Study Report

P3-C1-002

DARWIN EU® - Drug utilisation study on medicinal use of Pelargonii radix

11/11/2024

Version 5.0

Contents

Study Title	DARWIN EU® - Drug utilisation study on medicinal use of Pelargonii radix
Study Report Version identifier	V5.0
Dates Study Report updates	11/11/2024
EU PAS register number	EUPAS1000000150
Active substance	Pelargonii radix (root of *Pelargonium sidoides* DC / *Pelargonium reniforme* Curt.).
Medicinal product	N/A
Research question and objectives	Research question What was the real-world use of Pelargonii radix in children, adolescents, adults and elderly populations? Study objectives 1. To characterise the cohort of patients being treated with Pelargonii radix at the time of each treatment initiation of the drug of interest in terms of demographics and indication for prescribing. Additionally, to determine dose at the treatment initiation, the type of products used (including strength and formulation), initial quantity of the product, duration of treatment episodes and number of prescriptions of the drug of interest per treatment episode. Results were stratified by age category (below 3; 3-5; 6-11; 12-17; 18-65, >65 years) and database. 2. To determine incidence of use of Pelargonii radix among different age categories (below 3; 3-5; 6-11; 12-17; 18-65, >65 years) by country/database, during the study period (2014-2023). Note: Although dose at treatment initiation and duration of treatment episode were originally part of the objective 1, they were excluded from the final analyses. This decision is detailed in section 9.9.8 Deviations from the protocol.
Country(-ies) of study	Belgium and Germany
Author	Dina Vojinovic d.vojinovic@darwin-eu.org Nicolas Hunt n.hunt@darwin-eu.org

1. DESCRIPTION OF STUDY TEAM

Study team Role	Names	Organisation
Principal Investigator/Clinical Epidemiologist	Dina Vojinovic Nicholas Hunt Katia Verhamme	IQVIA Erasmus MC Erasmus MC
Data Scientist	Ger Inberg Cesar Barboza Maarten van Kessel Adam Black Ross Williams	Erasmus MC
Data Partner*	**Names**	**Organisation**
Local Study Coordinator/Data Analyst	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 2 databases in 2 European Union (EU) countries. All databases were previously mapped to the OMOP Common Data Model (CDM).

1. IQVIA Longitudinal Patient Database Belgium (IQVIA LPD Belgium), Belgium
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 source release date
Belgium	IQVIA LPD Belgium	Primary care	EHR	1.1 million	0.4 million	31/12/2023
Germany	IQVIA DA Germany	Primary care and outpatient specialist care	EHR	43.1 million	8.5 million	30/09/2023

LPD = Longitudinal Patient Database; DA = Disease Analyzer; EHR = Electronic Heath 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 Pelargonii radix

Rationale and Background

Preparations from Pelargonii radix have received marketing authorisations in some European member states for partly more than 30 years. They are used for the management of common cold and acute bronchitis, however further information is needed regarding its real-world use in different age groups, especially in the younger population of children under 12 years old.

Research question and Objectives

Research question

What is the real-world use of Pelargonii radix in children, adolescents, adults and elderly populations?

Study objectives

1. To characterise the cohort of patients being treated with Pelargonii radix at the time of each treatment initiation in terms of demographics and indication for prescribing. Additionally, to determine dose at the treatment initiation, the type of products used (including strength and formulation), initial quantity of the product, duration of treatment episodes and number of prescriptions of the drug of interest per treatment episode. All results were stratified by age category (below 3; 3-5; 6-11; 12-17; 18-65, >65 years) and database.
2. To determine incidence of use of Pelargonii radix among different age categories (below 3; 3-5; 6-11; 12-17; 18-65, >65 years) by country/database, during the study period (2014-2023).

Note: Although dose at treatment initiation and duration of treatment episode were originally part of the objective 1, they were excluded from the final analyses. This decision is detailed in section 9.9.8 Deviations from the protocol.

Research Methods

Study design

- New drug user cohort study (Objective 1, Patient-level drug utilisation analysis with regard to demographics, indication of drug use, initial dose, the type of products used, initial quantity of the product, duration of treatment episodes and number of prescriptions per treatment episode).
- Population-level cohort study (Objectives 2, Population-level drug utilisation study on selected medicines of interest).

Note: Initial dose and duration of the treatment episode were excluded from the final analyses. This decision is detailed in section 9.9.8 Deviations from the protocol.

