Study Report

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DARWIN EU® - Drug utilisation study on medicinal use of cannabis flos

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Version 5.0

Contents

Study Title	DARWIN EU® - Drug utilisation study on medicinal use of cannabis flos
Study Report Version	V5.0
Date	18/02/2025
EU PAS register number	EUPAS1000000228
Active substance	Cannabis flos (dried, whole or fragmented, flowering tops of *Cannabis sativa* L.)
Medicinal product	*Cannabis flos* containing products, provided such products are available in the datasets of interest.
Research question and objectives	Research question What is the (real-world) use of Cannabis flos that is prescribed for medicinal purposes? Study objectives 1. To estimate incidence rates and prevalence of use of Cannabis flos, overall and stratified by medicinal product, age, sex and country/database, during the study period from 2014 to 2023. 2. To characterise the cohort of patients being treated with the Cannabis flos at the time of new prescription of the medicinal products in terms of demographics, indication for prescribing, comorbidities and comedication. Additionally, to determine duration of treatment with Cannabis flos products. The results were stratified by medicinal product and database.
Country(-ies) of study	Netherlands and Germany
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TITLE

DARWIN EU® - Drug utilisation study on medicinal use of cannabis flos

1. DESCRIPTION OF STUDY TEAM

Study team role	Names	Organisation
Principal Investigator/Epidemiologist	Dina Vojinovic	IQVIA
Data Scientist	Isabella Kaczmarczyk	IQVIA
Data Partner*	**Names**	**Organisation**
IPCI	Katia Verhamme	Erasmus MC
	Mees Mosseveld	Erasmus MC
IQVIA DA Germany	James Brash	IQVIA

*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

This study was conducted using routinely collected data from two databases in two European Union (EU) countries. All databases were previously mapped to the OMOP Common Data Model (CDM). However, Cannabis flos containing products in this study were identified using source codes as no standard concepts exist for these products.

1. Integrated Primary Care Information Project (IPCI), the Netherlands
2. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany

Detailed information on data sources is described below.

Country	Name of Database	Health Care setting	Type of Data	Number of subjects	Number of active subjects*	Data lock for the last update.
Netherlands	IPCI	Primary care	EHR	2.9 million	1.4 million	30/04/2024
Germany	IQVIA DA Germany	Primary care and outpatient specialist care	EHR	43 million	8.5 million	31/12/2023

IPCI = Integrated Primary Care Information Project; DA = Data Analyzer; EHR = Electronic Health Record. *Active subjects = individuals who were still under observation within a certain period (e.g. a year) prior to data lock. Individuals whose follow-up has ended in the past may still participate in a study if their follow-up covers the study period.

3. ABSTRACT

Title

DARWIN EU® - Drug utilisation study on medicinal use of cannabis flos

Rationale and background

Cannabis flos (dried, whole or fragmented, flowering tops of *Cannabis sativa* L.) is not registered as medicinal product in the European Union (EU). However, there are different regulatory strategies among EU member states that enable some specific exemptions for its use and its supply by pharmacies, as a controlled substance under physician's prescription only. Scientific data is needed to inform and support regulatory work including a possible establishment of an EU herbal monograph.

Research question and Objectives

Research question

What is the (real-world) use of Cannabis flos that is prescribed for medicinal purposes?

Study objectives

1. To estimate incidence rates and prevalence of use of Cannabis flos, overall and stratified by medicinal product, age, sex and country/database, during the study period from 2014 to 2023.
2. To characterise the cohort of patients being treated with the Cannabis flos at the time of new prescription of the medicinal products in terms of demographics, indication for prescribing, comorbidities and comedication. Additionally, to determine duration of treatment with Cannabis flos products. The results were stratified by medicinal product and database.

Research Methods

Study design

- Population-level cohort study (Objective 1, Population-level drug utilisation study on medicinal products of interest).
- New drug user cohort study (Objective 2, Patient-level utilisation of medicinal products of interest with regard to demographics, indication of use, comorbidities, comedication and duration of treatment).

Population

Population-level utilisation of medicinal products of interest: Population-level drug utilisation analyses included all individuals registered in the respective databases between 1st of January 2014 and 31st of December 2023, with at least 1 year of data visibility prior becoming eligible for study inclusion. This requirement of at least 1 year of prior data history did not hold for children <1 year of age.

Patient-level utilisation of medicinal products of interest: Patient-level drug utilisation analyses included new users of medicinal product registered in the respective databases between 1st of January 2014 and 31st of December 2023. Patients had at least 1 year of data visibility prior to the index date and no use of the respective medicinal product in the previous 1 year. This requirement of at least 1 year of prior data history did not hold for children < 1 year of age.

Variables

Drug of interest

Cannabis flos (dried, whole or fragmented, flowering tops of *Cannabis sativa* L.)

Conditions of interest

Neuralgic pain, cancer, anxiety-related disorders, spasticity (multiple sclerosis (MS), spinal cord injury), neurological disorders (epilepsy, Tourette Syndrome, Huntington's disease, Parkinson disease, amyotrophic later sclerosis (ALS), Alzheimer's disease and other dementias), glaucoma, human immunodeficiency virus (HIV) infection, anorexia, sleep disorders (insomnia, sleep apnoea), inflammatory bowel disease, fibromyalgia, rheumatoid arthritis.

Data sources

1. Integrated Primary Care Information Project (IPCI), the Netherlands
2. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany

Sample size

No sample size has been calculated for this drug utilisation descriptive study, as our primary focus is to investigate medicinal use of Cannabis flos, irrespective of the sample size. Based on a preliminary feasibility assessment, the expected number of person-counts for the different products of the selected medication was 230 individuals in the IQVIA DA Germany and 734 individuals in the IPCI database.

Data analyses

Population-level utilisation of selected medicinal product of interest: Annual incidence rates (expressed as number of new users per 100,000 person-years (PY)) and annual period prevalence of use (expressed as the proportion of users in the study population) of Cannabis flos were estimated. The statistical analyses were performed based on OMOP CDM mapped data using the "*IncidencePrevalence*" R package. The results were stratified by Cannabis flos products, age, sex and database.

Patient-level utilisation of selected medicinal products of interest: Patient-level characterisation was conducted at index date including large-scale characterisation (demographics, comorbidities and comedication) and frequency of pre-specified conditions as a proxy for indications for prescribing Cannabis flos. The index date was the date of incident prescription of the selected medicinal products for each individual. Comorbidities, comedication and indications were assessed at the index date and in the period of 1 year prior to the index date. The duration of treatment with Cannabis flos was calculated and summarised, providing the minimum, quartiles and maximum. Treatment duration for Cannabis flos was presented only for the IPCI database since some of the data elements needed for calculating treatment duration in the IQVIA DA Germany were missing for Cannabis flos products and required imputation for the majority of Cannabis flos treatment episodes. Statistical analyses were conducted using the "*CohortCharacteristics*", "*PatientProfiles*" and "*DrugUtilisation*" R packages based on OMOP CDM mapped data. The analyses were stratified by Cannabis flos products and database.

For all analyses a minimum cell count of 5 was used when reporting results, with any smaller counts obscured.

Results

Incidence rates and prevalence of Cannabis flos product prescriptions – population-level drug utilisation

This study described the incidence rates and prevalence of Cannabis flos prescriptions between 2014 and 2023 using IQVIA DA Germany and IPCI databases, with stratification by age, sex and medicinal product.

Following the legalisation of Cannabis flos for medicinal use in Germany in March 2017, prescription incidence rates in the IQVIA DA Germany database were very low, ranging from 0.1 per 100,000 person-years (PY) in 2018 to 0.8 per 100,000 PY in 2023. Conversely, in the IPCI database, incidence rate was 8.8

per 100,000 PY in 2014, peaked at 11.1 per 100,000 PY in 2015 and subsequently declined to 2 per 100,000 PY by 2023, demonstrating a distinct temporal trend.

Age-specific analysis showed no prescriptions for Cannabis flos in individuals under 18 years across both databases. Among adults (≥18 years), the IQVIA DA Germany reported very low yet stable incidence rates, while IPCI demonstrated a more pronounced trend, with incidence rates starting at 11.1 per 100,000 PY in 2014, peaking at 13.8 per 100,000 PY in 2015 and then gradually declining to around 2.5 per 100,000 PY by 2023. Further stratification by sex showed slightly higher incidence rates in males than in females in the IQVIA DA Germany database, but no significant sex differences in the IPCI database.

The Cannabis flos containing products identified in both databases included Bedrocan, Bedrobinol, Bediol, Bedrolite and Bedica. Product-specific data in IQVIA DA Germany showed that, among the identified products, Bedica had no recorded prescriptions, while the number of prescriptions for Bedrobinol and Bedrolite was very low to produce detectable incidence rates. Incidence rates for Bedrocan ranged from 0.2 per 100,000 PY in 2019 to 0.8 per 100,000 PY in 2023. In the IPCI database, incidence rates for Bedrocan ranged from 5.4 per 100,000 PY in 2014 to 6.7 per 100,000 PY in 2015 before declining to 1.2 per 100,000 PY by 2023. Other products, including Bedica, Bediol and Bedrobinol, exhibited similar patterns, maintaining generally low and stable rates.

Prevalence trends mirrored those of incidence rates. IQVIA DA Germany showed negligible prevalence until 2018, with very low proportions thereafter. IPCI data indicated a slight initial increase in prevalence, peaking at 0.02% in 2016, then declining to 0.008% by 2023. Across both databases, age and sex trends paralleled incidence patterns, indicating rare and stable use of Cannabis flos products throughout the study period.

Characterisation of the cohort of patients with prescription of Cannabis flos products - Patient-level drug utilisation study

Analysis of Cannabis flos prescriptions from 2014 to 2023 revealed distinctive patterns in patient demographics and prescription details. In IQVIA DA Germany, Bedrocan was the most commonly initiated product (132 new initiators) among the identified products, while Bedrobinol and Bedrolite had the fewest initiations (7 and 5, respectively). The median age of initiation was around 46 years for most products, except for Bedrobinol, where the median age was 58 years. Males predominated across all products. In the IPCI database, the median age was approximately 58 years, with Bedrolite users being slightly younger (52 years). Females were more represented for Bedrocan, Bediol and Bedrobinol, while males were more prevalent for Bedrolite and Bedica.

Regarding pre-specified conditions used as proxies for indication for Cannabis flos product prescriptions in the year prior to the index date, anxiety was the most common pre-specified condition for Bedrocan (14% of treatment initiations) in the IQVIA DA Germany database, followed by sleep disorders (10%) and cancer (7%). In the IPCI database, cancer was the leading pre-specified condition for Bedrocan (16%) and Bedica (22%), with sleep disorders and anxiety also notable. Cancer, anxiety and sleep disorders were predominant pre-specified conditions for Bedica, Bedrobinol and Bediol.

Commonly recorded diagnostic codes, recorded within one year window prior to the index date, included pain diagnoses, essential hypertension and sleep disorders, with variations by product and database. In the IQVIA DA Germany database, diagnoses of general illness (27%) and chronic pain (17%) were commonly recorded for Bedrocan users, while back issues (11%) and hypertension (11%) were common in the IPCI data. Bedica users had frequent diagnoses of cough and low back pain, each present in 12% of the IPCI population, while Bedrobinol and Bediol users exhibited a variety of conditions, including backache, chronic obstructive lung disease, sleep disorders and anxiety, among other conditions.

Within the year prior to prescription of identified Cannabis flos products, commonly recorded medications included pain management and gastrointestinal agents. In the IQVIA DA Germany database, ibuprofen and pantoprazole were frequently prescribed among Bedrocan users, while the IPCI data showed common use of solutions (sodium chloride, sodium bicarbonate and potassium chloride), acetaminophen and diclofenac. Patterns varied by the Cannabis flos product and database.

Treatment duration was consistently 46 days in the IPCI with greater variability across identified products.

Discussion

The study offers insights into prescribing patterns of Cannabis flos products and characterizes patients using them as captured in two real-world data sources in the Netherlands and Germany. The IQVIA DA Germany database showed very low incidence rates and prevalence proportions, likely due to its focus on the primary care and the exclusion of certain cannabis prescribing specialties from data collection. Similarly, the IPCI database also exhibited low incidence rates and prevalence, which may be attributed to its emphasis on the primary care and the lack of representation of speciality care. Amongst the most frequently identified pre-specified conditions in these databases were anxiety, cancer and sleep disorders, while chronic pain emerged as a commonly recorded diagnoses. This aligns with existing literature that highlights the role of Cannabis flos in pain management. Overall, the findings of this study suggest that Cannabis flos containing products are likely prescribed through specialist care setting, which is not routinely collected in our currently available data sources.

4. LIST OF ABBREVIATIONS

Acronyms per term	Description
CDM	Common Data Model
DA	Disease Analyzer
DARWIN EU®	Data Analysis and Real World Interrogation Network
DRE	Digital Research Environment
DOI	Declaration of interests
DQD	Data Quality Dashboard
DRE	Digital Research Environment
DUS	Drug Utilisation Study
ED	Emergency Department
EEA	European Economic Area
EHR	Electronic Health Records
EMA	European Medicines Agency
EU	European Union
GDPR	General Data Protection Regulation
HMPC	Committee on Herbal Medicinal Products
ICD	International Classification of Diseases
ID	Index date
IP	Inpatient
LPD	Longitudinal Patient Database
MA	Marketing Authorisation
NA	Not applicable
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
OP	Outpatient
RCT	Randomised Controlled Trial
SD	Standard deviation
SNOMED	Systematized Nomenclature of Medicine
WHO	World Health Organisation

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Study deliverables	Timelines (planned)	Timelines (actual)
Draft Study Protocol	7th of June 2024	7th of June 2024
Final Study Protocol	July 2024	9th of July 2024
Creation of Analytical code	July 2024	July 2024
Registration in HMA-EMA Catalogue	June 2024	June 2024
Execution of Analytical Code on the data	August 2024	August 2024
Draft Study Report	August 2024	30th of August 2024
Final Study Report	August/September 2024	3rd of December 2024

7. RATIONALE AND BACKGROUND

Cannabis flos (dried, whole or fragmented, flowering tops of *Cannabis sativa* L.) is not registered as medicinal product in the European Union (EU). However, there are different regulatory strategies among EU member states that enable some specific exemptions for its use and its supply by pharmacies as a controlled substance, available only under physician's prescription.

The flowering top of the Cannabis sativa plant contains various cannabinoids, including tetrahydrocannabinol (THC).[1, 2] These cannabinoids possess potential anti-cachectic, muscle-relaxing, anxiolytic and analgesic properties, contributing to relaxation, anxiety reduction, pain relief and improved sleep quality.[2-6] Upon administration, the cannabinoids bind to the CB1 cannabinoid G-protein coupled receptors located in both central and peripheral neurons. Activation of CB1 receptors inhibits adenyl cyclase, enhances multiple signal transduction pathways and modulates the activity of various ion channels.[1, 2] This results in analgesic effects, may prevent muscle spasms and can potentially increase appetite.

This study aims to examine medicinal use of Cannabis flos products and profile of the individuals who use them in real-world setting. Furthermore, scientific data is needed to inform and support regulatory work including a possible establishment of an EU herbal monograph.

8. RESEARCH QUESTION AND OBJECTIVES

Research question

What is the (real-world) use of Cannabis flos that is prescribed for medicinal purposes?

Study objectives

1. To estimate incidence rates and prevalence of use of Cannabis flos, overall and stratified by medicinal product, age, sex and country/database, during the study period from 2014 to 2023.
2. To characterise the cohort of patients being treated with the Cannabis flos at the time of new prescription of the medicinal products in terms of demographics, indication for prescribing,

comorbidities and comedication. Additionally, to determine duration of treatment with Cannabis flos products. Results were stratified by product and database.

Description of the proposed objectives achieved in the study (**Table 1**).

Table 1. Primary and secondary research questions and objectives.

A. Objective 1.

Objective:	**Objective 1:** To estimate incidence rates and prevalence of use of Cannabis flos, overall and stratified by medicinal product, age, sex and country/database, during the study period from 2014 to 2023.
Hypothesis:	Not applicable
Population *(mention key inclusion-exclusion criteria):*	Population-level utilisation analyses included all individuals registered in the respective database between 1st of January 2014 and 31st of December 2023, with at least 1 year of data visibility prior to becoming eligible for study inclusion. This requirement of at least 1 year of prior data history did not hold for children <1 year of age.
Exposure:	Not applicable
Comparator:	Not applicable
Outcome:	Use of Cannabis flos (dried, whole or fragmented, flowering tops of *Cannabis sativa* L.)
Time *(when follow up begins and ends):*	Follow-up started on the respective date of the latest of the following: study start date (1st January 2014) or date at which individual had 1 year of prior history. End of follow-up was defined as earliest of the following: loss to follow-up, end of data availability, death or end of study period (31st of December 2023), whichever occurred first.
Setting:	Outpatient setting using data from the following 2 data sources: IPCI (Netherlands) and IQVIA DA Germany (Germany).
Main measure:	Annual incidence rates (expressed as number of new users of Cannabis flos per 100,000 person-years) and annual period prevalence (expressed as the proportion of Cannabis flos user in the study population), overall and stratified by medicinal product, age and sex. Annual incidence rates and annual period prevalence, for all products combined, were stratified by age and sex, while annual incidence rates and annual period prevalence for each product stratum were presented in an overall manner due to the limited sample size within each product stratum.

B. Objective 2.

Objective:	**Objective 2**: To characterise the cohort of patients being treated with Cannabis flos at the time of new prescription of the medicinal products in terms of demographics, indication for prescribing, comorbidity and

	comedication and to determine duration of treatment with Cannabis flos. Results were stratified by product and database.
Hypothesis:	Not applicable
Population ***(mention key inclusion-exclusion criteria):***	Patient-level utilisation of Cannabis flos containing products included new users of products registered in the respective database between 1st of January 2014 and 31st of December 2023, with at least 1 year of data visibility prior to index date. "New use" referred to a prescription of the medicinal products in the study period and without any use of respective medicinal products in the previous 1 year. This requirement of at least 1 year of prior data history did not hold for children <1 year of age.
Exposure:	Not applicable
Comparator:	Not applicable
Outcome:	Use of Cannabis flos (dried, whole or fragmented, flowering tops of *Cannabis sativa* L.)
Time ***(when follow up begins and ends):***	Follow-up started on the day of incident prescription of Cannabis flos (index date). End of follow-up was defined as earliest of loss to follow-up, end of data availability, death, end of study period (31st of December 2023) or end of treatment episode, whichever came first.
Setting:	Outpatient setting using data from the following 2 data sources: IPCI (Netherlands) and IQVIA DA Germany (Germany).
Main measures:	Large-scale characterisation (demographics, comorbidity and comedication) for new users of Cannabis flos at the index date and in a 1 year prior to the index date, stratified by medicinal products. Frequency and % of indications for prescribing Cannabis flos, based on pre-specified list of diagnoses, for new users of Cannabis flos at the index date and in 1 year prior to the index date, stratified by medicinal product. Duration of treatment of medicinal products expressed as minimum, p25, median, p75 and maximum, stratified by medicinal product.

