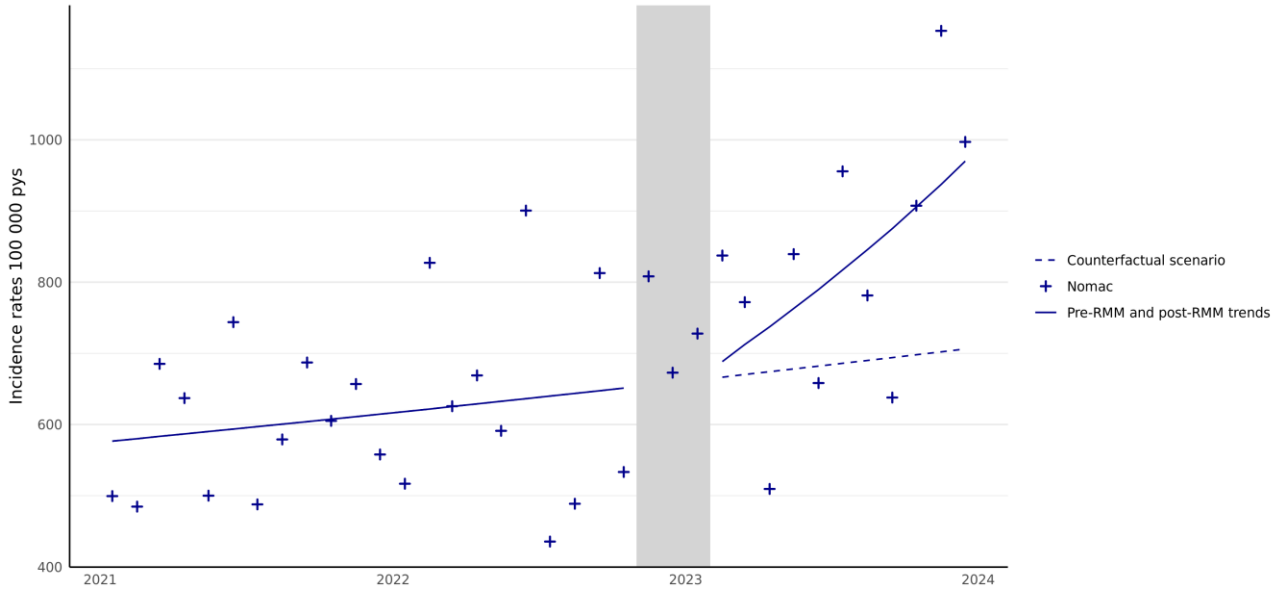


Figure information: Level change = 3.3% (-22.3% to 37.3%), Slope change = 2.9% (-0.8% to 6.8%)

Appendix II – Figure 12. ITS analysis of RMM implemented in 2022 on incidence rates of NOMAC for non-HRT use in IQVIA LPD Belgium.