Population

Patient-level utilisation of selected medicines of interest: Patient-level drug utilisation analyses included all treatment initiations of pre-specified medicines of interest in the period between 1st of January 2014 and 31st of December 2023. Patients had at least 365 days of data visibility prior to the date of their first prescription and no use of the respective medication of interest in the previous 30 days. This requirement of at least 1 year of prior data history did not hold for children <1 year of age.

Population-level utilisation of selected medicines of interest: Population-level drug utilisation analyses included all individuals registered in the database between 1st of January 2014 and 31st of December 2023, with at least 365 days 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.

Variables

Drug of interest

Preparations from Pelargonii radix (root of *Pelargonium sidoides* DC / *Pelargonium reniforme* Curt.).

Condition of interest

Upper respiratory tract infections and lower respiratory tract infections (acute bronchitis, acute rhinosinusitis common cold, cough, nasopharyngitis, sinusitis, tonsillitis, upper respiratory infection).

Data Sources

1. IQVIA Longitudinal Patient Database Belgium (IQVIA LPD Belgium), Belgium
2. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany

Sample size

No minimum sample size was required for this drug utilisation descriptive study, as our primary focus was to describe medicinal use of Pelargonii radix, irrespective of the sample size. Based on a preliminary feasibility assessment, the expected number of record counts for the different products of the selected medication differed across databases and age groups. For children, the range varied from 100 (IQVIA LPD Belgium, IQVIA DA Germany) to 27,700 (IQVIA DA Germany). Among adolescents, the range spanned from 100 (IQVIA LPD Belgium, IQVIA DA Germany) to 9,300 (IQVIA DA Germany), while in adults, it extended from 100 (IQVIA LPD Belgium, IQVIA DA Germany) to 54,400 (IQVIA DA Germany) record counts.

Data analyses

Patient-level utilisation of selected medicines of interest: Patient level characterisation was conducted at index date. Index date was the date at the time of first prescription of each new treatment episode of the drug of interest for each person. The frequency of indication of drug use was assessed by searching for predefined disease categories. Additionally, the top 10 SNOMED codes reported in window around index date were determined. The initial dose was estimated, and the minimum, quartiles and maximum values were provided. The type of products used including information on strength and formulation were also reported. The frequency of all Pelargonii radix products was retrieved and provided at index date. Duration of treatment episodes was calculated and summarized providing the minimum, quartiles, and maximum duration of treatment episodes. The initial quantity of the product (initial refers to first prescription of each treatment episode) was retrieved and summarized by calculating the median and interquartile range. The number of prescriptions per treatment episode was estimated and the minimum, quartiles and maximum number of repeated prescriptions of the index drug were reported. The statistical analyses were conducted using the "*DrugUtilisation*" (https://darwin-eu-dev.github.io/DrugUtilisation/) and "*PatientProfiles*" (https://darwin-eu-dev.github.io/PatientProfiles/) R Package based on OMOP-CDM mapped data and were stratified by age category (below 3; 3-5; 6-11; 12-17; 18-65, >65 years) and database.

Population-level utilisation of selected medicines of interest: Incidence rate of use of medicines of interests, expressed as numbers of treatment initiations per person-year, were estimated in separate age categories (below 3; 3-5; 6-11; 12-17; 18-65, >65 years) (Objective 2). The statistical analyses were performed based on OMOP-CDM mapped data using *"IncidencePrevalence"* R package (https://darwin-eu.github.io/IncidencePrevalence/).

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

Note: Initial dose and duration of the treatment episode were excluded from the final analyses. This decision is detailed in section 9.9.8 Deviations from the protocol.

Results

Characterisation of the cohort of patients being prescribed Pelargonii radix at the time of first prescription of each new treatment episode - Patient-level drug utilisation study

This study identified 57,115 new users of Pelargonii radix products in IQVIA DA Germany and 10,066 new users in IQVIA LPD Belgium, as well as 84,698 treatment episodes in IQVIA DA Germany and 13,020 in IQVIA LPD Belgium, after applying inclusion criteria. The number of study participants initiating Pelargonii radix treatment across different age categories in IQVIA DA Germany was: 3,487 for 0-2 years, 5,327 for 3-5 years, 6,783 for 6-11 years, 4,218 for 12-17 years, 34,021 for 18-65 years, and 6,993 for over 65 years. In IQVIA LPD Belgium, the number of study participants was 638 for 0-2 years, 914 for 3-5 years, 1,091 for 6-11 years, 894 for 12-17 years, 5,646 for 18-65 years, and 1,336 for over 65 years. The median ages at treatment initiation were consistent with the defined age categories. In terms of sex distribution, balanced or slightly male-dominated sex distribution was observed in the 0-17 years age groups in IQVIA DA Germany and in the 0-2 age group in IQVIA LPD Belgium, while the other age groups had a higher proportion of females.