9. RESEARCH METHODS

9.1 Study type and study design

The Study types with related study designs are selected from the Catalogue of Standard Data Analyses and described in the **Table 2** below.

A cohort study was conducted using routinely collected health data from 2 databases. The study comprised two consecutive parts:

- Population-based cohort study was conducted to address objective 1, assessing incidence rates and prevalence of use of Cannabis flos, overall and stratified by medicinal product, age, sex and country/database.
- New drug user cohort study was used to address objective 2; to characterise patient-level drug utilisation in terms of demographics, indication of use, comorbidities and comedication at the date of incident prescription of medicinal products and duration of treatment with Cannabis flos.

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

9.2 Study setting and data sources

This study was conducted using routinely collected data from 2 databases in 2 EU countries. All databases were previously mapped to the OMOP Common Data Model (CDM).

1. Integrated Primary Care Information Project (IPCI), the Netherlands
2. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany

For this study, 2 databases in the DARWIN EU® Database Catalogue were considered fit for purpose. The selection process was based on the size of the databases, the number of individuals prescribed Cannabis flos containing products, geographical spread and the experience gained from databases that participated in other similar DARWIN EU® studies. Based on the feasibility assessment performed, the suggested databases have data on Cannabis flos products.

Notably, the respective countries associated with these databases exhibit differing histories regarding the authorisation of Cannabis flos products for medicinal use. The Netherlands has the longest-standing experience, having authorised the prescription of Cannabis flos products since 2003.[7] In contrast, Germany legalised Cannabis flos-containing products for medical use in 2017 through a legislative change by the German parliament.[8]

Information on these data sources with a justification for their choice in terms of ability to capture the relevant data is described in **Table 2.**

Table 3. Description of the selected data sources.

Country	Name of Database	Justification for Inclusion	Health Care setting	Type of Data	Number of subjects	Number of active subjects*	Data lock for the last update
Netherlands	IPCI	Database covers primary care setting where selected pre-specified medicinal products of interest may be prescribed	Primary care	EHR	2.9 million	1.4 million	30/04/2024
Germany	IQVIA DA Germany	Database covers primary care and outpatient specialist care setting where selected pre-specified medicinal products of interest may be prescribed	Primary care and outpatient specialist care	EHR	43 million	8.5 million	31/12/2023

IPCI = Integrated Primary Care Information Project; DA = Data Analyzer; EHR = Electronic Health Record.

*Active subjects = individuals who were still under observation within a certain period (e.g. a year) prior to data lock. Individuals whose follow-up has ended in the past may still participate in a study if their follow-up covers the study period.

Integrated Primary Care Information Project (IPCI), The Netherlands

IPCI is collected from electronic health records (EHR) of patients registered with their general practitioners (GPs) throughout the Netherlands.[9] The selection of 374 GP practices is representative of the entire country. The database contains records from 2.9 million patients out of a Dutch population of 17M starting in 1996.[9] The median follow-up is 4.7 years. The observation period for a patient is determined by the date of registration at the GP and the date of leave per death. The observation period start date is refined by many quality indicators, e.g., exclusion of peaks of conditions when registering at the GP. All data before the observation period is kept as history data. IPCI database encompasses a broad spectrum of patient information, diagnoses (coded using the International Classification of Primary Care (ICPC-1)), measurements, therapies (classified by national product classification and WHO Anatomical Therapeutic Chemical (ATC) coding) and unstructured text. Medications are captured as prescription records, including details on the product, quantity, dosing directions, strength and indication. However, medications not prescribed in the GP setting might be underreported. Indications are primarily derived from GP-recorded diagnoses and, indirectly, from secondary care providers but the latter might not be complete. Approval needs to be obtained for each study from the Governance Board.[9]

IQVIA Disease Analyser (DA) Germany, Germany

The IQVIA DA Germany database contains deidentified electronic medical records from outpatient practices in Germany, including general and specialised medical practices, from 1992 onwards.[10] The dataset encompasses approximately 3% of all outpatient practices within Germany, ensuring a substantial representation of the national healthcare landscape.[10] The sampling method for practice selection accounted for the regional distribution of practices and physician age groups. Additionally, practices were required to have continuously provided data for at least 36 months (general practitioners) or 12 months (specialists).

The IQVIA DA Germany database included a wide range of practices such as general practice, internal medicine (gastroenterology, cardiology, rheumatology, pulmonology, diabetology) and other specialised fields (otolaryngology, gynaecology, paediatric, neurology and psychiatry, orthopaedics, urology and dermatology). However, IQVIA DA Germany does not cover all specialists, notably oncologists, haematologists, nephrologist and pain specialists are not represented among others.[10] For data protection reasons, patient visiting more than one provider are not cross identified and therefore recorded separately in the system. Observation time is defined by the first and last consultation dates. Notably, Germany has no mandatory GP system and patient have free choice of specialist.

The database captures a wide range of patient information, including demographics, diagnoses (classified according to the International Classification of Diseases (ICD), 10th revision), prescriptions of marketed products (using ATC codes) and clinical characteristics.[10, 11]

IQVIA DA Germany has been extensively used for pharmacoepidemiologic and pharmacoeconomic studies. Previous research has utilised this database for studies on various health conditions, including COVID-19 and cardiovascular outcomes, supporting its use in capturing comprehensive data on chronic diseases consistent with national statistics from the Federal Statistical Office.[11-13] Additionally, this database has also been utilised in previous studies on herbal products.[14-17]

No formal registration or approval is required for drug utilisation studies.

9.3 Study period

The study period was from 1st of January 2014 until the earliest of 31st December 2023 or respective lock for the last database update (refer to **Table 3** for detailed information on each database's latest data). A significant regulatory development within this timeframe was the enactment of legislation by the German Parliament in March 2017, authorising the medical use of Cannabis flos products. This legislative change is likely to have influenced temporal data distributions, particularly in relation to patterns of medicinal cannabis utilisation observed prior to and following legalisation.

9.4 Follow-up

For population-level utilisation of Cannabis flos containing products, follow-up started when study participants fulfilled inclusion criteria (i.e. present in the database between 1st of January 2014 and 31st of December 2023 and with at least 1 year of data visibility (not for children < 1 year of age)). End of follow-up was defined as the earliest of loss to follow-up, end of data availability, death or end of study period (31st December 2023), whatever came first.

For patient-level drug utilisation of Cannabis flos containing products, study participants were followed from the date of incident prescription of the product (index date) until loss to follow-up, end of data availability, death, end of the study period (31st of December 2023) or end of treatment episode, whatever came first.

Operational definition of index date and other primary time anchors are described in **Table 4**.

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

Study population name(s)	Time Anchor Description (e.g. time 0)	Number of entries	Type of entry	Washout window	Care Setting [1]	Code Type[2]	Diagnosis position	Incident with respect to…	Measurement characteristics per validation	Source of algorithm
All patients from the database eligible for the study – Incident use of Cannabis flos	Patients present in the database with at least 1 year of valid database history (except for children <1 year)	Multiple entries	Incident	[-365, ID]	OP	RxNorm	n/a	Use of Cannabis flos products	n/a	n/a
All patients from the database eligible for the study – Prevalent use of Cannabis flos	Patients present in the database with at least 1 year of valid database history (except for children <1 year)	Multiple entries	Prevalent	n/a	OP	RxNorm	n/a	n/a	n/a	n/a
All participants from the database eligible for the study initiating treatment with Cannabis flos products - Characterisation	Initiation of treatment with Cannabis flos products	Multiple entries	Incident	[-365, ID)	OP	RxNorm	n/a	Use of Cannabis flos products	n/a	n/a

[1] OP = outpatient

[2] The type(s) of clinical codes that were used to define the time 0 (or another primary anchor) criterion.

ID = index date; n/a = not applicable.

Both incidence and prevalence required an appropriate denominator population and their contributed observation time was first identified. Study participants in the denominator population started contributing person time on the respective date of the latest of the following: 1) study start date (1st January 2014) or 2) date at which they have 1 year of prior history. Participants stopped contributing person time at the earliest date of the following: 1) study end date (31st December 2023), 2) loss to follow-up, 3) end of data availability or 4) death.

An example of entry and exit into the denominator population is shown in **Figure 1**. In this example, person ID 1 had already sufficient prior history before the study start date and observation period ended after the study end date, so the person contributed during the complete study period. Person ID 2 and 4 enter the study only when they had sufficient prior history. Person ID 3 left when exiting the database (the end of observation period). Lastly, person ID 5 had two observation periods in the database. The first period contributed time from study start until end of observation period, the second started contributing time again once sufficient prior history was reached and exited at study end date.

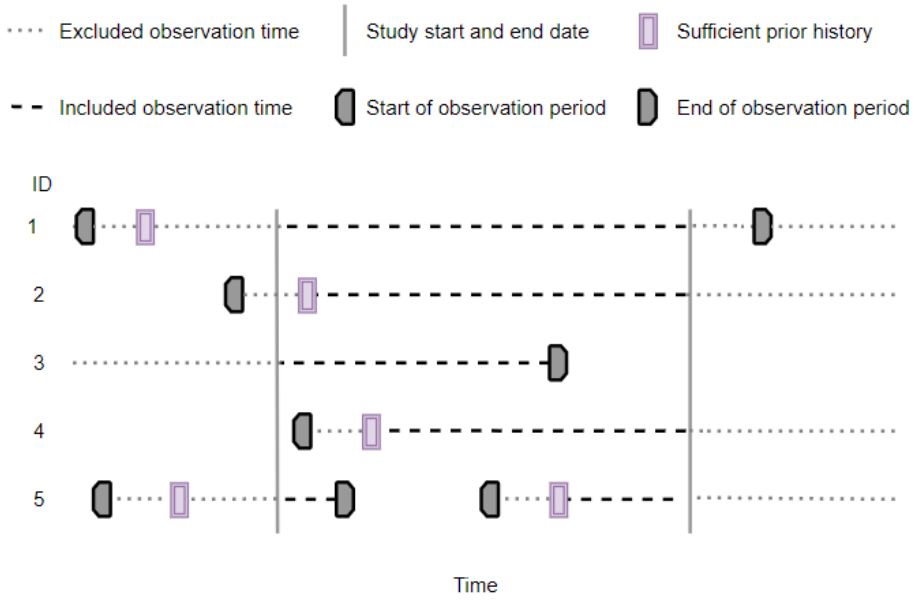


Figure 1. Included observation time for the denominator population.

9.5 Study population with in and exclusion criteria

9.5.1 Population-level utilisation of selected medicinal products

The study cohort included all individuals registered in the database between 1st of January 2014 and 31st of December 2023, with at least 1 year of data visibility prior to becoming eligible for study inclusion. This requirement of at least 1 year of prior data history did not hold for children <1 year of age.

Additional eligibility criteria were applied for the calculation of incidence rates: The observation time of participants prescribed Cannabis flos containing products was excluded during use and 1 year afterwards.

Furthermore, additional eligibility criteria were applied if incidence rates and prevalence were stratified by age and sex. Age-specific cohorts had age-boundary eligibility criteria and sex-specific cohorts had sex eligibility criteria.

9.5.2 Patient-level utilisation of selected medicinal products

All new users of Cannabis flos containing products in the period between 1st of January 2014 and 31st of December 2023 (or latest date available) were included. Notably, all patients had at least 1 year of data visibility prior to the date of their new prescription. “New use” referred to a prescription of the selected medicinal products in the study period and without any use of respective medicinal products in the previous 1 year. This requirement of at least 1 year of prior data history did not hold for children <1 year of age. “New use” in children younger than 1 year was defined as having no prescription for the selected medicinal products at any time before the index date.

The operational definitions of the inclusion criteria are presented by means of **Table 5.**

Table 5. Operational definitions of inclusion criteria.

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type	Diagnosis position[2]	Applied to study populations:	Measurement characteristics per validation	Source for algorithm
Observation period in the database during the period 2014-2023 (or the latest date available)	All individuals present in the period 2014-2023 (or the latest date available)	n/a	n/a	OP	n/a	n/a	All individuals within selected databases	n/a	n/a
Prior database history	Study participants were required to have 1 year of prior history observed before contributing observation time (except for children < 1 year of age)	After*	365 days	OP	n/a	n/a	All individuals within selected databases	n/a	n/a
Washout period	Individuals who initiated treatment were required to have not used selected pre-specified medication of interest 1 year before a “new” prescription	After*	365 days	OP	n/a	n/a	All individuals within selected databases	n/a	n/a

[1] OP = outpatient, n/a = not applicable.
[2] Specify whether a diagnosis code was required to be in the primary position (main reason for encounter).
*Order of application specifies whether the eligibility criterion was applied before or after selection of the study entry date. For example, selecting “before” means that all possible study entry dates were identified and then one or more was chosen. For instance, selecting 'after' means that the first possible study entry date was chosen, followed by the application of the inclusion and/or exclusion criteria. If the patient did not meet the criterion, then the patient dropped out.

9.6 Variables

9.6.1 Exposure

Not applicable.

9.6.2 Outcome

For this study, outcome of interest was use of Cannabis flos (dried, whole or fragmented, flowering tops of *Cannabis sativa L.)* containing products during the study period, as recorded in the study data sources. Prescribing is utilised as a proxy measurement for actual use, which is not directly captured in the available data.

Since Cannabis flos does not have standardised concepts within the OMOP CDM, a free-text search was employed to identify Cannabis flos containing products in the study data sources. The identified products were Bedrocan, Bedrobinol, Bediol, Bedrolite, Bedica, SIMM and SIMM18. Due to the absence of records for SIMM and SIMM18 during the study period, these products were not included in the study report.

The list of medication of interest is described in **Appendix I**. Detailed information regarding the outcome is described in **Table 6.**

Table 6. Operational definitions of outcome.

Exposure group name(s)	Details	Washout window	Assessment Window	Care Setting[1]	Code Type	Diagnosis position[2]	Applied to study populations	Incident with respect to…	Measurement characteristics per validation	Source of algorithm
Cannabis flos (dried, whole or fragmented, flowering tops of *Cannabis sativa* L.)	Code list provided in Appendix I	[-365, ID]	Calendar year	OP	RxNorm	n/a	All individuals present in the database during the study period	Previous use of Cannabis flos containing products	n/a	n/a

[1] OP = outpatient, n/a = not applicable.

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

ID = index date.

9.6.3 Other covariates

Covariates for population-level utilisation of selected medicinal products of interest

Covariates for stratification in population-level utilisation study included:

- Calendar year
- Age categories: 0-17 years and 18 years and older
- Sex: male or female
- Cannabis flos containing products identified in the study data sources: Bedrocan, Bedrobinol, Bediol, Bedrolite and Bedica

Population-level utilisation for all products combined was stratified by age and sex, while population-level utilisation for each product stratum was presented in an overall manner because of the limited sample size within each product stratum.

Covariates for patient-level utilisation of selected medicinal products of interest

Covariate for stratification in patient-level drug utilisation included Cannabis flos containing products identified in the study data sources:

- Bedrocan
- Bedrobinol
- Bediol
- Bedrolite
- Bedica

Other variables for patient-level utilisation of selected medicinal products of interest included:

- A list of pre-specified conditions used as a proxy to assess indication of use (the frequency of pre-specified conditions of interest was assessed at index date and within 1 year prior to the index date):
    - Cancer
    - Chemotherapy induced nausea and vomiting
    - Anxiety-related disorders
    - Neuralgic pain
    - Spasticity (multiple sclerosis (MS), spinal cord injury)
    - Neurological disorders (epilepsy, Tourette Syndrome, Huntington's disease, Parkinson disease, Amyotrophic lateral sclerosis (ALS), Alzheimer's disease and other dementias)
    - Glaucoma
    - Human immunodeficiency virus (HIV) infection
    - Anorexia
    - Sleep disorders (insomnia, sleep apnoea)
    - Inflammatory bowel disease
    - Fibromyalgia
    - Rheumatoid arthritis
- Top 10 of most frequent comorbidities from large-scale characterisation (the frequency of top recorded diagnosis codes was assessed at index date and within 1 year prior to the index date).

- Top 10 of most frequent drugs in each data source from large-scale characterisation (the frequency of most frequently recorded medication was assessed at the index date and within 1 year prior to the index date).

The operational definition of the covariates is described in **Table 7**. Index date is the start of the (new) incident prescription during the study period. The preliminary list of concepts for prespecified conditions of interest are described in **Appendix I**.

Table 7. Operational definitions of covariates.

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type	Diagnosis Position[2]	Applied to study populations	Measurement characteristics per validation	Source for algorithm
Indication of use	Check for pre-specified conditions of interest related to use of Cannabis flos	Counts	At ID and in window around ID [-365, ID]	OP	SNOMED	n/a	Persons with new use during the study period	n/a	n/a
Comorbidities	Large-scale patient characterisation with regard to recorded diagnosis codes	Counts	At ID and in window around ID [-365, ID]	OP	SNOMED	n/a	Persons with new use during the study period	n/a	n/a
Concomitant medication	Large-scale patient characterisation of new users with regard to recorded medication	Counts	At ID and in window around ID [-365, ID]	OP	RxNorm	n/a	Persons with new use during the study period	n/a	n/a

ID = index date;
[1] OP = outpatient, n/a = not applicable;
[2] Specify whether a diagnosis code was required to be in the primary position (main reason for encounter).

9.7 Study size

No sample size has been calculated for this drug utilisation descriptive study, as our primary focus was to investigate medicinal use of Cannabis flos, irrespective of the sample size. Based on a preliminary feasibility assessment, the expected number of person counts for the different products of the selected medication was 230 individuals in the IQVIA DA Germany and 734 individuals in the IPCI.