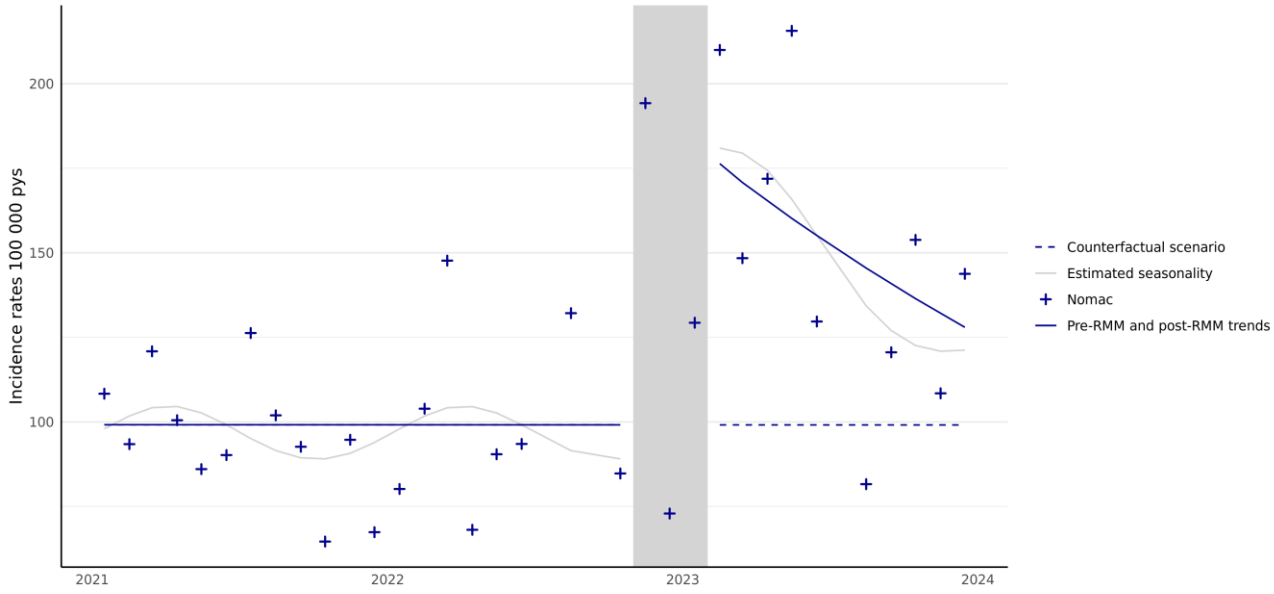


Figure information: Level change = 77.9% (-5.4% to 234.5%), Slope change = -3.2% (-10.5% to 4.8%)

Appendix II – Figure 13. ITS analysis of RMM implemented in 2022 on incidence rates of NOMAC for HRT use in IQVIA LPD Belgium.

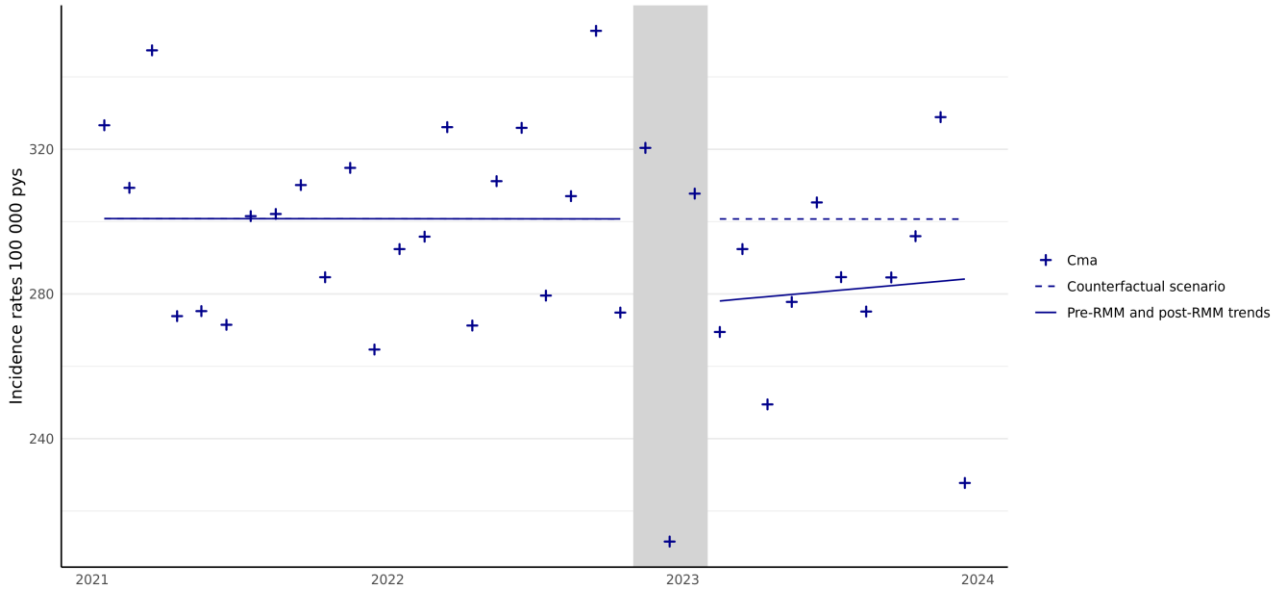


Figure information: Level change = -7.5% (-18.7% to 5.2%), Slope change = 0.2% (-1.5% to 2%)

Appendix II – Figure 14. ITS analysis of RMM implemented in 2022 on incidence rates of CMA for non-HRT use in IQVIA DA Germany.