The most common pre-specified conditions associated with the initiation of Pelargonii radix treatment across different age groups and databases were upper respiratory infections. Acute bronchitis was consistently reported across all age groups, with higher frequencies in IQVIA DA Germany. The common cold and upper respiratory infections were prevalent in both databases, with high frequencies in the younger age groups in IQVIA LPD Belgium. Cough was a common condition in all age groups, and sinusitis and tonsillitis were observed but less frequent.

In terms of Pelargonii radix products, the Pelargonium sidoides root extract 2.67 MG/ML oral solution was the most commonly prescribed product for children in the 0-2, 3-5 and 6-11 years age groups in IQVIA DA Germany. Similarly, the same 2.67 MG/ML oral solution was also the most commonly prescribed for children in these same age groups in IQVIA LPD Belgium. As children aged, usage shifted to the 800 MG/ML oral solution and 20 MG oral tablets in IQVIA DA Germany database in the age group 12-17 years and 20 MG oral tables for children in 12-17 age group in IQVIA LPD Belgium. The median initial quantity of the product across all age groups in the children population in IQVIA DA Germany was generally one, with a consistent median of one prescription per treatment episode. In IQVIA LPD Belgium, data on initial quantity was missing for ages below 6 years. For adults, the 800 MG/ML oral solution and 20 MG oral tablets were predominately used in IQVIA DA Germany, while 20 MG oral tables were used in IQVIA LPD Belgium. The median initial quantity was one bottle for oral solution in IQVIA DA Germany and 21 tables for oral tablets in adults in IQVIA LPD Belgium, and the median number of prescriptions per treatment episode was consistently one.

Incidence rates of prescriptions of Pelargonii radix among different age categories – Population-level drug utilisation study

The incidence of Pelargonii radix use showed distinct patterns across age groups and databases over time. Younger age groups, specifically those aged 0 to 2 and 3 to 5, exhibited higher incidence rates of Pelargonii radix use compared to older age groups. In IQVIA DA Germany, the 3 to 5 age group had the highest incidence rate, estimated at 7 initiated treatments/1,000 person-years (PY) in 2014, with rates remaining relatively stable until 2019, when it decreased slightly to 4 initiated treatments/1,000 PY in 2021 before

coming back to initial 7/1,000 PY by the end of the study period. Similarly, the incidence rates for the 0 to 2, 6 to 11, and 12 to 17 age groups remained steady at around 5, 4, and 2 /1,000 PY, respectively.

In IQVIA LPD Belgium, the highest incidence of prescriptions of Pelargonii radix was also observed in the 3 to 5 age group, with an initial rate of 27 initial prescriptions/1,000 PY in 2014. This rate declined over time until 2020, followed by an increase thereafter. The 0 to 2 age group showed fluctuating incidence rates between 9 initiated treatments/1,000 PY and 18/1,000 PY, while the incidence rates in 6 to 11 and 12 to 17 age groups ranged between 7 and 19/1,000 PY and 3 and 17/1,000 PY, respectively, over the study period.

For adults aged 18 to 65 and those over 65, incidence rates remained low and stable throughout the study in both databases.

Discussion

The study offers a thorough analysis of Pelargonii radix utilisation at both patient and population levels. Overall, the prevalence of upper respiratory infections, particularly acute bronchitis and the common cold, supports the traditional use of Pelargonii radix products for respiratory conditions. This rationale for use applies across age groups, including in children 0 to 2 and 3 to 5 years old. The study also highlights a significant shift in formulation preferences and strengths across different age groups. Younger children, specifically those aged 0 to 2 and 3 to 5, exhibit the highest incidence rates of Pelargonii radix product use compared to older children and adults. Overall, these findings provide valuable insights into the real-world usage patterns of Pelargonii radix.