9.8 Data transformation

Analyses were conducted separately for each database. Before study initiation, test runs of the analytics were performed on a subset of the data sources and quality control checks were performed. After all the tests were passed (see section 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 in R Studio and reviewed and approved the - by default - aggregated results.

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

This section described the details of the analysis approach and rationale for the choice of analysis, with reference to the Catalogue of Data Analysis, which describes the type of analysis in function of the study type.

The analysis included calculation of population-based incidence rates and prevalence, as described in section 9.9.4. The type of analysis by study type is presented in **Table 8**.

Table 8. 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 pre-selected medicinal products of interest
Patient Level DUS	Off-the-shelf	- Characterisation of patient-level features - Frequency and % of pre-specified conditions - Frequency and % of recorded diagnosis codes - Frequency and % of recorded medication - Estimation of minimum, p25, median, p75 and maximum treatment duration

9.9.1 Patient privacy protection

Cell suppression was applied as required by databases to protect people's privacy. Cell counts <5 were masked.

9.9.2 Main statistical methods

R-packages

We used the R package "*IncidencePrevalence*" for population-level estimation of drug utilisation and "*CohortCharacteristics*", "*PatientProfiles*" and "*DrugUtilisation*" for patient-level drug utilisation analyses including patient-level characterisation.

Drug exposure calculations

Drug eras were defined as follows: Exposure started at date of the first prescription after a washout of 365 days. For each prescription, the estimated duration of use was retrieved from the drug exposure table in the CDM, using the start and end date of the exposure. Subsequent prescriptions were combined into continuous exposed episodes (drug eras) using the following specifications:

Two drug eras were merged into one continuous drug era if the distance in days between end of the first era and start of the second era was ≤ 30 days. The time between the two joined eras was considered as exposed to the dose in the first era as shown in **Figure 2**, first row.

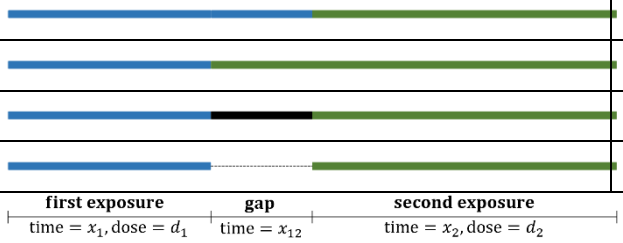
Gap era joint mode	Schematics	Dose in between	Cumulative dose	Cumulative time
"first"		d_1	$d_1 \cdot (x_1 + x_{12}) + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"second"		d_2	$d_1 \cdot x_1 + d_2 \cdot (x_2 + x_{12})$	$x_1 + x_{12} + x_2$
"zero"		0	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"join"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

Figure 2. Gap era joint mode.

New user cohort

New users were selected based on their incident prescriptions of the respective drug of interest after the start of the study. For each patient, at least 1 year of data visibility was required prior to a prescription. Individuals who initiated treatment were required to not have been exposed to the drug of interest for at least 1 year prior to the current prescription. If the start date of a prescription did not fulfil the exposure washout criteria of 1 year of no use, the whole exposure was eliminated. New drug user cohort study was used to characterise patient-level drug utilisation in terms of demographics, pre-specified conditions used to assess indication of use, recorded diagnosis codes and recorded medication at the date of incident prescription of Cannabis flos containing products and duration of treatment with these products.

9.9.3 Methods to derive parameters of interest

Age

Age at index date was calculated using January 1st of the year of birth as proxy for the actual birthday. Date per month was either not present or could not be made available for governance reasons. If available, date was often set to first of the month for patient's privacy. The following age groups were used for stratification for population-level analyses: 0-17 and ≥ 18 years of age.

Sex

Results for population-level analyses were presented stratified by sex (male, female, both).

Calendar time

Calendar time was determined on the calendar year during which the index prescription was issued. The calendar time for subsequent prescriptions was based on the year they are issued following the washout period of 365 days.

Indication

Indication was determined based on recordings of pre-defined conditions (see 9.6.3 – other variables), either on the date of the new (incident) prescription for the respective drug (index date) [primary definition] or within assessment window extending up to 1 year prior to the index date. If none of the specific indications was recorded on index date or during the assessment window, but there was a record for any other condition, the person was considered having an "other" indication.

Characterisation of patient-level features

Large-scale patient-level characterisation was conducted. Concepts in the "condition" domain were assessed at index date and within the window of 1 year prior to the index date. The top-10 conditions were presented.

9.9.4 Methods planned to obtain point estimates with confidence intervals of measure of occurrence

Population-level drug utilisation study

Prevalence and incidence calculations were conducted for Cannabis flos containing products.

Incidence calculations

Annual incidence rates of the identified Cannabis flos containing products were calculated as the number of new users of Cannabis flos products after 1 year of no use per 100,000 PY of the population at risk of getting exposed during the period for each calendar year. Those study participants who enter the denominator population then contributed time at risk up to start of their new Cannabis flos prescription during the study period. Multiple prescriptions were allowed, with participants' time contributions paused during a defined outcome washout period of 365 days. Participants without drug exposure contributed time at risk as described above. Time-at-risk of subjects who died was censored at the time of death. Similarly, time at risk of subjects who were lost to follow-up were censored at the time of loss to follow-up [last contact]. Subjects with data until the end of the study period without experiencing exposure were administratively censored at the end of the study period. Incidence rates were given together with 95% Poisson confidence intervals.

An illustration of the calculation of incidence of selected pre-specified medication of interest is shown below in **Figure 3**. Patient ID 1 and 4 contributed time at risk up to the point at which they became incident users of selected pre-specified medication of interest. Patient ID 2 and 5 were not seen to use pre-specified medication of interest and so contributed time at risk but no incident outcomes. Meanwhile, patient ID 3 first contributed time at risk starting at the day when the washout period of a previous exposure, before study started, has ended and ending when the next exposure of pre-specified medication of interest was starting. A second period of time at risk again started after the washout period. For person ID 4, only the first and third exposures of pre-specified medication of interest count as incident use, while the second exposure started within the washout period of the first exposure. The time between start of the first exposure until the washout period after the second exposure was not considered as time at risk.

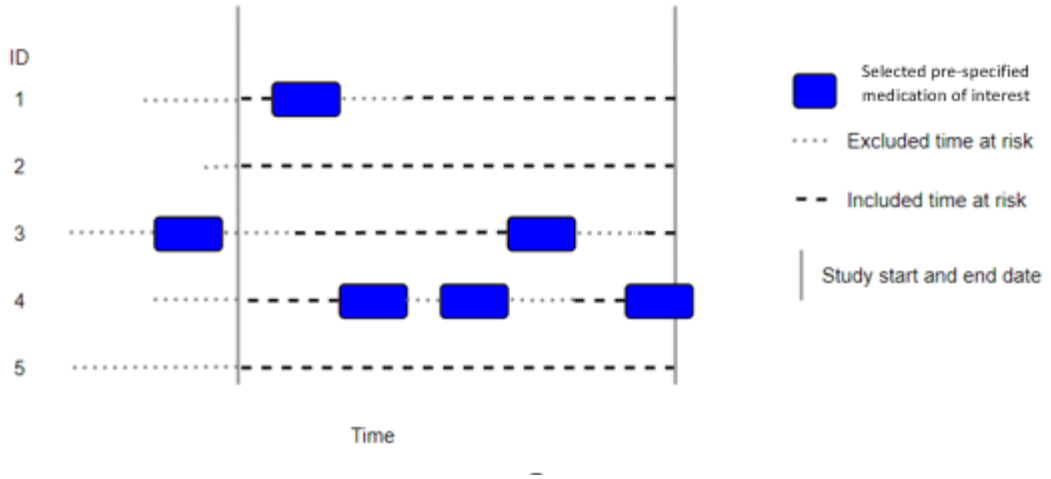


Figure 3. Incidence example.

Prevalence calculations

Prevalence was calculated as annual period prevalence which summarised the total number of individuals who use the drug of interest during a given year divided by the total study population at risk of getting exposed during that year. Therefore, period prevalence gave the proportion of individuals exposed at any time during a specified interval. Binomial 95% confidence intervals were calculated.

An illustration of the calculation of period prevalence was shown below in **Figure 4**. Between time t+2 and t+3, two of the five study participants are users of pre-selected medication of interest giving a prevalence of 40%. Meanwhile, for the period t to t+1 all five also had some observation time during the year with one of the five study participants being a user of pre-selected medication of interest.

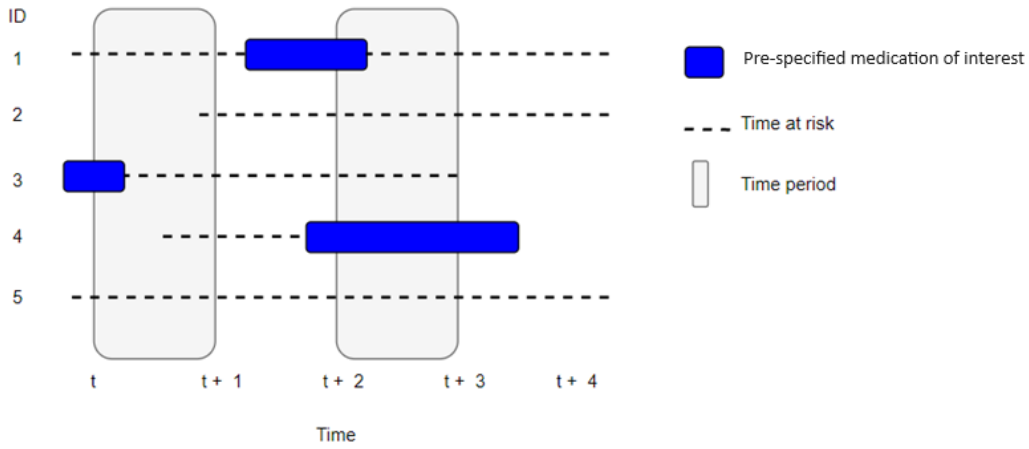


Figure 4. Period prevalence example.

Prescription pattern across healthcare setting

To assess the prescribing patterns of Cannabis flos across different medical specialities, a structured SQL-based approach was implemented using the IQVIA Germany DA OMOP dataset. All relevant Cannabis flos prescriptions were identified by filtering the drug exposure table for specific drug_source_concept_id values and were linked to health care providers and their corresponding specialities. For each speciality, the total number of Cannabis flos prescriptions and the count of distinct providers involved were provided.

Patient-level drug utilisation study

New drug user patient-level characteristics on index date

For concepts assessed as part of large-scale characterisations, the number of persons (N, %) with a record within the pre-specified time windows was provided.

Indication

The number and percentage of persons (N, %) with a record of the respective pre-specified conditions, used as a proxy to assess indication, were provided. If a person had a record of more than one pre-specified condition, that person was included in both specific indication groups separately.

Treatment duration

Treatment duration was determined by calculating the difference in days between drug_exposure_start_date and drug_exposure_end_date for each treatment episode, with an additional day included to account for both the start and end dates in the exposure period. This calculation assumed accurate recording of both dates, as discrepancies could affect the estimated duration of exposure time. Continuous exposure was assumed throughout the interval between the start and end dates, allowing for a maximum interruption of 30 days. Periods of drug exposure before the cohort start or after the cohort end date were excluded. Missing exposure data was treated as zero, indicating no exposure during periods with missing information.

The drug_exposure_start_date represented the prescription start date and drug_exposure_end_date denoted the day the drug exposure ended (https://ohdsi.github.io/CommonDataModel/cdm54.html#drug_exposure). In cases where the end date was not explicitly available in the data, it was inferred using one of the following methods: (1) adding the duration or days supply to the start date, (2) using quantity divided by daily dose or concentration or (3) applying predefined rules such as assigning a default value of 29 days for written prescriptions.

Treatment duration was summarised providing the minimum, quartiles, maximum duration of treatment episodes. For databases, where duration could not be calculated due to e.g., missing information on quantity or dosing, treatment duration was not provided.

9.9.5 Missing values

For the drug utilisation studies we assumed that the absence of a prescription record meant that the person did not receive the respective drug. For indications, we assumed that the missingness of a record of the respective condition meant that that condition was not the indication for the drug prescription.

9.9.6 Sensitivity analysis

Not applicable.

9.10 Evidence synthesis

Results from analyses described in section 9.9 Data analysis were presented separately for each database and no meta-analysis of results was conducted.

9.11 Deviations from the protocol

Treatment duration for Cannabis flos products was initially intended to be presented. However, due to OMOP CDM conventions, several assumptions and imputations were applied to estimate treatment duration for Cannabis flos containing products in the IQVIA DA Germany database. Specifically, certain data elements needed for calculating treatment duration were missing, leading to the imputation of a fixed (default) value for the vast majority of treatment episodes for Cannabis flos containing products, in accordance with the Extract, Transform, Load (ETL) process (https://ohdsi.github.io/CommonDataModel/cdm54.html#drug_exposure). These imputations may not accurately reflect real-world treatment patterns of Cannabis flos containing products and could be misinterpreted as actual observed durations in IQVIA DA Germany. Therefore, these results were excluded from the final analysis.

10. DATA MANAGEMENT

10.1 Data management

All databases were mapped to the OMOP common data model. This enabled the use of standardised analytics and tools across the network since the structure of the data and the terminology system was harmonised. The OMOP CDM was developed and maintained by the Observational Health Data Sciences and Informatics (OHDSI) initiative and was described in detail on the wiki page of the CDM: https://ohdsi.github.io per 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 then returned the results set which only contained aggregated data. The results from each of the contributing data sites were then combined in tables and figures for the study report.

10.2 Data storage and protection

For this study, participants from various EU member states processed personal data from patients which was collected in national/regional electronic health record databases. Due to the sensitive nature of this personal medical data, it was 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 were already used for pharmaco-epidemiological research and had a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control were adhered to. In agreement with these regulations, rather than combining person level data and performing only a central analysis, local analyses were run, which generate non-identifiable aggregate summary results.

The output files were stored in the DARWIN Digital Research Environment (DRE). These output files did not contain any data that allowed identification of subjects included in the study. The DRE implemented further security measures in order to ensure a high level of stored data protection to comply with the local

implementation of the General Data Protection Regulation (GDPR) (EU) 679 per 20161 in the various member states.

11. QUALITY CONTROL

General database quality control

A number of open-source quality control mechanisms for the OMOP CDM have been developed (see Chapter 15 of The Book of OHDSI http://book.ohdsi.org per DataQuality.html). In particular, it was expected that data partners will have run the OHDSI Data Quality Dashboard tool (https://github.com per OHDSI per DataQualityDashboard). This tool provided 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 was 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 had one or more subcategories and were evaluated in two contexts: validation and verification. Validation related to how well data align with external benchmarks with expectations derived from known true standards, while verification related to how well data conform to local knowledge, metadata descriptions and system assumptions.

Study specific quality control

When it comes to assessing the reliability of data sources, the data partners were asked to describe their internal data quality process on the source data as part of the DARWIN EU® onboarding procedure. To further ensure data quality, we utilised the Achilles tool, which systematically characterizes the data and presents it in a dashboard format that was inspected. The generated data characteristics such as age distribution, condition prevalence per year, data density, measurement value distribution was compared against expectations for the data. Additionally, the data quality dashboard (DQD) provided more objective checks on plausibility consistently across the data sources. In terms of relevance, a more general-purpose diagnostic tools, "*CohortDiagnostics"* and "*DrugExposureDiagnostics"*, were developed. Furthermore, timeliness is guarded by extracting the release dates for each dataset in the network and monitoring when data are out-of-date with the expected refresh cycle (typically quarterly or half-yearly). In addition, it was important to have clear understanding of the time period covered by each released database, as this can vary across different domains. To facilitate this, the CdmOnboarding (and Achilles) packages contain a 'data density' plot. This plot displayed the number of records per OMOP domain on a monthly basis. This allowed to get insights when data collection started, when new sources of data were added and when until when data was included.

For the purpose of this study, the diagnostic data packages, "*CohortDiagnostics"* and "*DrugExposureDiagnostics"* were not utilised. These DARWIN EU® diagnostics packages were designed to work with existing concept ids, but the Cannabis flos containing products in this study were identified based on the source codes.

The study code was based on four R packages namely the "*IncidencePrevalence", "CohortCharacteristics",* "*PatientProfiles*" and *"DrugUtilisation"* packages. These packages included numerous automated unit tests to ensure the validity of the codes, alongside software peer review and user testing. The R packages were made publicly available via GitHub.

12. RESULTS

The full set of results for this study is available through an interactive web-application ("Shiny App") at https://data-dev.darwin-eu.org/P3-C1-006-DUS-Cannabis-flos/.

12.1 Population-level utilisation of selected medicinal products

12.1.1 Participants

Table 9 shows the number of individuals included in the estimation of the incidence rates for Cannabis flos product prescriptions as part of population-level utilisation study. The results are stratified by database and calendar year during the study period. All results of this study, including the number of events, population size and person-years for each age group and database per calendar year can be found in an interactive web-application ("shiny app") at https://data-dev.darwin-eu.org/P3-C1-006-DUS-Cannabis-flos/.

Table 9. Number of individuals in the source population during the study period, per calendar year, age group and database.

	IQVIA DA Germany*			IPCI*		
Year	Overall	0 - 17	≥18	Overall	0 - 17	≥18
2014	7,502,669	943,930	6,558,739	843,443	182,462	668,896
2015	7,945,800	982,497	6,963,303	980,061	213,859	775,410
2016	8,302,860	1,010,271	7,292,589	1,142,241	243,990	909,873
2017	8,819,120	1,076,602	7,742,518	1,199,215	254,216	957,922
2018	9,099,929	1,102,169	7,997,760	1,216,270	254,368	974,970
2019	9,046,255	1,085,546	7,960,709	1,240,009	258,460	994,695
2020	9,003,908	1,064,248	7,939,660	1,327,746	272,882	1,068,336
2021	8,658,168	1,014,734	7,643,434	1,387,456	286,817	1,114,464
2022	7,696,116	915,101	6,781,015	1,385,637	284,896	1,112,907
2023	5,880,264	728,572	5,151,692	1,232,176	248,444	995,224

DA - Disease Analyzer; IPCI - Integrated Primary Care Information Project;

*Number of individuals is presented overall and for two age groups (0-17 and ≥18 years). Some individuals meet eligibility criteria in several calendar years and potentially in different age-groups and may enter the study repeatedly.