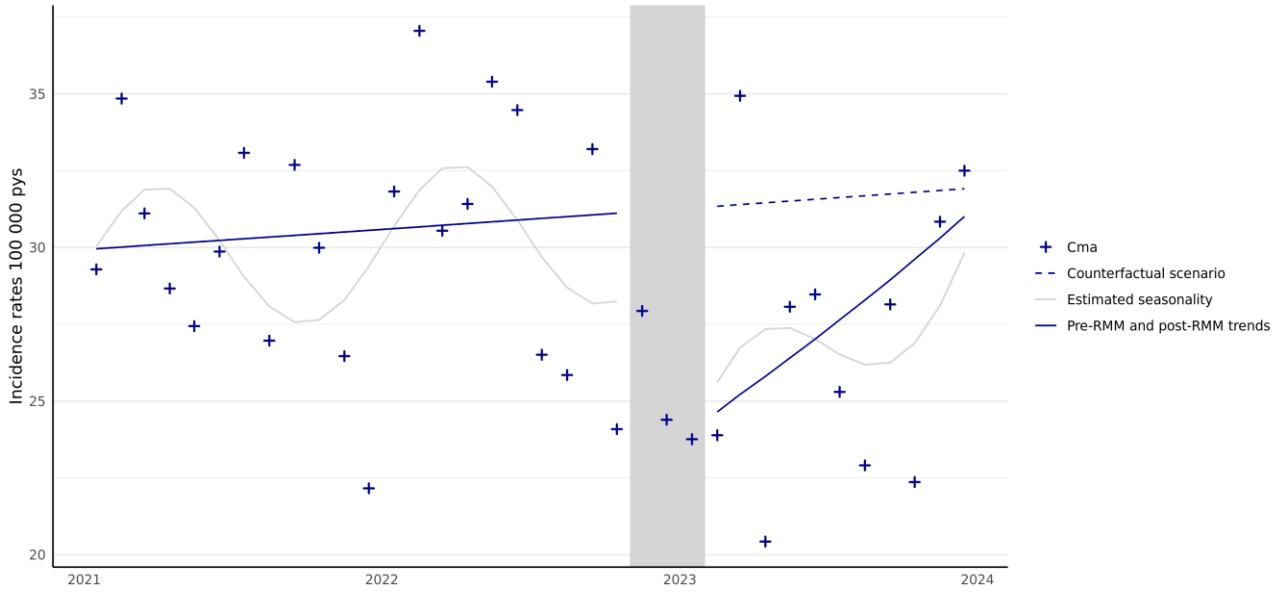


Figure information: Level change = -21.4% (-37.8% to -0.5%), Slope change = 2.1% (-1.1% to 5.5%)

Appendix II – Figure 15. ITS analysis of RMM implemented in 2022 on incidence rates of CMA for HRT use in IQVIA DA Germany.

Appendix II - Table 21. Estimated effects (risk ratio, RR) of the intervention implemented in 2018 for NOMAC, by database and covariates of interest.

Settings				Step change			Slope change	
Database	Strata name	Regression model	Regression coefficient (β_2), (SE)	p-value	RR (95% CI)	Regression coefficient (β_3), (SE)	p-value	RR (95% CI)
IQVIA DA Germany	Overall	Negative binomial	-0.338 (0.142)	0.018	0.714 (0.540 to 0.943)	0.025 (0.008)	0.002	1.025 (1.009 to 1.042)
	Low dose	Negative binomial	-0.338 (0.142)	0.018	0.714 (0.540 to 0.943)	0.025 (0.008)	0.002	1.025 (1.009 to 1.042)
	Non-HRT	Negative binomial	-0.3548 (0.1431)	0.013	0.701 (0.530 to 0.928)	0.026 (0.008)	0.001	1.027 (1.01 to 1.043)
IQVIA LPD Belgium	Overall	Negative binomial	-0.0775 (0.1207)	0.521	0.926 (0.731 to 1.172)	-0.002 (0.007)	0.776	0.998 (0.984 to 1.012)
	High dose	Poisson	0.0136 (0.1253)	0.913	1.014 (0.793 to 1.296)	0.003 (0.007)	0.702	1.003 (0.989 to 1.017)
	Low dose	Poisson	-0.11 (0.139)	0.428	0.896 (0.683 to 1.176)	-0.006 (0.008)	0.490	0.994 (0.978 to 1.011)
	Non-HRT	Negative binomial	-0.125 (0.124)	0.316	0.883 (0.693 to 1.126)	-0.003 (0.007)	0.703	0.997 (0.983 to 1.012)
	HRT	Poisson	0.0199 (0.233)	0.932	1.020 (0.646 to 1.611)	0.010 (0.013)	0.473	1.010 (0.983 to 1.036)