4. LIST OF ABBREVIATIONS

Acronyms/term	Description
BSS	Bronchitis Severity Score
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
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 deliverable	Timelines (planned)	Timelines (actual)
Draft Study Protocol	28th March 2024	28th March 2024
Final Study Protocol	April 2024	May 2024
Creation of Analytical code	April 2024	April/May 2024
Registration in HMA-EMA Catalogue	May 2024	May 2024
Execution of Analytical Code on the data	May 2024	May 2024
Draft Study Report	May 2024	24th May 2024
Final Study Report	June 2024	November 2024

7. RATIONALE AND BACKGROUND

Pelargonii radix (root of P*elargonium sidoides* DC / *Pelargonium reniforme* Curt.) received Marketing authorization (MA) in some member states of the EU based on well-established use for the symptomatic treatment of acute upper respiratory tract infections (e.g., common cold, sinusitis, acute bronchitis). One Pelargonium preparation has been on the market for more than 30 years and is registered in several member states as traditional herbal medicinal product with the indication of common cold.[1] Systematic literature reviews on the product indicate its usage for managing acute bronchitis and common colds.[2, 3] Both the liquid and dry forms are administered orally and in some member states it can be dispensed over the counter.

Several randomised controlled trials (RCTs) have been conducted on the effectiveness and safety of pelargonium for treating acute bronchitis in adult populations.[4-6] Furthermore, there is RCT evidence supporting the use of products containing Pelargonii radix in young children.[7-9] However, it is important to note that Pelargonium radix products are generally not recommended for children under the age of 6 years, based on Herbal Medicinal Products Committee (HMPC) herbal monograph.[1] This lower age limit was established by a majority vote of the members, although not all agreed and the restriction is not mandatory. Consequently, some products may be indicated for children younger than 6 years. The EMA's Committee on HMPC evaluated use of Pelargonium for acute bronchitis and concluded that while there were only small differences in the outcomes of interest between treatment and placebo, they identified methodological shortcomings. Specifically, there were concerns about the use of the at the time non-validated Bronchitis Severity Score (BSS).[10]

To our knowledge, there are no observational studies examining the usage of Pelargonii radix products or profiling the individuals who use them in real-world settings, whether in adults or children. However, there is a need for further information, particularly regarding their real-world utilisation in various age groups, with a specific focus on the younger population of children under 12 years old.

8. RESEARCH QUESTION AND OBJECTIVES

Research question

What was the real-world use of Pelargonii radix in children (0-11 years), adolescents (12-17 years), adults (18-65 years) and elderly (>65 years) populations?

Study objectives

1. To characterise the cohort of patients being treated with Pelargonii radix at the time of each treatment initiation of the drug of interest in terms of demographics and indication for prescribing. Additionally, to determine dose at the treatment initiation, the type of products used (including strength and formulation), initial quantity of the product, duration of treatment episodes and number of prescriptions of the drug of interest per treatment episode. Results were stratified by age category (below 3; 3-5; 6-11; 12-17; 18-65, >65 years) and database.
2. To determine incidence of use of Pelargonii radix among different age categories (below 3; 3-5; 6-11; 12-17; 18-65, >65 years) by country/database, during the study period (2014-2023).

Description of the proposed objectives to be achieved in the study is displayed in **Table 1**.

Table 1. Study objective and design elements for achieving them.