12.1.2 Descriptive data and main results

12.1.2.1 Incidence rates of use of Cannabis flos products overall

Figure 5 illustrates annual incidence rates of Cannabis flos product prescriptions, expressed as the number of new users of Cannabis flos products per 100,000 PY, following a one-year period of non-use, across different databases and over calendar years.

In the IQVIA DA Germany, incidence rates were consistently low and stable throughout the study period, showing minimal variation. Following the legalisation of Cannabis flos for medicinal use in Germany in March 2017, Cannabis flos prescriptions began to appear in the dataset starting in 2018. The observed incidence rates were very low, ranging from 0.1 per 100,000 PY in 2018 to 0.8 per 100,000 PY in 2023.

Given that the IQVIA DA Germany database includes data from both general practitioners and selected specialists, we further examined the distribution of prescribing providers by specialty. The analysis revealed that over 70% of the providers were general practitioners, with neuropsychiatrists accounting for 10%. Moreover, more than 60% of Cannabis flos prescriptions originated from general practice, while 25% were prescribed by neuropsychiatry and psychotherapy specialists.

In the IPCI database, the incidence rates of Cannabis flos prescriptions demonstrated a distinct temporal trend. In 2014, the incidence rate was 8.8 per 100,000 PY, peaked at 11.1 per 100,000 PY in 2015 and then showed a decline to 3.7 per 100,000 PY in 2018. This downward trend continued steadily through to 2 per 100,000 PY in 2023.

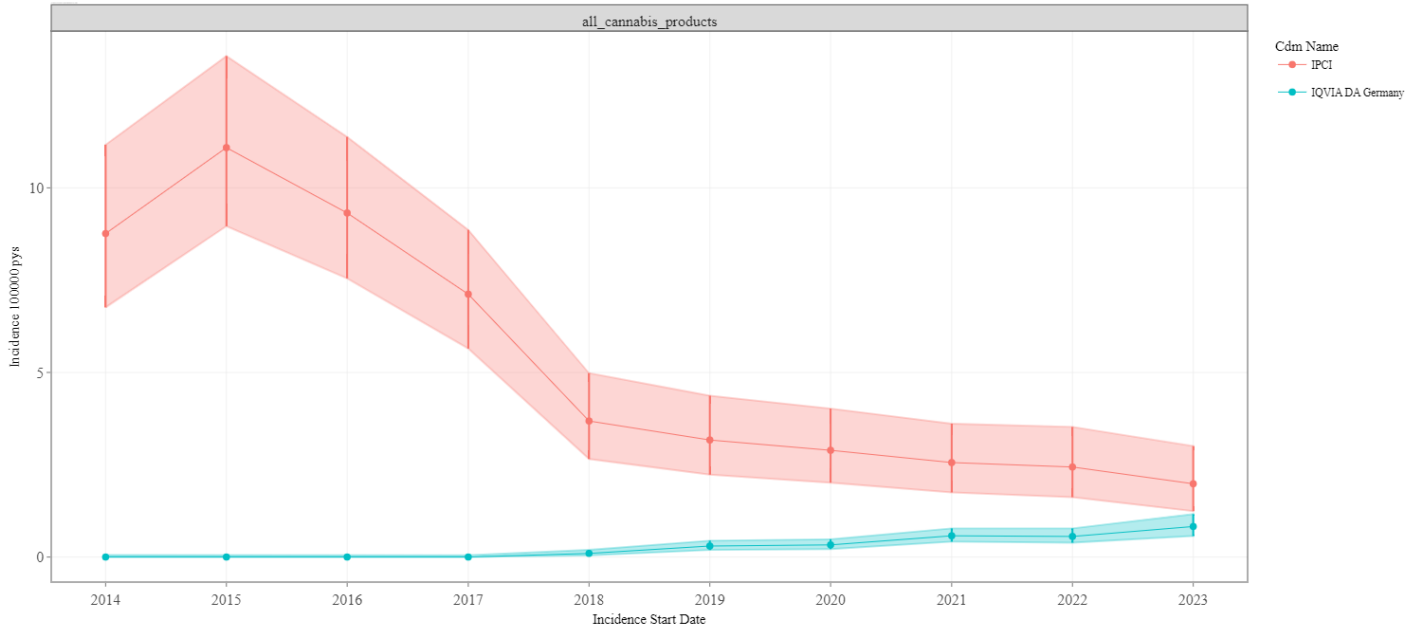


Figure 5. Incidence rates of new Cannabis flos product prescriptions per 100,000 PY across databases during the study period (2014–2023).

12.1.2.2 Incidence rates of use of Cannabis flos products overall, stratified by age

Figure 6 displays incidence rates of Cannabis flos product prescriptions, stratified by age groups and databases during the study period.

In the IQVIA DA Germany database, the incidence rates of Cannabis flos prescriptions remained consistently low across both age groups (0-17 years and ≥18 years) throughout the study period. Among children (0-17 years), the incidence rates were consistently zero from 2018 to 2023, indicating no new users of Cannabis flos products. Among the adults (≥18 years), although the rates remained low, there is a slight upward trend observed over time. The incidence rates ranged from 0.1 per 100,000 PY in 2018 to 0.9 per 100,000 PY by 2023.

In contrast, the IPCI database revealed a more pronounced trend in the incidence rates, particularly among adults. For individuals aged ≥18, the incidence rates were higher, starting at approximately 11.1 per 100,000 PY in 2014, peaking at 13.8 per 100,000 PY in 2015 and then gradually declining to around 2.5 per 100,000 PY by 2023. This pattern indicated an initial surge in new users of Cannabis flos products, followed by a steady decrease over time. In children (0-17 years), the incidence rates in the IPCI database were consistently zero, with no new users observed throughout the study period. There were sporadic cases in 2015 and 2019, however due to small number of events (n < 5), these figures could not be presented.

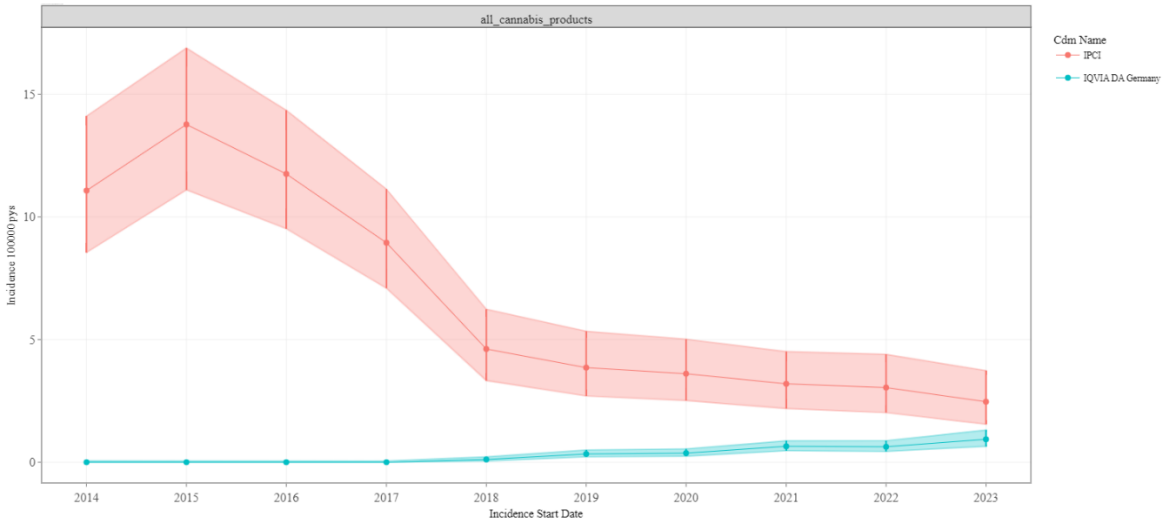


Figure 6. Annual incidence rates of Cannabis flos product prescriptions per 100,000 PY by age group and databases during the study period (2014–2023). The annual incidence rates for the 0–17 years age group were consistently zero and are therefore not displayed in a separate plot. The plot above shows the annual incidence rates for the ≥18 years age group.

12.1.2.3 Incidence rates of use of Cannabis flos products overall, stratified by sex

The **Figure 7** illustrates the annual incidence rates of Cannabis flos products prescriptions, stratified by sex and database during study period. Overall, the analysis revealed a distinct prescribing pattern across the databases.

In the IQVIA DA Germany database, the incidence rates for Cannabis flos prescriptions remained consistently low for both sexes throughout the study period. The incidence rates ranged from 0 per 100,000 PY in 2018 to 0.7 per 100,000 PY by 2023 among females and from 0.1 per 100,000 PY in 2018 to 1 per 100,000 PY by 2023 among males.

In contrast, the IPCI database revealed a more variable prescription pattern for Cannabis flos, with similar trends observed for both sexes. The data indicated an initial increase in new users, followed by a subsequent decline. For males, the incidence rate was 8.5 per 100,000 PY in 2014, peaked at 11.3 per 100,000 PY in 2015 and then decreased to 2.2 per 100,000 PY by 2023. For females, the rate started at 9.0 per 100,000 PY in 2014, reached a peak of 11.3 per 100,000 PY in 2016 and declined to 1.8 per 100,000 PY by 2023.

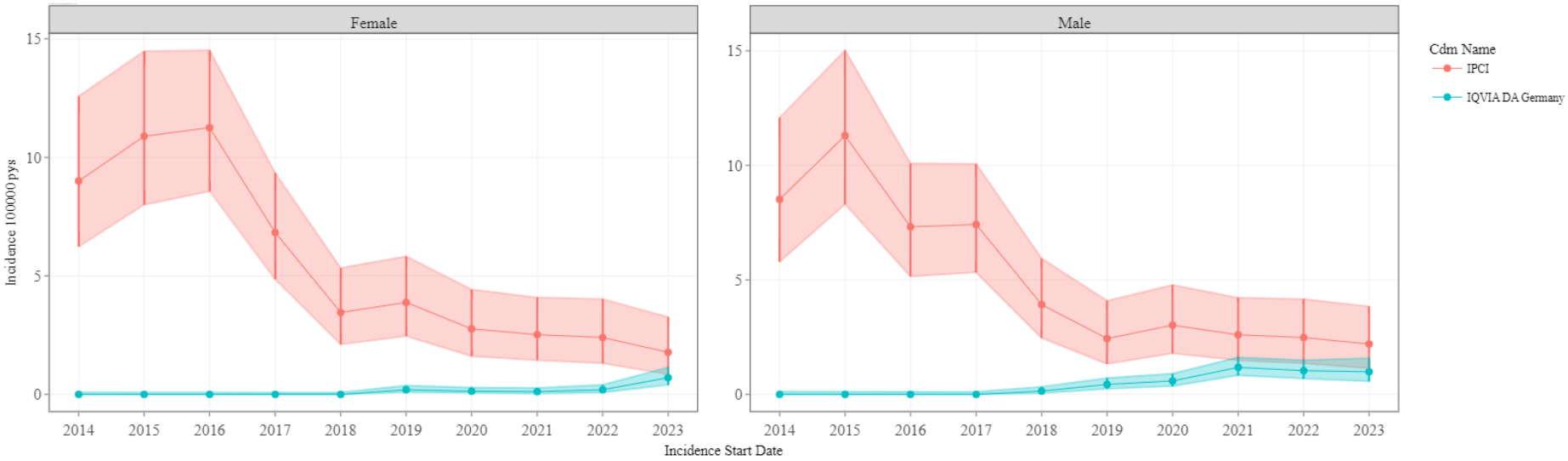


Figure 7. Incidence rates of Cannabis flos product prescriptions per 100,000 PY by sex and databases during the study period (2014–2023).

12.1.2.4 Incidence rates of Cannabis flos prescribing, stratified by product

The Cannabis flos products identified in the study data sources included Bedrocan, Bedrobinol, Bediol, Bedrolite and Bedica. **Figure 8** and **Figure 9** illustrate the annual incidence rates of Cannabis flos prescriptions for these products. These rates are expressed as the number of new users for each specific product per 100,000 PY, stratified by database, over the study period.

In IQVIA DA Germany, no prescriptions were recorded for Bedica, resulting in zero incidence rates. Similarly, the number of prescriptions for Bedrobinol and Bedrolite was too low to produce detectable incidence rates. Bediol exhibited very low incidence rates, approximately 0.07 per 100,000 PY, while incidence rates for Bedrocan ranged from 0.2 per 100,000 PY in 2019 to 0.8 per 100,000 PY in 2023.

In the IPCI database, the incidence rates for Bedica were relatively stable over time, with slight fluctuations from 1.8 per 100,000 PY in 2014 to 0.6 per 100,000 PY by 2023. Bediol exhibited a similar pattern, with a gradual increase from 1.9 per 100,000 PY in 2014 to 2.7 per 100,000 PY in 2015, followed by a decrease to 0.5 per 100,000 PY by 2021. The incidence rates for Bedrobinol remained stable with minor fluctuations, ranging from 1.4 per 100,000 PY in 2014 to 0.4 per 100,000 PY by 2023. Bedrolite had very low prescription counts (six or fewer) throughout the study period. For Bedrocan, the incidence rate began at 5.4 per 100,000 PY in 2014, peaked at 6.7 per 100,000 PY in 2015 and then gradually declined to 1.8 per 100,000 PY in 2018, stabilizing at lower levels with an incidence rate of 1.2 per 100,000 PY by 2023.

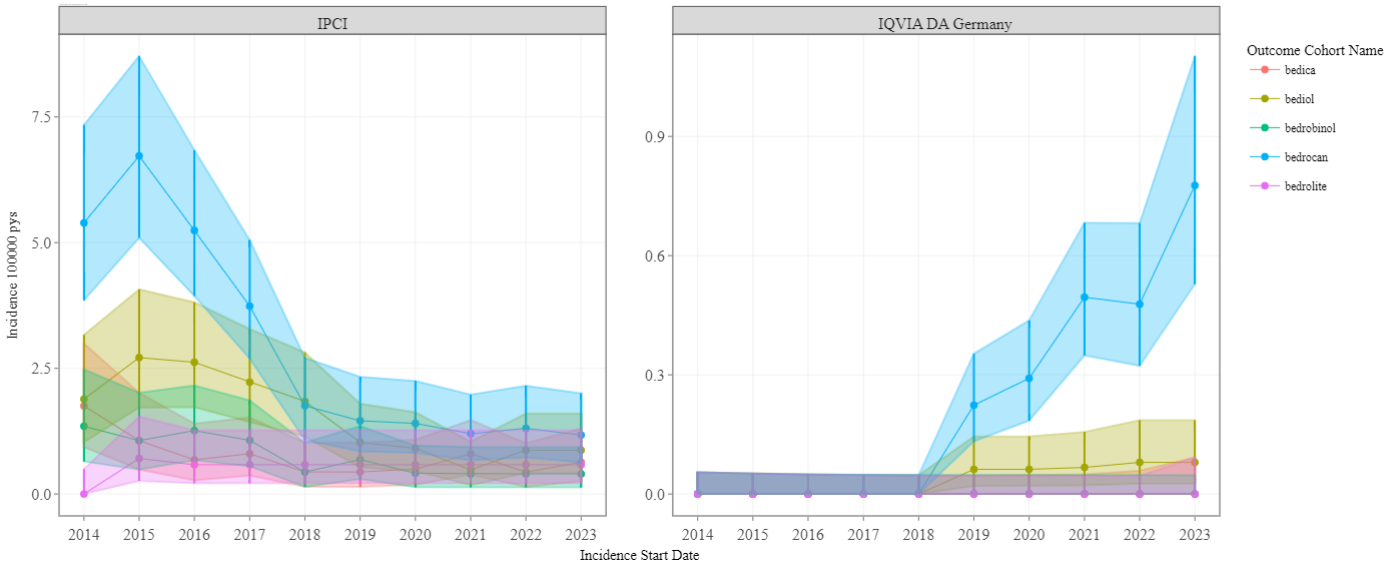


Figure 8. Annual incidence rates of specific Cannabis flos product prescriptions per 100,000 PY per database during the study period (2014–2023).

Figure 9. Annual incidence rates of Cannabis flos products of interest per 100,000 PY by database during the study period.

12.1.2.5 Prevalence of use of Cannabis flos products overall

Figure 10 illustrates period prevalence of Cannabis flos product prescriptions across databases and during the study period. The trends observed in the overall use of Cannabis flos products largely reflect those of incident use. All details, including the number of events and population for each calendar year can be found in the "shiny app" (https://data-dev.darwin-eu.org/P3-C1-006-DUS-Cannabis-flos/).

In the IQVIA DA Germany database, prevalence for Cannabis flos products prescriptions remained very low overall during the study period in terms of absolute numbers. In 2018, the first prescription records appeared (n=8), resulting in a very low prevalence of 0.00009%. The number of prescriptions continued to increase in the subsequent years, leading to a prevalence of 0.001% in 2023.

In the IPCI database, prevalence for Cannabis flos products prescriptions was also very low overall and generally stable during the study period in absolute numbers. Initially, from 2014 to 2016, there was a slight increase in prevalence, reaching its peak of 0.02% in 2016. However, after 2016, the prevalence began to decrease slightly and by the end of the study period in 2023, the prevalence was 0.008%.