[1] Negative binomial models were used in the presence of overdispersion. None of the models was adjusted for seasonality.
All regression coefficients and model results can be explored in the "Shiny App".

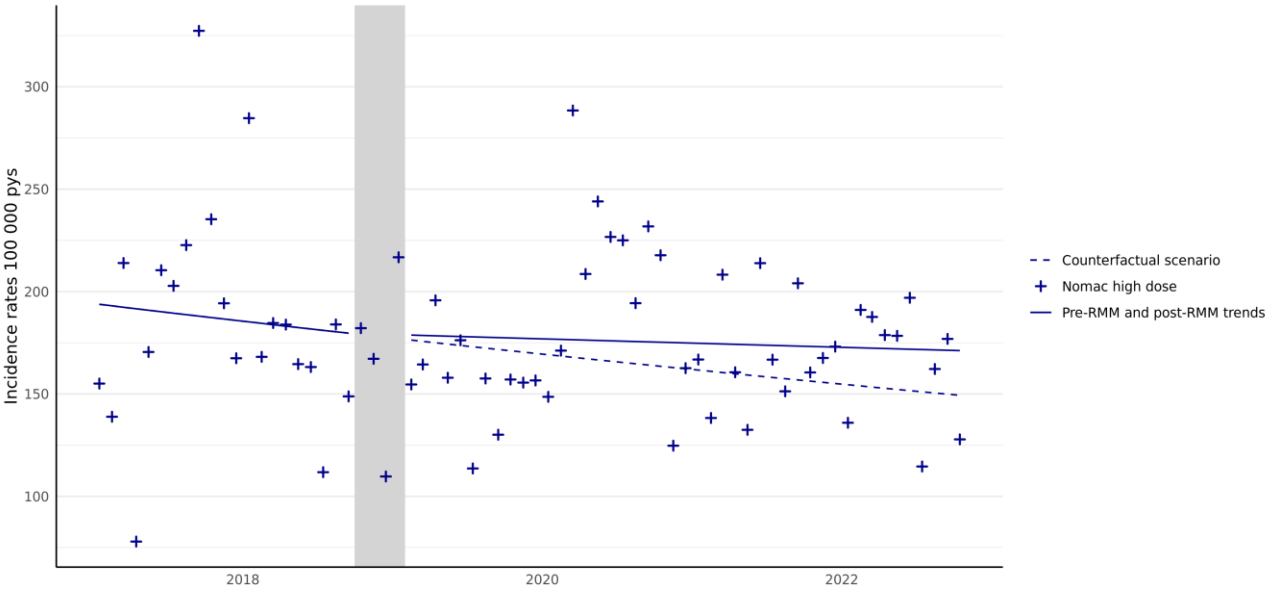


Figure information: Level change = 1.4% (-20.7% to 29.6%), Slope change = 0.3% (-1.1% to 1.7%)

Appendix II – Figure 16. ITS analysis of RMM implemented in 2018 on incidence rates of high-dose NOMAC in IQVIA LPD Belgium.