Objective:	**Objective 1:** To characterise the cohort of patients being treated with Pelargonii radix at the time of first prescription of each new treatment episode of the drug of interest in terms of number of individuals and treatment episodes, demographics, and indication for prescribing. Additionally, to determine dose at treatment initiation, the type of product used (formulation and strength), initial quantity of the product, duration of each treatment episode and number of prescriptions of the drug of interest per treatment episode. Results were stratified by age category (below 3; 3-5; 6-11; 12-17; 18-65, >65 years) and database. **Objective 2**: To determine incidence of use of Pelargonii radix among different age categories (below 3; 3-5; 6-11; 12-17; 18-65, >65 years) by country/database, during the study period (2014-2023).
Hypothesis:	Not applicable
Population *(mention key inclusion-exclusion criteria):*	**Objective 1**: Patient-level utilisation of selected medicines of interest: We included all treatment initiations of Pelargonii radix in the period between 1st of January 2014 and 31st of December 2023. Patients had to have at least 365 days of data visibility prior to the date of their first prescription and no use of the respective medication of interest in the previous 30 days. This requirement of at least 1 year of prior data history did not hold for children <1 year of age. **Objective 2**: Population-level utilisation of selected medicines of interest: All individuals registered in the database between 1st of January 2014 and 31st of December 2023, with at least 365 days 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:	Pelargonii radix (root of *Pelargonium sidoides* DC / *Pelargonium reniforme* Curt.).
Comparator:	None
Outcome:	None
Time *(when follow up begins and ends):*	**Objective 1:** Patient-level drug utilisation: Follow-up started on the date of incident prescription/dispensation of Pelargonii radix (index date). **Objective 2:** Population-level drug utilisation: Follow-up started on the respective date of the latest of the following: 1) study start date (1st January 2014), 2) date at which they had 1 year of prior history. 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 of December 2023), whichever came first. Additionally, for objective 1, end of follow-up was defined as end of that treatment episode.
Setting:	Outpatient setting using data from the following 2 data sources: IQVIA LPD Belgium (Belgium) and IQVIA DA Germany (Germany).
Main measures:	**Objective 1**: Number of individuals and treatment episodes as well as characterisation (age, sex) and proportion of treatment initiations of medication of interest with one of the defined indications of use at index date stratified by different age categories. Initial dose of prescribed medication of interest expressed as the minimum, p25, median, p75 and maximum values stratified by age categories. The distribution of Pelargonii radix products prescribed (strength, formulation) by age categories. Duration of treatment episodes of medication of interest expressed as minimum, p25, median, p75 and maximum duration of treatment episodes stratified by age categories. Initial quantity of medication of interest expressed as median and interquartile range stratified by age categories. Number of prescriptions of medication of interest per treatment episode expressed as minimum, p25, median, p75 and maximum stratified by age categories. **Objective 2**: Incidence rates (expressed as numbers of treatment initiations per person-year) of Pelargonii radix use stratified by different age categories.

Note: Initial dose and duration of the treatment episode were excluded from the final analyses. This decision is detailed in section 9.9.8 Deviations from the protocol.

9. RESEARCH METHODS

9.1 Study type and study design

The Study Types with related Study Designs are described in the **Table 2** below and were selected from the Draft Catalogue of Data analytics.

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

- A new drug user cohort study was used to address objective 1; to characterise patient-level drug utilisation in terms of number of individuals and treatment episodes, patient demographics and indication for Pelargonii radix prescribing and to determine dose at the treatment initiation, the type of products used (including strength and formulation), initial quantity of the product, duration of treatment episodes and number of prescriptions of selected pre-specified drug of interest per treatment episode, stratified by different age categories.
- A population-based cohort study was conducted to address objective 2, assessing the incidence rates of the respective medication of interest, stratified by different age categories.

Table 2. Description of potential study types and related study designs (based on DARWIN EU® Catalogue of standardised analyses).

Study type	Study design	Study classification
Patient Level DUS	New drug/s user cohort	Off the shelf
Population Level DUS	Population Level Cohort	Off the shelf

Note: Initial dose and duration of the treatment episode were excluded from the final analyses. This decision is detailed in section 9.9.8 Deviations from the protocol.

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. IQVIA Longitudinal Patient Database Belgium (IQVIA LPD Belgium), Belgium
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 the medication of interest, 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 had data on the medication of interest.

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

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 (https://ohdsi.github.io/Achilles), which systematically characterises 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, were 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, more general-purpose diagnostic tools, "*CohortDiagnostics*" (https://github.com/darwin-eu-dev/CohortDiagnostics) and "*DrugExposureDiagnostics*" (https://darwin-eu-dev.github.io/DrugExposureDiagnostics), were developed. "*CohortDiagnostic*" package evaluated phenotype algorithms for OMOP CDM datasets, offering a standard set of analytics for understanding patient capture including data generation. It provided additional insights into cohort characteristics, record counts and index event misclassification. "*DrugExposureDiagnostic*" package assessed ingredient specific diagnostics for drug exposure records. Furthermore, timeliness was guarded by extracting the release dates for each dataset in the network and monitoring when data were 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 (https://github.com/darwin-eu/CdmOnboarding) contained 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 until when data was included.

Table 3. Description of the selected data sources.

Country	Name of Database	Justification for Inclusion	Health Care setting (e.g. primary care, specialist care, hospital care)	Type of Data (EHR, claims, registries)	Number of subjects	Number of active subjects*	Data lock for the last update (source release date)
Belgium	IQVIA LPD Belgium	Database covers primary care setting where selected pre-specified medication of interest may be prescribed/dispensed.	Primary care	EHR	1.1 million	0.4 million	31/12/2023
Germany	IQVIA DA Germany	Database covers primary care/outpatient specialist care setting where selected pre-specified medication of interest may be prescribed/dispensed.	Primary care and outpatient specialist care	EHR	43.1 million	8.5 million	30/09/2023

LPD = Longitudinal Patient Database; DA = Disease Analyzer; EHR = Electronic Heath 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.