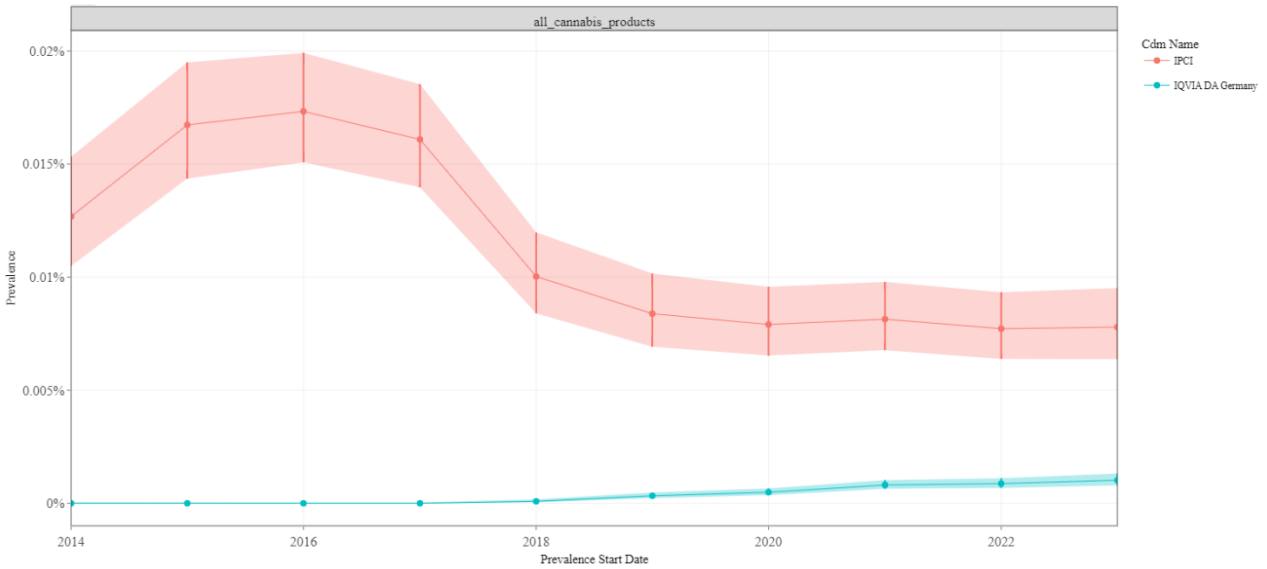


Figure 10. Prevalence of Cannabis flos product prescriptions, expressed as number of individuals exposed to Cannabis flos in the study population, across databases, during the study period (2014–2023).

12.1.2.6 Prevalence of use of Cannabis flos products overall, stratified by age

Figure 11 shows period prevalence of Cannabis flos products, expressed as number of individuals exposed to Cannabis flos products in the study population, stratified by age groups and databases.

In the IQVIA DA Germany database, there were no records of Cannabis flos prescriptions among children (0-17 years), resulting in prevalence of zero for this age group. For adults (≥18 years), the first prescriptions were recorded in 2018 but the prevalence remained extremely low at 0.0001% and this low level persisted throughout the subsequent years.

In the IPCI database, prescriptions for Cannabis flos products in children (0-17 years) were either non-existent or too sparse (<5 cases) to report a meaningful prevalence. For adults (≥18 years), the trends mirrored those observed in the overall analyses. Initially, from 2014 to 2016, there was a slight increase in prevalence, peaking at 0.02% in 2016. Afterwards, the prevalence began to decline slightly and by the end of the study period in 2023, it had decreased to 0.01%. However, in absolute numbers, overall usage remained very low and stable during the study period for this age group.

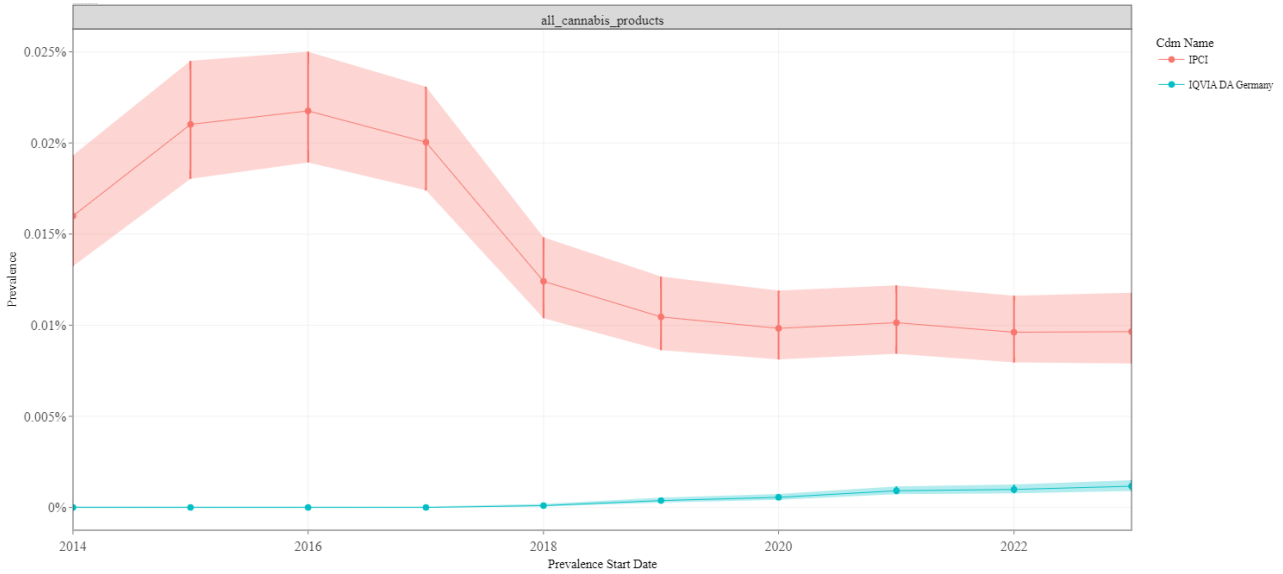


Figure 11. Prevalence of Cannabis flos product prescriptions, stratified by age groups and databases during the study period (2014–2023). Prevalence for the 0–17 years age group was consistently zero and is therefore not displayed in a separate plot. The plot above shows prevalence for the ≥18 years age group.

12.1.2.7 Prevalence of use of Cannabis flos products overall, stratified by sex

Figure 12 illustrates the period prevalence of Cannabis flos products, stratified by sex across different databases.

In the IQVIA DA Germany database, the overall trend in period prevalence was consistent with the general findings observed across the broader analyses. Specifically, the prevalence remained very low and stable across both genders throughout the study period, showing minimal variation in absolute numbers. A slightly higher prevalence was observed in males compared to females.

Similarly, the IPCI database displayed a comparable pattern. The period prevalence of Cannabis flos products was consistently low and stable, with no discernible differences between male and female patients.

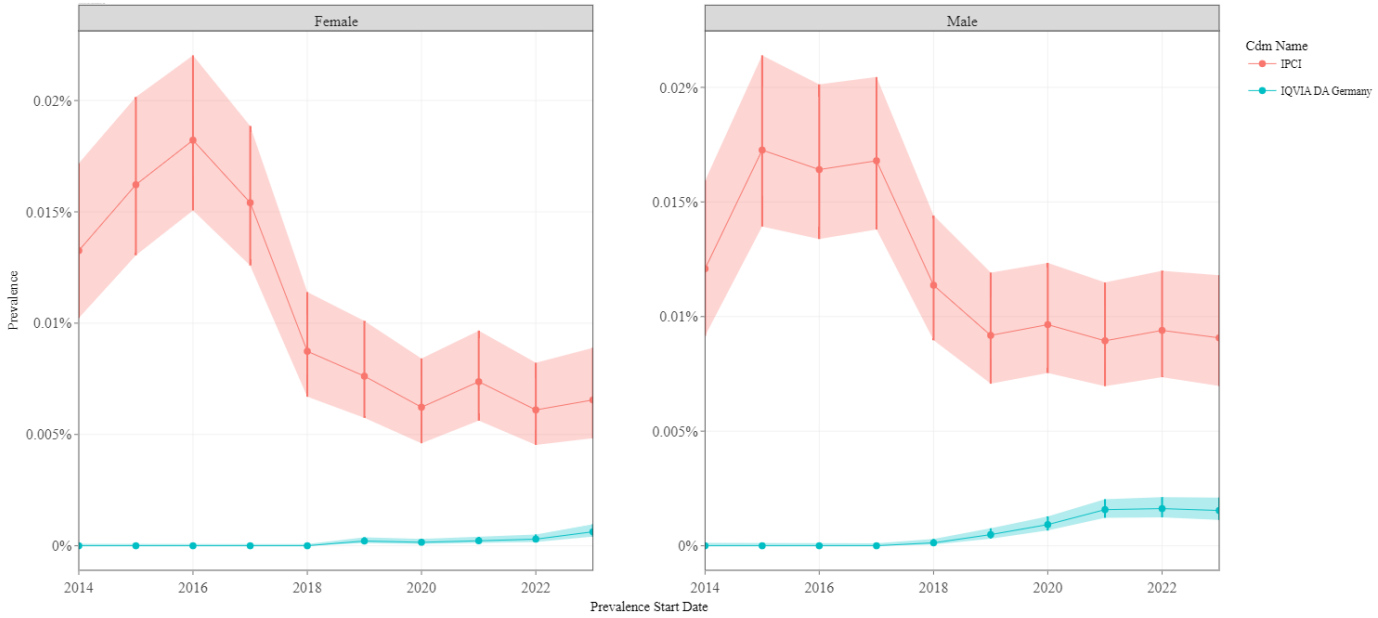


Figure 12. Prevalence of Cannabis flos product prescriptions stratified by sex and databases during the study period (2014–2023).

12.1.2.8 Prevalence of use of Cannabis flos prescribing stratified by product

Figure 13 and **Figure 14** illustrate the annual prevalence of Cannabis flos prescriptions for identified products Bedica, Bediol, Bedrobinol, Bedrocan and Bedrolite. These proportions are represented as the number of all users for each specific product within the study population, stratified by database, during the study period. The overall trend in period prevalence was consistent with the findings observed in the incidence analyses.

In IQVIA DA Germany, prevalence for Bedica, Bedrolite and Bedrobinol remained negligible throughout the study period. Either there were no prescriptions, or the number of prescriptions was too low to yield a detectable prevalence estimate. For Bediol, the number of prescriptions recorded in the database was very low, with a peak of nine prescriptions in 2022, leading to a low prevalence. The number of prescription records for Bedrocan increased during the study period, but prevalence remained very low.

In the IPCI database, the prevalence for all Cannabis flos products was consistently very low and relatively stable over time. The highest prevalence was observed for Bedrocan, with 0.008% in 2014, peaking at 0.01% in 2016 and then gradually declining to 0.006% in 2018, a level that persisted in the subsequent years. Other Cannabis flos products had even lower prevalence, but the general pattern corresponded to the overall trends observed in the study.

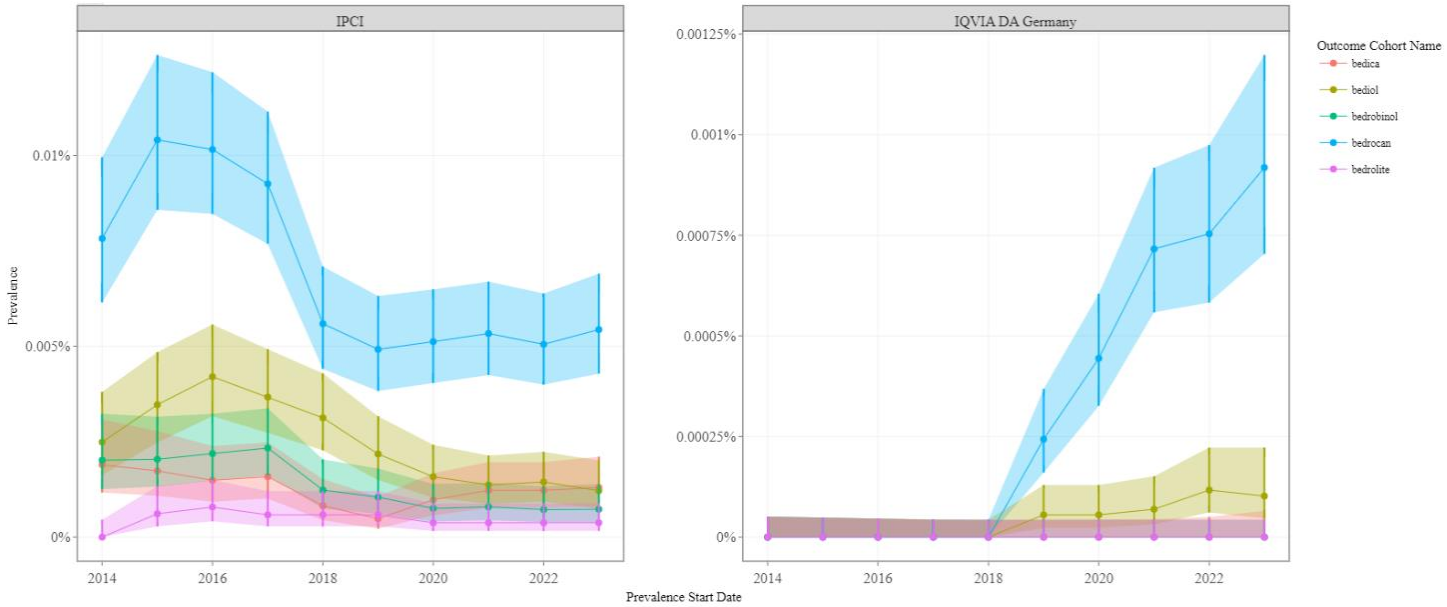


Figure 13. Prevalence of Cannabis flos product prescriptions across databases during the study period (2014–2023).

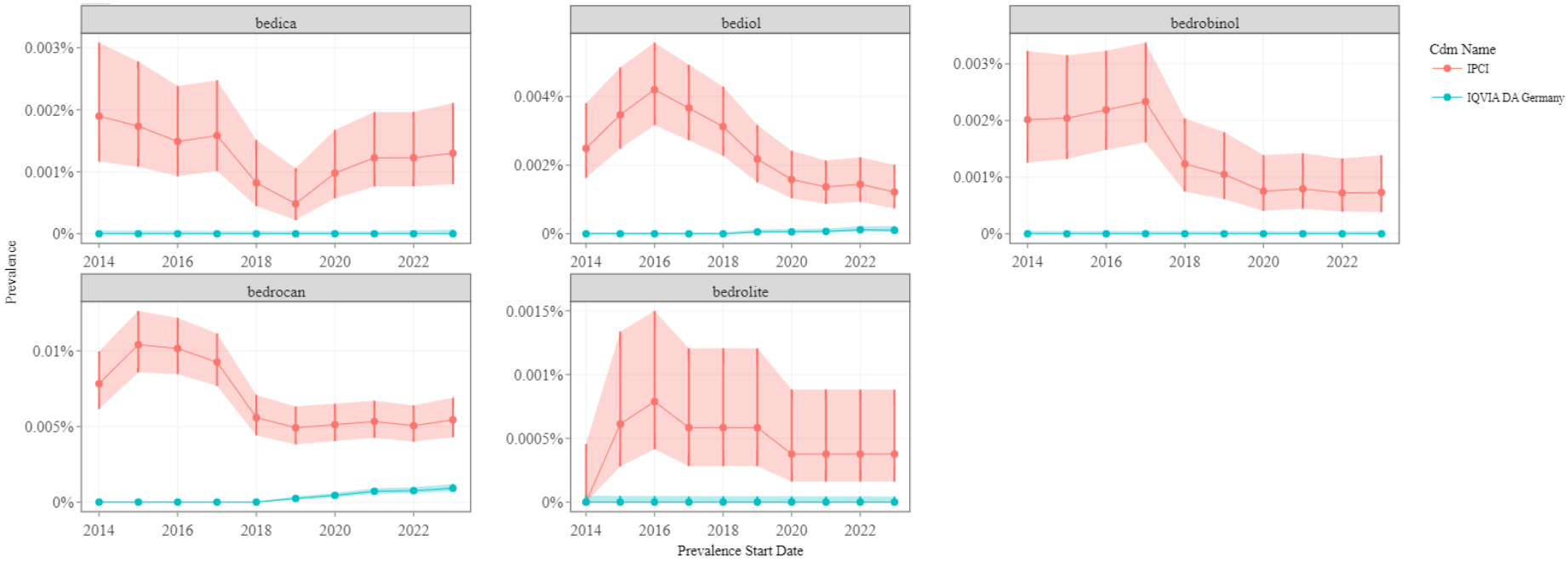


Figure 14. Prevalence of Cannabis flos product prescriptions by database during the study period (2014–2023).

12.2 Patient-level drug utilisation

12.2.1 Participants

Table 10 provides the number of individuals prescribed Cannabis flos products and the corresponding number of records, categorised by product and database.

In the IQVIA DA Germany database, Bedrocan prescriptions were identified for 165 individuals with 520 records. After applying eligibility criteria, which included, a 1-year washout period, restricting cohort start and end date between 2014 and 2023, ensuring one year of prior observation for all participants except for children under the age of one and after applying the definition of treatment episode which involves joining exposures separated by 30-days or less, the final eligible cohort consisted of 132 individuals and 143 records. In the IPCI database, 444 individuals and 1,970 records were initially identified based on Bedrocan prescriptions. Following application of the eligibility criteria and the definition of treatment episode, the final eligible cohort included 270 individuals and 289 records.

Bediol prescriptions in the IQVIA DA Germany dataset were initially recorded for 24 individuals with 65 records. After applying the eligibility criteria, the final cohort consisted of 21 individuals and 23 records. In the IPCI database, 211 individuals and 693 episodes were initially identified, which was reduced to 146 individuals and 153 episodes after applying the eligibility criteria.

Bedrobinol prescriptions were recorded for 9 individuals and 12 records in the IQVIA DA Germany database. After refining cohort using the eligibility criteria and the definition of treatment episode, the final cohort was reduced to 7 individuals and 7 records. In the IPCI database, the initial cohort of 117 individuals with 391 records was refined to 67 individuals and 74 records.

For Bedrolite, the IQVIA DA Germany dataset initially identified 9 individuals with 20 records. After applying the eligibility criteria, the final cohort comprised 5 individuals with 5 records. In the IPCI database, the initial 30 individuals with 76 records were refined to 24 individuals with 25 records.

Lastly, no qualifying treatment initiations were identified for Bedica in the IQVIA DA Germany database. In the IPCI database, 88 individuals with 313 records were initially identified. The final cohort consisted of 65 individuals and 73 records, after applying the specified criteria.

Table 10. Study attrition of individuals based on prescribing of Cannabis flos containing products and relevant inclusion criteria, stratified by product and database.