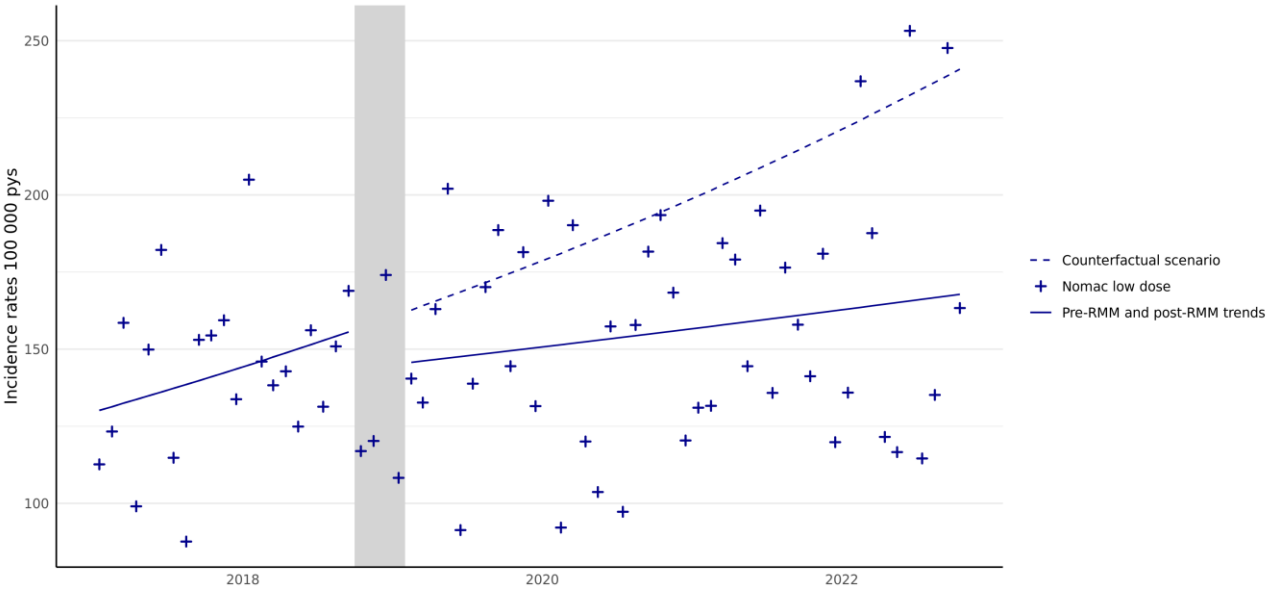


Figure information: Level change = -10.4% (-31.7% to 17.6%), Slope change = -0.6% (-2.2% to 1.1%)

Appendix II – Figure 17. ITS analysis of RMM implemented in 2018 on incidence rates of low-dose NOMAC in IQVIA LPD Belgium.