	IQVIA DA Germany		IPCI	
	Number of records	Number of individuals	Number of records	Number of individuals
Database population	-	43,058,800	-	2,870,300
Bedrocan				
Initial qualifying events	520	165	1,970	444
Join exposures separated by 30 or less days	336	165	899	444
Require prior use washout of 365 days	179	165	484	444
Require prior observation of 365 days	143	132	338	312
Require cohort_start_date between 2014-01-01 to 2023-12-31	143	132	289	270
Bediol				
Initial qualifying events	65	24	693	211
Join exposures separated by 30 or less days	43	24	410	211
Require prior use washout of 365 days	26	24	227	211
Require prior observation of 365 days	23	21	173	166
Require cohort_start_date between 2014-01-01 to 2023-12-31	23	21	153	146
Bedrobinol				
Initial qualifying events	12	9	391	117
Join exposures separated by 30 or less days	10	9	248	117
Require prior use washout of 365 days	9	9	127	117
Require prior observation of 365 days	7	7	90	82
Require cohort_start_date between 2014-01-01 to 2023-12-31	7	7	74	67
Bedrolite				
Initial qualifying events	20	9	76	30
Join exposures separated by 30 or less days	11	9	54	30
Require prior use washout of 365 days	9	9	31	30
Require prior observation of 365 days	5	5	25	24
Require cohort_start_date between 2014-01-01 to 2023-12-31	5	5	25	24
Bedica				
Initial qualifying events	0	0	313	88
Join exposures separated by 30 or less days	0	0	190	88
Require prior use washout of 365 days	0	0	100	88
Require prior observation of 365 days	0	0	79	71
Require cohort_start_date between 2014-01-01 to 2023-12-31	0	0	73	65

DA = Disease Analyzer; IPCI = Integrated Primary Care Information Project.

12.2.2 Descriptive data

Table 11 provides a detailed overview of demographic characteristics of individuals prescribed Cannabis flos products at the time of new prescription of the specified medicinal products across databases between 2014 and 2023. The results are stratified by product.

In IQVIA DA Germany, the absolute numbers of treatment initiators varied significantly by the specified product. The highest number of new initiators was recorded for Bedrocan (132 individuals), while the lowest number was recorded for Bedrobinol and Bedrolite, with 7 and 5 individuals, respectively. The median age at the time of prescription (index date) was consistent across new users of different Cannabis flos products, including Bedrocan, Bediol and Bedrolite, with a median age around 46 years. However, the median age of new users of Bedrobinol was higher, at around 58 years, although the sample size was limited (7 individuals and 7 records). The sex distribution across these products predominately featured males, with proportions ranging from 57% for Bediol to 100% for Bedrolite.

In the IPCI database, the median age of participants prescribed the medicinal products of interest was approximately 58 years for Bedrocan, Bediol, Bedrobinol and Bedica, while the participants prescribed Bedrolite had a slightly lower median age, around 52 years. Sex distribution in the IPCI revealed a higher proportion of females for Bedrocan, Bediol and Bedrobinol, whereas Bedrolite and Bedica had a higher prevalence of males.

Table 11. Demographic characteristics of individuals who are prescribed Cannabis flos containing products at the time of new prescription, stratified by product and database.

	Bedrocan	Bediol	Bedrobinol	Bedrolite	Bedica
IQVIA DA Germany					
Number of records	143	23	7	5	0
Number of individuals	132	21	7	5	0
Cohort start date (minimum)	25-5-2018	22-8-2018	7-12-2018	18-9-2018	-
Cohort end date (maximum)	31-12-2023	20-9-2023	28-6-2023	13-1-2023	-
Age at index (years), median (IQR)	45 (36 - 59)	46 [44 - 58]	58 (39 - 65)	46 (34 - 52)	-
Age range (years)	19 - 88	32 - 74	31 - 81	22 - 63	-
Sex, n (%)					
• Female	37 (26)	10 (43)	<5	0	-
• Male	106 (74)	13 (57)	<5	5 (100)	-
IPCI					
Number of records	289	153	74	25	73
Number of individuals	270	146	67	24	65
Cohort start date (minimum)	17-1-2014	15-1-2014	9-4-2014	16-1-2015	6-2-2014
Cohort end date (maximum)	31-12-2023	31-12-2023	22-10-2023	11-3-2023	31-12-2023
Age at index (years), median (IQR)	58 (48 - 68)	57 (48 - 69)	58 (48 - 68)	52 (40 - 62)	58 (45 - 66)
Age range (years)	18 - 93	12 - 86	20 - 87	17 - 89	15 - 86
Sex, n (%)					
• Female	155 (54)	80 (52)	39 (53)	12 (48)	26 (36)
• Male	134 (46)	73 (48)	35 (47)	13 (52)	47 (64)

DA = Disease Analyzer; IPCI = Integrated Primary Care Information Project.

12.2.3 Main results

12.2.3.1 Frequency of pre-specified conditions

Table 12 displays the frequency of pre-specified conditions of interest in individuals being prescribed Cannabis flos products within the year prior to the index date. The index date refers to the date of a new prescription for each new treatment. For clarity, the results from the time window "at index date" are omitted from this table but are presented in the "shiny app" https://data-dev.darwin-eu.org/P3-C1-006-DUS-Cannabis-flos/).

In the IQVIA DA Germany database, the most frequently reported pre-specified condition before treatment initiations with Bedrocan was anxiety, accounting for 14% of treatment initiations. Sleep disorders were reported in 10 %, while cancer was reported in 7% of treatment initiations. Multiple sclerosis was noted in 5% of Bedrocan users. For Bedrobinol, Bediol and Bedrolite, no pre-specified conditions were identified, or the counts were below the reporting threshold of five, making them undetectable.

In the IPCI database, cancer was the most common pre-specified condition for treatment initiations with Bedrocan, accounting for 16%. Sleep disorders followed at 11% and anxiety was reported in 10%. Other conditions included fibromyalgia (4%), multiple sclerosis (2%) and rheumatoid arthritis (2%). For Bedica, the leading pre-specified conditions were cancer (22%), anxiety (15%) and sleep disorders (8%). Similarly, treatment initiations with Bedrobinol were most often linked to anxiety (15%) and sleep disorders (11%), with cancer accounting for 9%. For Bediol, the most frequent conditions were cancer (16%), anxiety (15%) and sleep disorders (12%), while fibromyalgia was reported in 6% of cases. No specific conditions were identified for Bedrolite or the counts were below the reporting threshold of five.

Across both databases, pre-specified conditions such as Alzheimer's disease, amyotrophic lateral sclerosis, chemotherapy-induced nausea and vomiting, epilepsy, glaucoma, HIV infection, Huntington's disease, neuralgic pain, Parkinson disease, spasticity, spinal cord injury and Tourette syndrome were not observed within a year prior to initiation of treatment with Cannabis flos containing products in the study population and period.

Table 12. Frequency of pre-specified conditions of interest in individuals being prescribed Cannabis flos products in a window prior to the index date (1 year prior to the index date), stratified by product and database.

	IQVIA DA Germany*				IPCI*				
	Bedrocan (n = 143)	Bedrobinol (n = 7)	Bediol (n = 23)	Bedrolite (n = 5)	Bedrocan (n = 289)	Bedica (n = 73)	Bedrobinol (n = 74)	Bediol (n = 153)	Bedrolite (n = 25)
Alzheimer's disease and other dementias, n (%)	0	0	0	0	NA	NA	0	0	0
amyotrophic lateral sclerosis, n (%)	0	0	0	0	NA	0	0	0	0
anorexia, n (%)	0	0	0	0	0	0	0	0	0
anxiety, n (%)	20 (14)	NA	NA	0	30 (10)	11 (15)	11 (15)	23 (15)	NA
cancer, n (%)	10 (7)	NA	NA	0	47 (16)	16 (22)	7 (9)	24 (16)	NA
chemotherapy induced nausea and vomiting, n (%)	0	0	0	0	0	0	0	0	0
epilepsy, n (%)	NA	0	0	0	0	0	0	NA	0
fibromyalgia, n (%)	NA	0	0	0	11 (4)	NA	NA	9 (6)	NA
glaucoma, n (%)	0	0	0	0	NA	0	0	NA	0
HIV infection, n (%)	0	0	0	0	0	0	0	NA	0
Huntington's disease, n (%)	0	0	0	0	0	0	0	0	0
inflammatory bowel disease, n (%)	NA	NA	0	0	NA	0	NA	NA	0
multiple sclerosis, n (%)	7 (5)	0	NA	0	5 (2)	NA	NA	NA	0

	IQVIA DA Germany*				IPCI*				
	Bedrocan (n = 143)	Bedrobinol (n = 7)	Bediol (n = 23)	Bedrolite (n = 5)	Bedrocan (n = 289)	Bedica (n = 73)	Bedrobinol (n = 74)	Bediol (n = 153)	Bedrolite (n = 25)
neuralgic pain, n (%)	0	0	0	0	0	0	0	0	0
Parkinson's disease, n (%)	0	0	0	0	NA	0	0	NA	0
rheumatoid arthritis, n (%)	NA	0	0	NA	5 (2)	NA	NA	NA	0
sleep disorder, n (%)	15 (10)	NA	NA	NA	31 (11)	6 (8)	8 (11)	19 (12)	NA
spasticity, n (%)	0	0	0	0	0	0	0	0	0
spinal cord injury, n (%)	NA	0	0	0	0	0	0	0	0
Tourette syndrome, n (%)	NA	0	0	0	0	0	0	0	0

DA = Disease Analyzer; IPCI = Integrated Primary Care Information Project; NA – not applicable (pre-specified conditions were identified but the counts were below the reporting threshold of five);
*Number of records is displayed per Cannabis product.

12.2.3.2 Frequency of comorbidities

Table 13 presents the frequency of top recorded diagnoses among individuals prescribed Cannabis flos products. These were individual diagnosis codes rather than aggregated lists of codes for a specific pre-specified condition of interest. The results presented in the report reflect diagnoses recorded within one year window prior to the index date (the time of first prescription of each new treatment episode). The results are stratified by Cannabis flos product and database during study period. For clarity, the results from the time window "at index date" are omitted from this table but are presented in the "shiny app" (https://data-dev.darwin-eu.org/P3-C1-006-DUS-Cannabis-flos/). The prevalence of comorbidities varied across the different Cannabis flos products and databases, with commonly observed conditions including chronic pain, essential hypertension and sleep disorders, with some variation in their frequency depending on the specific product and database.

For Bedrocan in the IQVIA DA Germany database, out of 143 treatment initiations, the most frequently recorded diagnosis was a general illness, affecting 27% of this sample. Chronic pain was present in 17%, while nerve root disorder was reported in 10%. Other notable conditions included inflammatory disorders of the digestive tract in 8%, essential hypertension in 7% and acute upper respiratory infections, sleep disorders, pain disorders with psychological factor and depressive disorders, each observed in 6%. No comorbidities were identified for Bedrobinol, Bediol and Bedrolite within one year window prior to the index date or the counts were below the reporting threshold of five.

In the IPCI database, also for Bedrocan but with a larger sample size of 289 treatment initiations, the most common recorded diagnoses included findings of back issues in 11% and essential hypertension in 11%. Obstipation and low back pain were noted in 10% and 9%, respectively. Sleep disorders and generalised aches and pains were present in 9%, followed by findings in the thoracic region in 8% and cough in 8%. Localised abdominal pain and urinary tract infections were also reported as comorbidities in 8% of treatment initiations.

For the Bedica product, involving 73 treatment initiations in the IPCI database, the top recorded diagnoses were cough and low back pain, each present in 12% of the population. Eczema and urinary tract infectious disease were also reported in 11% of cases. Chronic obstructive lung disease and malignant tumours of the lung affected 8% of the population each.

Regarding the Bedrobinol product, which involved 74 treatment initiations, the most frequently recorded diagnoses included findings of back issues and chronic obstructive lung disease, each affecting 12% of the population. Sleep disorders were observed in 11% of cases, while obstipation and stomach ache were each reported in 9%. Cough, awareness of heartbeat and anxiety were each present in 8% of patients, alongside generalised abdominal pain and findings in the shoulder region.

For the Bediol product, among 153 treatment initiations, backache with radiation and essential hypertension were the most commonly recorded diagnoses, each present in 12% of the population. Localised abdominal pain was noted in 12%, while low back pain and obstipation were noted in 10% of patients. Findings in the thoracic and shoulder regions were reported in 10% and 9%, respectively, while sleep disorders affected 9% of the population. Urinary tract infectious disease and anxiety were observed each in 9% of the cases.

Finally, in the Bedrolite product group, which involved 25 treatment initiations, excessive cerumen in the ear canal and urinary tract infectious disease were the most frequently reported comorbidities, each affecting 20% of the population. The remaining conditions did not meet the reporting threshold.

These data highlight the diversity of recorded diagnoses across different Cannabis flos containing products and patient groups, reflecting varied underlying health issues among those prescribed these treatments.

Table 13. Frequency of top 10 recorded diagnosis codes in individuals being prescribed Cannabis flos products in a window prior index date (1 year before index date), stratified by product and database.

IQVIA DA Germany*			**IPCI***		
Bedrocan (n = 143)	Bedrocan (n = 289)	Bedica (n = 73)	Bedrobinol (n = 74)	Bediol (n = 153)	Bedrolite (n = 25)
Illness, 38 (27%)	Finding of back, 33 (11%)	Cough, 9 (12%)	Finding of back, 9 (12%)	Backache with radiation, 19 (12%)	Excessive cerumen in ear canal, 5 (20%)
Chronic pain, 25 (17%)	Essential hypertension, 31 (11%)	Low back pain, 9 (12%)	Chronic obstructive lung disease, 9 (12%)	Essential hypertension, 18 (12%)	Urinary tract infectious disease, 5 (20%)
Nerve root disorder, 15 (10%)	Obstipation, 28 (10%)	Eczema, 9 (12%)	Sleep disorder, 8 (11%)	Localized abdominal pain, 18 (12%)	
Inflammatory disorder of digestive tract, 12 (8%)	Low back pain, 27 (9%)	Excessive cerumen in ear canal, 8 (11%)	Obstipation, 7 (9%)	Finding of region of thorax, 16 (10%)	
Essential hypertension, 10 (7%)	Sleep disorder, 26 (9%)	Urinary tract infectious disease, 8 (11%)	Stomach ache, 7 (9%)	Low back pain, 16 (10%)	
Acute upper respiratory infection, 9 (6%)	Generalized aches and pains, 25 (9%)	Malignant tumor of lung, 6 (8%)	Cough, 6 (8%)	Obstipation, 16 (10%)	
Sleep disorder, 9 (6%)	Finding of region of thorax, 24 (8%)	Chronic obstructive lung disease, 6 (8%)	Awareness of heart beat, 6 (8%)	Sleep disorder, 14 (9%)	
Pain disorder with psychological factor, 8 (6%)	Cough, 23 (8%)	Hypercholesterolemia, 6 (8%)	Anxiety, 6 (8%)	Finding of shoulder region, 14 (9%)	

IQVIA DA Germany*			**IPCI***		
Bedrocan (n = 143)	Bedrocan (n = 289)	Bedica (n = 73)	Bedrobinol (n = 74)	Bediol (n = 153)	Bedrolite (n = 25)
Depressive disorder, 8 (6%)	Localized abdominal pain, 23 (8%)	Finding of knee region, 6 (8%)	Generalized abdominal pain, 6 (8%)	Urinary tract infectious disease, 14 (9%)	
Disorder of musculoskeletal system, 8 (6%)	Urinary tract infectious disease, 22 (8%)	Peripheral nerve disease, (8%)	Finding of shoulder region, (8%)	Anxiety, 13 (9%)	

DA = Disease Analyzer; IPCI = Integrated Primary Care Information Project;

*Due to low sample size for Bedrobinol (n = 7), Bediol (n = 23) and Bedrolite (n = 5), all frequencies for recorded diagnosis codes are omitted from the table.

12.2.3.3 Frequency of comedication

Table 14 presents the top 10 of the most frequently recorded medication among individuals prescribed Cannabis flos products within a one-year window prior to the index date (the time of incident prescription of the selected medicinal products). The results were stratified by Cannabis flos product and database. For clarity, the results from the time window "at index date" were omitted from this table but are presented in the "shiny app" (https://data-dev.darwin-eu.org/P3-C1-006-DUS-Cannabis-flos/). The pattern of recorded medication use varied across different Cannabis flos products and the databases but the common pattern included pain management, gastrointestinal health and electrolyte balance. Additionally, there was evidence of managing anxiety and sleep disorders.

In the IQVIA DA Germany database, among individuals prescribed Bedrocan, ibuprofen was the most frequently recorded medication within a one-year window prior the index date, accounting for 18%. Proton pump inhibitor, pantoprazole, followed with 15%, while non-opioid analgesic and antipyretic dipyrone and anticonvulsant and neuropathic pain agent, pregabalin, constituted 15% and 10%, respectively. Opioid antagonist, naloxone and the SARS-CoV-2 vaccine each accounted for 8%. Diazepam (22%) was recorded among individuals prescribed Bediol, while the frequency of recorded medication for Bedrobinol (n = 7) and Bedrolite (n = 5) could not be reported either due to counts below the reporting threshold of five or the absence of other medications records within a one-year window prior to the index date.

In the IPCI database the most commonly recorded prescriptions within a year prior the index date for all Bedrocan incident prescriptions were solutions like sodium bicarbonate, sodium chloride and potassium chloride, constituting 32%, followed by acetaminophen (28%), diclofenac (23%), tramadol (22%) and oxycodone (21%). Amoxicillin (18%) and omeprazole (17%) were also frequently used. A similar pattern was observed for incident prescriptions of Bedica in the IPCI database. The most frequently recorded medication included acetaminophen (26%), followed by other medication used to treat pain-related conditions including diclofenac (25%), tramadol (18%) and oxycodone (18%). Additionally, solutions (potassium chloride, sodium chloride and sodium bicarbonate) (19% - 21%) and omeprazole (18%) were also commonly used.

For Bedrobinol incident prescribing in the IPCI database, pantoprazole (24%), amoxicillin (23%), solutions (sodium chloride, sodium bicarbonate and potassium chloride) (23%), as well as tramadol (20%), acetaminophen (19%) and oxycodone (16%) were the most common medication. For Bediol, solutions (sodium chloride, potassium chloride, sodium bicarbonate) (26% - 28%) were the most frequently prescribed, followed by acetaminophen (21%), amoxicillin (20%), tramadol (19%), pantoprazole (18%), omeprazole (17%) and oxycodone (16%). Finally, for Bedrolite incident prescribing, tramadol was the most frequently recorded medication (32%), followed by acetaminophen (28%) and several medications each accounting for 20%, including sodium bicarbonate, naproxen, amoxicillin, pantoprazole and oxazepam.

Table 14. Frequency of recorded medication in individuals being prescribed Cannabis flos products in a window prior to the index date (1 year prior to the index date), stratified by the Cannabis flos product and database.

IQVIA DA Germany*		IPCI*				
Bedrocan (n = 143)	Bediol (n = 23)	Bedrocan (n = 289)	Bedica (n = 73)	Bedrobinol (n = 74)	Bediol (n = 153)	Bedrolite (n = 25)
ibuprofen, 26 (18%)	diazepam, 5 (22%)	sodium bicarbonate, 92 (32%)	acetaminophen, 19 (26%)	pantoprazole, 18 (24%)	sodium chloride, 43 (28%)	tramadol, 8 (32%)
pantoprazole, 22 (15%)	-	potassium chloride, 92 (32%)	diclofenac, 18 (25%)	sodium bicarbonate, 17 (23%)	potassium chloride, 43 (28%)	acetaminophen, 7 (28%)
dipyrone, 21 (15%)	-	sodium chloride, 91 (31%)	amoxicillin, 17 (23%)	amoxicillin, 17 (23%)	polyethylene glycol 3350, 42 (27%)	polyethylene glycol 3350, 5 (20%)
pregabalin, 14 (10%)	-	polyethylene glycol 3350, 89 (31%)	sodium chloride, 15 (21%)	sodium chloride, 17 (23%)	sodium bicarbonate, 40 (26%)	sodium bicarbonate, 5 (20%)
naloxone, 11 (8%)	-	acetaminophen, 81 (28%)	polyethylene glycol 3350, 15 (21%)	polyethylene glycol 3350, 17 (23%)	acetaminophen, 32 (21%)	naproxen, 5 (20%)
SARS-CoV-2 (COVID-19) vaccine, mRNA spike protein, 11 (8%)	-	diclofenac, 66 (23%)	potassium chloride, 15 (21%)	potassium chloride, 17 (23%)	amoxicillin, 31 (20%)	clavulanate, 5 (20%)

IQVIA DA Germany*		IPCI*				
Bedrocan (n = 143)	Bediol (n = 23)	Bedrocan (n = 289)	Bedica (n = 73)	Bedrobinol (n = 74)	Bediol (n = 153)	Bedrolite (n = 25)
tilidine, 10 (7%)	-	tramadol, 64 (22%)	sodium bicarbonate, 14 (19%)	tramadol, 15 (20%)	tramadol, 29 (19%)	amoxicillin, 5 (20%)
levothyroxine, 9 (6%)	-	oxycodone, 61 (21%)	tramadol, 13 (18%)	acetaminophen, 14 (19%)	pantoprazole, 28 (18%)	pantoprazole, 5 (20%)
tramadol, 9 (6%)	-	amoxicillin, 52 (18%)	omeprazole, 13 (18%)	fusidate, 13 (18%)	omeprazole, 26 (17%)	sodium chloride, 5 (20%)
zopiclone, 9 (6%)	-	omeprazole, 50 (17%)	oxycodone, 13 (18%)	oxycodone, 12 (16%)	oxycodone, 24 (16%)	oxazepam, 5 (20%)

DA = Disease Analyzer; IPCI = Integrated Primary Care Information Project;

*Due to low sample size for Bedrobinol and Bedrolite, all frequencies for recorded medication are omitted from the table.

12.2.3.4 Duration of treatment

Information on treatment duration across different Cannabis flos products and two databases is provided in **Table 15.** In the IQVIA DA Germany database, treatment duration for Cannabis flos products was initially intended to be presented. However, following OMOP CDM conventions, several assumptions and imputations were applied to estimate treatment duration for Cannabis flos containing products. As a result, the vast majority of treatment durations for Cannabis flos products were imputed. Therefore, these results were excluded from the final analysis. This decision is explained in detail in the section Deviations from the Protocol.

In IPCI, the median duration of treatment for all Cannabis flos products was consistently 46 days across all products, with a broader interquartile range, indicating more variability in treatment duration within this population. The median treatment duration for Bedrocan was 46 days, with an IQR of 28 to 91 days. Bedica showed a median duration of 46 days, with an IQR of 20 to 90 days. For Bedrobinol, the median treatment duration was 46 days, with an IQR of 15 to 90 days, while the Bediol product had a median duration of 46 days, with an IQR of 17 to 88 days. Finally, Bedrolite had a median duration of 46 days, with an IQR of 20 to 47 days.

Table 15. Duration of use in individuals prescribed Cannabis flos products, stratified by product and database.

	IQVIA DA Germany*				IPCI*				
	Bedrocan (n = 143)	Bedrobinol (n = 7)	Bediol (n = 23)	Bedrolite (n = 5)	Bedrocan (n = 289)	Bedica (n = 73)	Bedrobinol (n = 74)	Bediol (n = 153)	Bedrolite (n = 25)
Duration (days), median (IQR)*	-	-	-	-	46 (28, 91)	46 (20, 90)	46 (15, 90)	46 (17, 88)	46 (20, 47)
Duration (days), minimum and maximum	-	-	-	-	1 - 3,093	1 -576	1 - 1,917	1 - 1,495	1 - 1,089

DA = Disease Analyzer; IPCI = Integrated Primary Care Information Project; * Several assumptions and imputations were made regarding the variables needed to calculate treatment duration in IQVIA DA Germany. Since the vast majority of records for treatment duration of Cannabis flos-containing products were imputed, the treatment duration was not presented.

12.3 Other analysis

Not applicable

13. MANAGEMENT AND REPORTING OF ADVERSE EVENTS PER ADVERSE REACTIONS

Adverse events per 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 was a need to describe the procedures for the collection, management and reporting of individual cases of adverse events per adverse reactions.

14. DISCUSSION

14.1 Key results

Incidence rates and prevalence of Cannabis flos product prescriptions - Population-level utilisation study

Incidence rates of Cannabis flos products prescriptions across databases, age groups, sex and specific products revealed distinct pattern. In the IQVIA DA Germany database, which includes a sample of general practices and a selection of specialist practices, incidence rates remained consistently very low throughout the study period, ranging from 0.1 per 100,000 PY in 2018 to 0.8 per 100,000 PY in 2023. In contrast, the IPCI database, covering a sample of general practices in the Netherlands, showed a distinct temporal trend. Incidence rates started at 8.8 per 100,000 PY in 2014, reached a peak at 11.1 per 100,000 PY in 2015 and decreased steadily to 2 per 100,000 PY by 2023.

Stratified by age, no prescriptions for Cannabis flos were observed in individuals under 18 years across both databases. Among adults (≥18 years), the IQVIA DA Germany database showed persistently low and stable incidence rates over the study period, whereas the IPCI database revealed a notable decline in incidence following an initial peak. Incidence rates of Cannabis flos products prescriptions, stratified by sex, revealed higher rates in males compared to females in the IQVIA DA Germany database. In contrast, the IPCI database showed similar trends in incidence rates with no significant differences between sexes.

Cannabis flos containing products were identified through a free-text search because standardized concepts were not available for Cannabis flos in OMOP CDM. The identified products included Bedrocan, Bedrobinol, Bediol, Bedrolite and Bedica. Two other products (SIMM and SIMM18) were also identified in the database but due to the absence of records during the study period, these products were not further considered in the study. Regarding product-specific trends, IQVIA DA Germany data indicated negligible rates for Bedica and very low rates for Bedrobinol and Bedrolite, with Bedrocan approaching a slight increase by the end of the study period. In contrast, IPCI data revealed higher initial rates for Bedrocan, with a peak followed by a gradual decline. Other products, including Bedica, Bediol and Bedrobinol, exhibited similar patterns, generally maintaining low and stable incidence rates.

Prevalence trends reflected those of incidence rates, with the IQVIA DA Germany database showing very low prevalence throughout the study period. The IPCI database exhibited a modest initial rise in prevalence, which then declined. Across both databases, patterns by age and sex were consistent with incidence findings. Overall, the use of Cannabis flos products remained infrequent, with both incidence and prevalence rates staying very low and stable throughout the study.

Characterisation of the cohort of patients with prescription of Cannabis flos products - Patient-level utilisation study

Analysis of Cannabis flos prescriptions from 2014 to 2023 across IQVIA DA Germany and IPCI databases revealed distinct usage patterns. In the IQVIA DA Germany database, Bedrocan was the most frequently prescribed product, while Bedrobinol and Bedrolite had the fewest treatment initiations. The median age at initiation was generally around 46 years, except for Bedrobinol users, who had a median age of 58 years. Males predominated among users across all products in the IQVIA DA Germany. In contrast, in the IPCI database, the median age was approximately 58 years, with Bedrolite users being slightly younger at 52 years. The sex distribution differed by product: females were more prevalent among users of Bedrocan, Bediol and Bedrobinol, whereas males predominated among users of Bedrolite and Bedica.

Pre-specified conditions in individuals being prescribed Cannabis flos products within the year prior to the index date varied between databases. In the IQVIA DA Germany database, anxiety was the most frequent pre-specified condition for treatment initiators with Bedrocan, followed by sleep disorders and cancer. In IPCI, cancer was the most common pre-specified condition for treatment initiations with Bedrocan and Bedica, followed by sleep disorders and anxiety. Commonly recorded diagnosis codes across both databases included chronic pain, essential hypertension and sleep disorders, though specific conditions varied by product and database. Bedrocan users in IQVIA DA Germany frequently reported chronic pain, while IPCI data highlighted back issues and essential hypertension. Commonly recorded drugs included medicinal products for pain management and gastrointestinal agents, with patterns differing by product and database. Treatment duration was consistently 46 days in IPCI. In IQVIA DA Germany, treatment duration was not reported, even though it was originally intended to be, because the vast majority of treatment durations for Cannabis flos containing products was missing and subsequently imputed based to OMOP conventions.

14.2 Limitations of the research methods

The study was informed by routinely collected healthcare data and it is important to consider several factors that may influence the interpretation of the results.

General limitations:

Medicinal product prescriptions: A recording of a prescription did not mean that the patient took the drug. Therefore, assumptions of actual use were made.

Characterisation of pre-specified conditions as proxy to assess indication: The accuracy and consistency of pre-defined condition recording, crucial for patient characterisation and identification of the (potential) indication may vary across the databases included in the study. The actual reason for prescribing the drug of interest was not recorded as such in the databases. We assessed indication via proxy based on a recording of pre-defined conditions around the date of therapy initiation. Therefore, the estimation of potential indication might be incomplete.

Setting: For this study, we included data from 2 data sources (IPCI and IQVIA DA Germany). Results of these databases do not necessarily reflect prescription in other countries/databases.

Additionally, the IQVIA DA Germany database comprises a sample of general and a selection of specialised practices. While the database included internal medicine specialties (gastroenterology, cardiology, rheumatology, pulmonology, diabetology) and a selection of other specialised practices (otolaryngology, gynaecology, paediatric, neurology and psychiatry, orthopaedics, urology and dermatology) , it does not fully capture the situation in specialised settings, as practices like anaesthesiology and oncology were not included.

Study-specific limitations:

Unaccounted medicinal Cannabis flos use: There could be use of Cannabis for medicinal purposes that was acquired without prescription (in the Netherlands in "coffee shops" for example). This would not be covered by the available data.

Mapping: Cannabis flos containing products are not mapped to the OMOP CDM, as there are no standard RxNorm concepts for these products. The Cannabis flos products were identified by the local teams using source codes, using a slightly different search string. As a result, certain relevant products may not have been captured, potentially leading to an incomplete representation of the products in this study. This could be prevented with standardisation of Cannabis flos products. This requires adding of Cannabis flos products to vocabulary.

Treatment duration: In IQVIA DA Germany, some of the data elements needed for calculating treatment duration for Cannabis flos containing products were missing, leading to the imputation of treatment duration for Cannabis flos containing products with a fixed value for the vast majority of treatment episodes, as per the extract transform load (ETL) process (https://ohdsi.github.io/CommonDataModel/cdm54.html#drug_exposure). These imputations may not accurately reflect real-world treatment patterns of Cannabis flos containing products and could be misinterpreted as actual observed durations. As a result, treatment duration was not presented for the IQVIA DA Germany database.

14.3 Interpretation

Evidence from observational studies examining the usage of Cannabis flos products or characterisation of patients prescribed these therapies remains limited. This study focussed on analysing prescribing patterns of Cannabis flos products across different age groups, emphasising both patient-level characterisation and population-level utilisation.

The incidence rates of Cannabis flos prescribing demonstrated distinct patterns across the examined databases. In IQVIA DA Germany database, the incidence remained very low throughout the study period, ranging from 0.1 per 100,000 PY in 2018 to 0.8 per 100,000 PY in 2023. Since this database captures data from both GPs and selected specialists, the distribution of prescribing providers was further analysed by specialty. The analysis showed that over 70% of the prescribing providers were GPs, with neuropsychiatrists accounting for approximately 10%. Moreover, more than 60% of Cannabis flos prescriptions were issued by GPs, with an additional 25% prescribed by neuropsychiatry and psychotherapy specialists. In contrast, previous studies based on surveys accompanying insurance-covered cannabis prescriptions in Germany reported that anaesthesiologists accounted for 43% of all cannabis-based medicine prescriptions, with general practitioners contributing 20% and internists and neurologists each accounting for 13%.[18] Nearly half of the physicians held additional qualifications in pain therapy, while 37% were trained in palliative medicine.[19] Similar trends were observed in a study evaluating prescriptions of cannabis products in German pharmacies.[20]

It is important to note that the IQVIA DA Germany database predominantly captures data from GPs and a limited subset of specialists. However, it does not include data from specialist groups such as oncologists,

anaesthesiologist, haematologists and pain specialists who are more likely to prescribe Cannabis flos containing products, particularly for cancer treatment and pain management. Consequently, our findings do not seem to reflect the full extent of Cannabis flos use in the respective country but instead represent a limited subset of the population based on the healthcare settings captured by the selected database.

Similarly, the low incidence rate observed in the IPCI database can be attributed to its primary care focus and the lack of data from specialist care setting. The incidence rate was 8.8 per 100,000 PY in 2014, peaked at 11.1 per 100,000 PY in 2015 and then gradually declined to 2 per 100,000 PY by 2023.

Age and sex analyses revealed consistent patterns across databases. For both IQVIA DA Germany and IPCI, prescriptions were absent among individuals under 18 years, reflecting a lack of paediatric use. Among adults, incidence rates in the IQVIA DA Germany remained stable but low, whereas the IPCI database showed a more pronounced trend with a notable peak in 2015 and subsequent decline.

A product-specific search identified Bedrocan, Bedrobinol, Bediol, Bedrolite and Bedica in both databases. Bedrocan emerged as the most frequently initiated product in IQVIA DA Germany, while Bedrobinol and Bedrolite showed minimal use. In the IPCI database, Bedrocan had the highest initial incidence but exhibited a declining trend, with products such as Bedica and Bediol following a similar trajectory.

Analysis of pre-specified conditions in individuals being prescribed Cannabis flos containing products revealed database-specific trends. In the IQVIA DA Germany, anxiety was the most frequently reported pre-specified condition for treatment initiations with Bedrocan. Although, neuropathic pain, as we defined it, was not explicitly recorded in the IQVIA DA Germany, chronic pain diagnoses were captured in the large-scale characterization, accounting for 17% . However, neuropathic pain was not explicitly recorded, likely due to the lack of data from pain specialist care settings. To contextualise these findings within the existing literature, a previous survey study indicated that 68.8% of all cannabis medicine prescriptions in Germany were utilised for pain management, while 11.3% were prescribed for spasticity, 8.2% for anorexia or wasting and 11.7% for other symptoms.[18] The discrepancy in the frequency of chronic pain diagnoses in our findings when compared to literature findings, may stem from the absence of pain specialist care settings in IQVIA DA Germany database.

In IPCI, cancer emerged as the most frequent pre-specified condition associated with Cannabis flos products. Additionally, several diagnoses related to pain were noted in the large-scale characterisation. Literature findings from a Dutch study indicated that chronic pain was the predominant indication for cannabis use (60%), followed by ADHD (7%), cancer (7%) and multiple sclerosis (7%).[21]

In summary, this study provides insights into the prescribing patterns of Cannabis flos products across different populations and regions. The observed differences in incidence rates, product preferences and associated conditions underscore the importance of contextualising cannabis-based therapies within specific healthcare settings from which the data is derived.

14.4 Generalisability

This study utilised the data from 2 EU countries focusing on primary care settings. The findings from this study are not to be generalised to other countries, healthcare settings or databases. The recorded number of Cannabis flos prescriptions in the selected databases does not seem to reflect the full extent of Cannabis flos use in the respective countries, as specialist care setting, including oncology and anaesthesiology, likely major prescribers of Cannabis flos, is not captured. Consequently, the results may only represent a limited subset of the entire population of Cannabis flos users based on the settings covered by the selected databases.

14.5 Other information

Not applicable

15. CONCLUSION

This study provides insights into the prescribing patterns of Cannabis flos containing products and characteristics of patients using them as captured in two real-world data sources from Germany and the Netherlands. The IQVIA DA Germany database revealed low incidence rates and prevalence potentially related to primary care setting of the database and absence of certain Cannabis flos prescribing specialties. Similarly, low incidence rates and prevalence observed in the IPCI database may also be related to the primary care focus of the database and absence of specialist care data. At patient level, anxiety, cancer and sleep disorders were identified as the most frequent pre-specified conditions, while pain diagnoses and pain management medication and gastrointestinal health agents emerged as commonly recorded diagnoses and medications. Overall, the findings of this study suggest that Cannabis flos containing products are mainly prescribed through specialty care setting, which are not routinely collected in our currently available data sources. This study may provide useful information for future studies on Cannabis flos containing products, which should consider including data from specialised healthcare practices..

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17. ANNEXES

Appendix I: The concepts for drug exposure and indications (pre-defined conditions) are outlined below. This list was finalised following a thorough review conducted after the study protocol approval and prior to the parametrisation of the study code.

The corresponding source codes for drug exposure in each participating database are also detailed below. Due to the absence of standardized RxNorm concept IDs for Cannabis flos products, source codes were utilised. A free-text search strategy was employed to identify Cannabis flos containing products in the study databases. This search strategy incorporated keywords such as "cannabi*" (to capture various forms of the term “cannabis”) and terms related to ‘bloem,' 'flower,' and 'flos'. These terms were selected to ensure comprehensive retrieval of records related to cannabis flower products. Search queries were tailored to the specific databases, considering language and terminology variations, to accurately capture the products of interest.