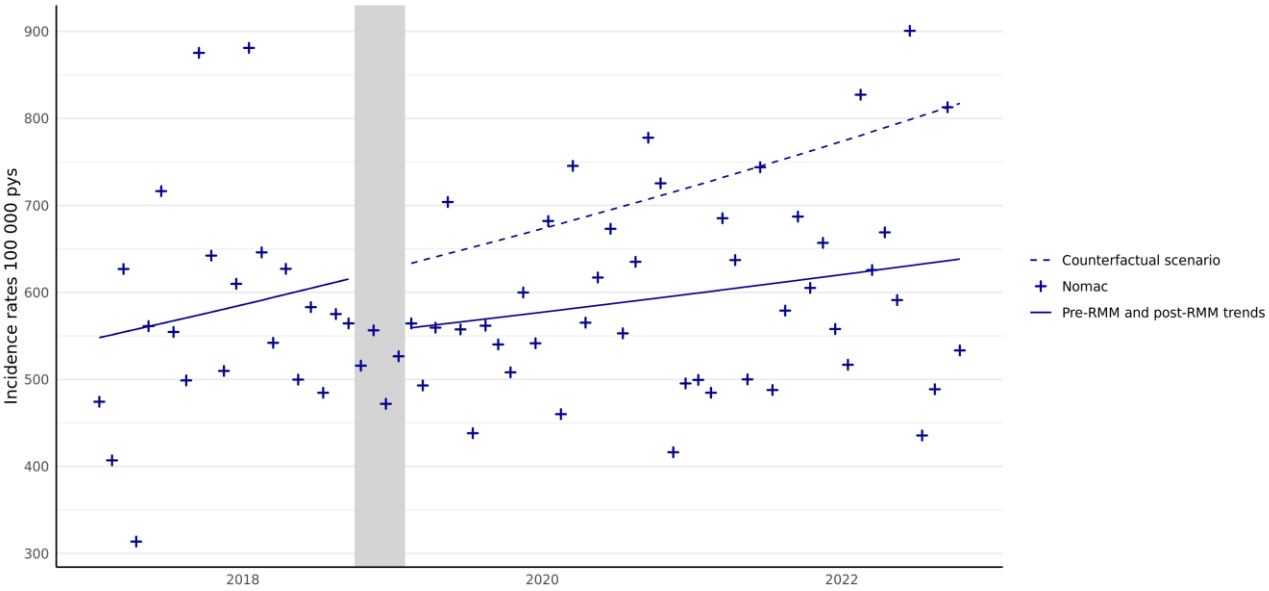


Figure information: Level change = -11.7% (-30.8% to 12.6%), Slope change = -0.3% (-1.7% to 1.2%)

Appendix II – Figure 18. ITS analysis of RMM implemented in 2018 on incidence rates of NOMAC for non-HRT use in IQVIA LPD Belgium.

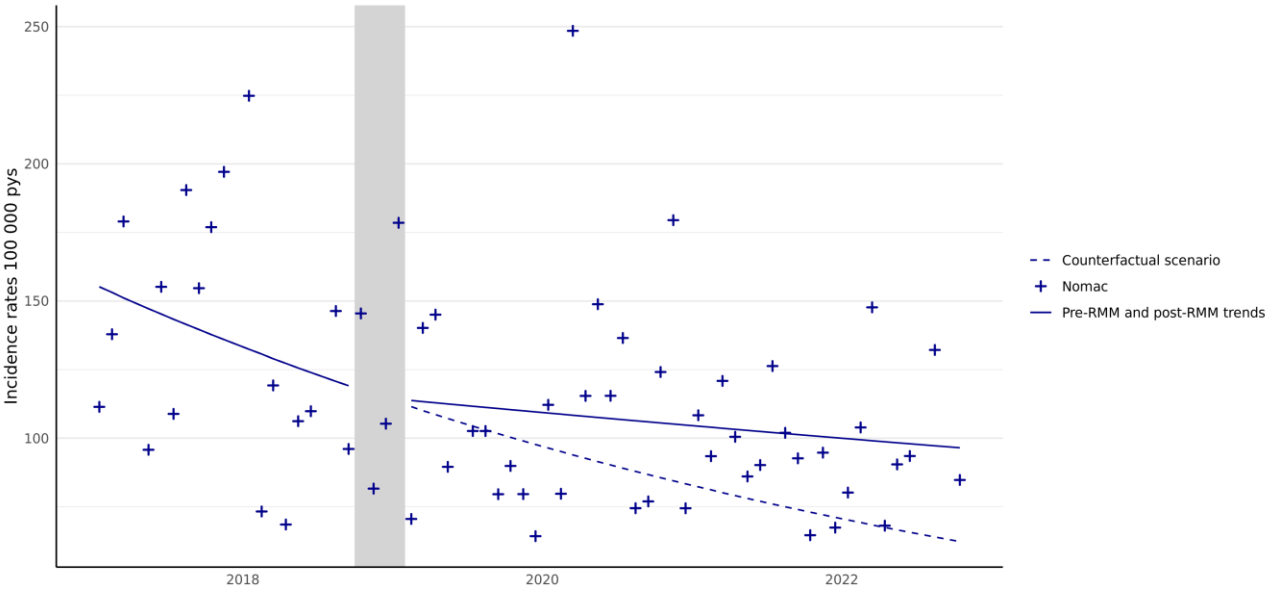


Figure information: Level change = 2% (-35.4% to 61.1%), Slope change = 1% (-1.6% to 3.6%)

Appendix II – Figure 19. ITS analysis of RMM implemented in 2018 on incidence rates of NOMAC for HRT use in IQVIA LPD Belgium.