Source code description	Source code ID	Source vocabulary	Excluded
CANNABIS FLOS BEDROCAN	2014884488	IPCI	-
CANNABIS FLOS SIMM 18	2014884496	IPCI	-
CANNABIS FLOS BEDROBINOL	2015009939	IPCI	-
CANNABIS FLOS BEDICA GRANULAAT	2015207439	IPCI	-
CANNABIS FLOS BEDIOL GRANULAAT	2015220478	IPCI	-
CANNABIS FLOS BEDROLITE GRANULAAT	2016019873	IPCI	-
CANNABIS FLOS BEDROCAN THEE SACHET 100MG AHZ	2016410742	IPCI	-
CANNABIS FLOS BEDICA GRANULAAT	2016730003	IPCI	-
CANNABIS FLOS BEDIOL GRANULAAT	2016730011	IPCI	-
CANNABIS FLOS BEDROCAN	2016730046	IPCI	-
CANNABIS FLOS BEDROLITE GRANULAAT	2016730062	IPCI	-
CANNABIS FLOS BEDROBINOL	2016747763	IPCI	-
CANNABIS FLOS BEDROCAN	2034093569	IPCI	-
CANNABIS FLOS SIMM 18	2034093577	IPCI	-
CANNABIS FLOS BEDROBINOL	2034360753	IPCI	-
CANNABIS FLOS BEDIOL GRANULAAT	2035009731	IPCI	-
CANNABIS FLOS BEDICA GRANULAAT	2035691168	IPCI	-
CANNABIS FLOS BEDROLITE GRANULAAT	2036744361	IPCI	-
CANNABIS FLOS BEDROCAN THEE SACHET 100MG AHZ	2037484747	IPCI	-
CANNABIS FLOS BEDROLITE GRANULAAT	2037663773	IPCI	-
CANNABIS FLOS BEDROCAN	2037663838	IPCI	-
CANNABIS FLOS BEDICA GRANULAAT	2037675712	IPCI	-
CANNABIS FLOS BEDIOL GRANULAAT	2037675720	IPCI	-
CANNABIS FLOS BEDROBINOL	2037675739	IPCI	-
CANNABIS FLOS BEDROCAN	2051621254	IPCI	-
CANNABIS FLOS SIMM 18	2051621262	IPCI	-
CANNABIS FLOS SIMM	2051681818	IPCI	-
CANNABIS FLOS BEDROBINOL	2051709968	IPCI	-

CANNABIS FLOS SIMM 18	2034093577	IPCI	-
CANNABIS FLOS BEDROBINOL	2034360753	IPCI	-
CANNABIS FLOS BEDIOL GRANULAAT	2035009731	IPCI	-
CANNABIS FLOS BEDICA GRANULAAT	2035691168	IPCI	-
CANNABIS FLOS BEDROLITE GRANULAAT	2036744361	IPCI	-
CANNABIS FLOS BEDROCAN THEE SACHET 100MG AHZ	2037484747	IPCI	-
CANNABIS FLOS BEDROLITE GRANULAAT	2037663773	IPCI	-
CANNABIS FLOS BEDROCAN	2037663838	IPCI	-
CANNABIS FLOS BEDICA GRANULAAT	2037675712	IPCI	-
CANNABIS FLOS BEDIOL GRANULAAT	2037675720	IPCI	-
CANNABIS FLOS BEDROBINOL	2037675739	IPCI	-
CANNABIS FLOS BEDROCAN	2051621254	IPCI	-
CANNABIS FLOS SIMM 18	2051621262	IPCI	-
CANNABIS FLOS SIMM	2051681818	IPCI	-
CANNABIS FLOS BEDROBINOL	2051709968	IPCI	-
CANNABIS FLOS BEDICA GRANULAAT	2051832204	IPCI	-
CANNABIS FLOS BEDIOL GRANULAAT	2051840908	IPCI	-
CANNABIS FLOS BEDROLITE GRANULAAT	2052423472	IPCI	-
CANNABIS FLOS BEDROCAN THEE SACHET 100MG AHZ	2052689073	IPCI	-
CANNABIS BLOEM SIMM 18	2061069841	IPCI	-
CANNABIS BLOEM BEDROCAN	2061069868	IPCI	-
CANNABIS BLOEM SIMM	2061075205	IPCI	-
CANNABIS BLOEM BEDROBINOL	2061076880	IPCI	-
CANNABIS BLOEM BEDICA	2061081477	IPCI	-
CANNABIS BLOEM BEDIOL	2061082015	IPCI	-
CANNABIS BLOEM BEDROLITE	2061117064	IPCI	-
CANNABIS BLOEM BEDROCAN KRUIDENTHEE 100MG	2061143510	IPCI	-
CANNABIS BLOEM SIMM 18	2062117935	IPCI	-
CANNABIS BLOEM BEDROCAN	2062117943	IPCI	-
CANNABIS BLOEM SIMM	2062121851	IPCI	-
CANNABIS BLOEM BEDROBINOL	2062123021	IPCI	-
CANNABIS BLOEM BEDICA	2062125857	IPCI	-
CANNABIS BLOEM BEDIOL	2062126292	IPCI	-
CANNABIS BLOEM BEDROLITE	2062150754	IPCI	-
CANNABIS BLOEM BEDROCAN KRUIDENTHEE 100MG	2062169897	IPCI	-
CANNABIS BLOEM BEDROCAN	2063083127	IPCI	-
CANNABIS BLOEM SIMM 18	2063083135	IPCI	-
CANNABIS BLOEM SIMM	2063084220	IPCI	-
CANNABIS BLOEM BEDROBINOL	2063084743	IPCI	-
CANNABIS BLOEM BEDICA	2063085855	IPCI	-
CANNABIS BLOEM BEDIOL	2063086096	IPCI	-
CANNABIS BLOEM BEDROLITE	2063093106	IPCI	-

CANNA.BL.BET.M A91 BEDROLITE 5G	803460	IQVIA DA Germany	-
CANNA.BL.BET.M CA7 BEDROLITE 5G	803464	IQVIA DA Germany	-
CANNA.BL.BET.M BDE BEDROLIT.1 per 9 5G	1974591	IQVIA DA Germany	-
CANNA.BL.BET.M C0L BEDROLITE 5G	1974592	IQVIA DA Germany	-
CANNA.BL.BET.M FO0 BEDROLITE 5G	36038896	IQVIA DA Germany	-
CANNA.BL.BET.M CA7 BEDROLITE 20G	2043459080	IQVIA DA Germany	-
CANNA.BL.BET.M D&N BEDROLITE 5G	2044482212	IQVIA DA Germany	-
CANNA.BL.BET.M C0L BEDROCAN 5G	803177	IQVIA DA Germany	-
CANNABIS BET.M C per H BEDROCAN	803448	IQVIA DA Germany	-
CANNA.BL.BET.M CY+ BEDROCAN 5G	803455	IQVIA DA Germany	-
CANNA.BL.BET.M CA7 BEDROCAN 100G	803462	IQVIA DA Germany	-
CANNA.BL.BET.M CA7 BEDROCAN 10G	803463	IQVIA DA Germany	-
CANNA.BL.BET.M FO0 BEDROCAN 5G	803468	IQVIA DA Germany	-
CANNA.BL.BET.M AX0 BEDROCAN	803469	IQVIA DA Germany	-
CAN.BL.BET.M CC4>> BEDROCAN	803470	IQVIA DA Germany	-
CANNA.BL.BET.M A01 BEDROCAN	994793	IQVIA DA Germany	-
CANNA.BL.BET.M CA7 BEDROCAN 5G	995708	IQVIA DA Germany	-
CANNA.BL.BET.M CA7 BEDROCAN 20G	995709	IQVIA DA Germany	-
CANNA.BL.BET.M AX0 BEDROCAN	1974588	IQVIA DA Germany	-
CANNA.BL.BET.M B12 BEDROCAN 5G	1974590	IQVIA DA Germany	-
CANNA.BL.BET.M CF& BEDROCAN 5G	1974611	IQVIA DA Germany	-
CANNA.BL.BET.M C per A BEDROCAN 5G	1974624	IQVIA DA Germany	-
CANNA.BL.BET.M LC4 BEDROCAN 5G	1974630	IQVIA DA Germany	-
CANNA.BL.BET.M C0L BEDROCAN 400G	36038718	IQVIA DA Germany	-
CANNA.BL.BET.M AX0 BEDROCAN	36038889	IQVIA DA Germany	-
CANNA.BL.BET.M AX0 BEDROCAN	36038890	IQVIA DA Germany	-
CANNA.BL.BET.M A98 BEDROCAN 5G	36038894	IQVIA DA Germany	-
CANNA.BL.BET.M V&R BEDROCAN 5G	36038897	IQVIA DA Germany	-
CAN.BL.BET.M AC9>> BEDROCAN	36038899	IQVIA DA Germany	-
CAN.BL.BET.M ORI>> BEDROCAN	36038900	IQVIA DA Germany	-
CANNA.BL.BET.M A01 BEDROCAN	36505180	IQVIA DA Germany	-
CANNA.BL.BET.M A01 BEDROCAN	37595317	IQVIA DA Germany	-
CANNA.BL.BET.M A01 BEDROCAN	37595318	IQVIA DA Germany	-
CANNA.BL.BET.M E5A BEDROC.CANN. 5G BEDROCAN	2042697837	IQVIA DA Germany	-
CANNA.BL.BET.M AX7 BEDROC.22 per 1 5G BEDROCAN	2043197173	IQVIA DA Germany	-
CANNA.BL.BET.M A91 BEDROCAN 5G	2043198478	IQVIA DA Germany	-
CANNA.BL.BET.M A91 BEDROCAN 5G	2043459193	IQVIA DA Germany	-
CANNA.BL.BET.M AX7 BEDROC.22 per 1 10G BEDROCAN	2043461047	IQVIA DA Germany	-
CANNA.BL.BET.M CFD BEDROCAN 5G	2044252006	IQVIA DA Germany	-
CAN.BL.BET.M HM2>> BEDROC.22 per 1 5G BEDROCAN	2044252744	IQVIA DA Germany	-
CANNA.BL.BET.M HDY BEDROC.22 per 1 5G BEDROCAN	2044253543	IQVIA DA Germany	-
CANNA.BL.BET.M TSO BEDROCAN 5G	2045346951	IQVIA DA Germany	-

CANNA.BL.BET.M NH1 BEDROCAN 10 5G	2045348074	IQVIA DA Germany	-
CANNA.BL.BET.M S9P BEDROCAN 5G	2046069505	IQVIA DA Germany	-
CANNA.BL.BET.M P+L BEDROCAN 5G	2046069506	IQVIA DA Germany	-
CAN.BL.BET.M C2H>> BEDROC.22 per 1 5G BEDROCAN	2046883492	IQVIA DA Germany	-
CANNA.BL.BET.M M4B BEDROCAN 5G	2046883564	IQVIA DA Germany	-
CANNABIS BET.M AEX BEDROCAN 100G	2046883739	IQVIA DA Germany	-
CANNA.BL.BET.M E5A BEDROC.ENUA 5G BEDROCAN	2046883917	IQVIA DA Germany	-
CANNA.BL.BET.M G7E BEDROC.22 per 1 5G BEDROCAN	2046884292	IQVIA DA Germany	-
CANNA.BL.BET.M FG6 BEDROBINOL 5G	803465	IQVIA DA Germany	-
CANNA.BL.BET.M FO0 BEDROBINOL 5G	803467	IQVIA DA Germany	-
CAN.BL.BET.M AC9>> BEDROBINOL	1974562	IQVIA DA Germany	-
CANNA.BL.BET.M C0L BEDROBINOL 5G	36038717	IQVIA DA Germany	-
CANNA.BL.BET.M B12 BEDROBINOL 5G	2046069455	IQVIA DA Germany	-
CANNA.BL.BET.M C0L BEDIOL 5G	803176	IQVIA DA Germany	-
CANNA.BL.BET.M D&N BEDIOL 5G	36038895	IQVIA DA Germany	-
CANNA.BL.BET.M FO0 BEDIOL 5G	36506808	IQVIA DA Germany	-
CANNA.BL.BET.M A01 BEDIOL 6.5 per 8 5G	37595319	IQVIA DA Germany	-
CANNA.BL.BET.M VYD BEDIOL 5G	2042696660	IQVIA DA Germany	-
CAN.BL.BET.M AC9>> BEDIOL 6.3 per 8 5G	2042698474	IQVIA DA Germany	-
CANNABIS BET.M SB2 BEDIOL 5G	2043458780	IQVIA DA Germany	-

List of concepts for indication (pre-defined conditions)

Cancer

All malignant neoplastic disease and their descendants were included.

Concept name	Concept id	Descendants	Excluded
Malignant neoplastic disease	443392	Yes	-

Chemotherapy induced nausea and vomiting

Concept name	Concept id	Descendants	Excluded
Chemotherapy-induced nausea and vomiting	40385744	Yes	-

Anxiety-related disorders

Concept name	Concept id	Descendants	Excluded
Anxiety	441542	Yes	-

Neuralgic pain

Concept name	Concept id	Descendants	Excluded

Neurogenic pain	4133040	yes	-

Spasticity

Concept name	Concept id	Descendants	Excluded
Spasticity	4329728	Yes	-
X-linked intellectual disability, limb spasticity, retinal dystrophy, diabetes insipidus syndrome	37115758	Yes	-
Paroxysmal dystonic choreoathetosis with episodic ataxia and spasticity	37395940	Yes	-
Intellectual disability, spasticity, ectrodactyly syndrome	35622325	Yes	-
Hypomyelination with brain stem and spinal cord involvement and leg spasticity	36680577	Yes	-
Early-onset progressive neurodegeneration, blindness, ataxia, spasticity syndrome	36675179	Yes	-
Autosomal recessive cerebellar ataxia with late-onset spasticity	35622036	Yes	-

Spinal cord injury

Concept name	Concept id	Descendants	Excluded
Spinal cord injury	4235863	Yes	-

Multiple sclerosis

Concept name	Concept id	Descendants	Excluded
Multiple sclerosis	374919	Yes	-

Epilepsy

Concept name	Concept id	Descendants	Excluded
Seizure disorder	4029498	Yes	-
X-linked intellectual disability and epilepsy with progressive joint contracture and facial dysmorphism syndrome	36714067	Yes	-
Triple X syndrome, epilepsy, and hypogammaglobulinemia	4123240	Yes	-
Skeletal dysplasia with epilepsy and short stature syndrome	37398922	Yes	-
Myoclonic epilepsy myopathy sensory ataxia	44782474	Yes	-
Intellectual disability, epilepsy, bulbous nose syndrome	36715461	Yes	-
Autosomal recessive cerebellar ataxia, epilepsy, intellectual disability syndrome due to RUBCN deficiency	37204209	Yes	-

Alopecia, psychomotor epilepsy, periodontal pyorrhea, intellectual disability syndrome	36715349	Yes	-

Tourette Syndrome

Concept name	Concept id	Descendants	Excluded
Gilles de la Tourette's syndrome	379782	Yes	-

Parkinson disease

Concept name	Concept id	Descendants	Excluded
Parkinson disease	381270	Yes	-

Huntington's disease

Concept name	Concept id	Descendants	Excluded
Huntington chorea	374341	Yes	-

Amyotrophic lateral sclerosis

Concept name	Concept id	Descendants	Excluded
Amyotrophic lateral sclerosis	373182	Yes	-

Alzheimer's disease and other dementias

Concept name	Concept id	Descendants	Excluded
Dementia	4182210	Yes	-
Inclusion body myopathy with early-onset Paget disease and frontotemporal dementia	45766396	Yes	-
GRN-related frontotemporal dementia	45765477	Yes	-
Frontotemporal dementia with parkinsonism-17	45765480	Yes	-
Frontotemporal dementia	4043378	Yes	-
Cerebral degeneration presenting primarily with dementia	4092747	Yes	-

Glaucoma

Concept name	Concept id	Descendants	Excluded
Glaucoma	437541	Yes	-
Neonatal diabetes, congenital hypothyroidism, congenital glaucoma, hepatic fibrosis, polycystic kidney syndrome	37110062	Yes	-
Imperforate pectinate glaucoma	4143359	Yes	-

Human immunodeficiency virus (HIV) infection

Concept name	Concept id	Descendants	Excluded
Human immunodeficiency virus infection	439727	Yes	-
World Health Organization human immunodeficiency virus infection clinical stage	604976	Yes	-
Parasitic infestation due to human immunodeficiency virus infection	606044	Yes	-
Non-Hodgkin lymphoma associated with Human immunodeficiency virus infection	40484012	Yes	-
Mycosis due to human immunodeficiency virus infection	3655580	Yes	-
Hepatitis B associated with Human immunodeficiency virus infection	40482214	Yes	-
Disorder of skin due to human immunodeficiency virus infection	606930	Yes	-
Bacterial infection due to human immunodeficiency virus infection	3654645	Yes	-
HIV (human immunodeficiency virus) disease resulting in haematological and immunological abnormalities	46284256	Yes	-

Anorexia

Concept name	Concept id	Descendants	Excluded
Loss of appetite	442165	Yes	-

Sleep disorders (including but not limited to insomnia, sleep apnoea)

Concept name	Concept id	Descendants	Excluded
Sleep disorder	435524	Yes	-

Inflammatory bowel disease

Concept name	Concept id	Descendants	Excluded
Inflammatory bowel disease	4074815	Yes	-
Ulcerative colitis	81893	Yes	-
Crohn's disease	201606	Yes	-

Fibromyalgia

Concept name	Concept id	Descendants	Excluded
Fibromyalgia	40405599	Yes	-
Secondary fibromyalgia	46284893	Yes	-

Rheumatoid arthritis

Concept name	Concept id	Descendants	Excluded
Rheumatoid arthritis	80809	Yes	-
Juvenile rheumatoid arthritis	4253901	Yes	-
Deformity of hand due to rheumatoid arthritis	46273442	Yes	-
Deformity of foot due to rheumatoid arthritis	4334806	Yes	-
Dilated cardiomyopathy due to rheumatoid arthritis	4060405	Yes	-
Polyneuropathy in rheumatoid arthritis	4102493	Yes	-
Myopathy due to rheumatoid arthritis	4107913	Yes	-