IQVIA Longitudinal Patient Database (LPD) Belgium, Belgium

LPD Belgium is a computerised network of GPs who contribute to a centralised database of anonymised data of patients with ambulatory visits. Currently, around 300 GPs from 234 practices are contributing to the database covering 1.1M patients from a total of 11.5M Belgians (10.0%). The database covers time from 2005 through the present. Observation time is defined by the first and last consultation dates. Drug information is derived from GP prescriptions. Drugs obtained over the counter by the patient outside the prescription system are not reported. No explicit registration or approval is necessary for drug utilisation studies.

IQVIA Disease Analyser (DA) Germany, Germany

DA Germany is collected from extracts of patient management software used by GPs and specialists practicing in ambulatory care settings.[11] Data coverage includes more than 34M distinct person records out of at total population of 80M (42.5%) in the country and collected from 2,734 providers. Patient visiting more than one provider are not cross identified for data protection reasons and therefore recorded as separate in the system. Dates of service include from 1992 through present. Observation time is defined by the first and last consultation dates. Germany has no mandatory GP system and patient have free choice of specialist. As a result, data are collected from visits to General, Paediatric Medicine, Obstetrics / Gynaecology, Orthopaedic Surgery, Dermatology, Otolaryngology, Diabetic medicine, Urology, Neuropsychiatry, Cardiology, Gastroenterology, Pulmonary Disease, Rheumatology, Neurology, Psychotherapy, Child and Adolescent Psychiatry and Psychiatry. Drugs are recorded as prescriptions of marketed products. No 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 (see **Table 3** for more details on each database's latest data).

9.4 Follow-up

The operational definition of start of follow-up (i.e., index date or time 0) is 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/ validation	Source of algorithm
All participants from the database eligible for the study initiating treatment with the selected pre-specified medication of interest - Characterisation	Initiation of treatment with medication of interest	Multiple entries	Incident	[-30, ID]	OP	RxNorm	n/a	Use of selected pre-specified medication of interest	n/a	n/a
All patients from the database eligible for the study – Incident use of Pelargonii radix	Patient present in the database with at least 1 year of valid database history (except for children <1 year).	Multiple entries	Incident	[-30, ID]	OP	RxNorm	n/a	Use of selected pre-specified medication	n/a	n/a

[1]OP = outpatient, ID = index date; n/a = not applicable;

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

For patient-level drug utilisation of pre-selected medication of interest, study participants were followed from the date of incident prescription/dispensation of selected pre-specified medication of interest (index date) until end of that treatment episode, loss to follow-up, end of data availability, death, or end of the study period (31st of December 2023), whatever came first.

For population-level drug utilisation of pre-specified medication of interest, follow-up started when study participants fulfil inclusion criteria and 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), whichever came first. Incidence required appropriate denominator populations with individuals aged below 3, between 3-5, 6-11, 12-17, 18-65, >65 years and their contributed observation time was first identified. Study participants in the denominator population began contributing person time on the respective date of the latest of the following: 1) study start date (1st January 2014), 2) date at which they have 1 year of prior history and 3) date at which they reach a minimum age. Participants stopped contributing person time at the earliest date of the following: 1) end of available data in each of the data sources (date of last data extraction), 2) death, 3) study end date (31st December 2023), 4) date at which the observation period of the specific person ends or 5) the last day in which they have the maximum age.

An example of entry and exit into the denominator population is shown in **Figure 1**. In this example, person ID 1 entered study upon reaching a minimum age and left at the study end date. Person 2 entered study at study start date and exited upon reaching the maximum age. Person 3 had already sufficient prior history before the study start date but entered the study upon reaching a minimum age and left the study at the study end date. Person 4 entered the study upon reaching minimum age and left when exiting the database (the end of observation period). Person ID 5 entered the study only with sufficient prior history and exit at the study end date. Lastly, person ID 6 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 maximum age.

For additional information regarding the "*IncidencePrevalance"* package, please refer to the documentation available on CRAN - Package IncidencePrevalence (r-project.org) (https://darwin-eu.github.io/IncidencePrevalence/).

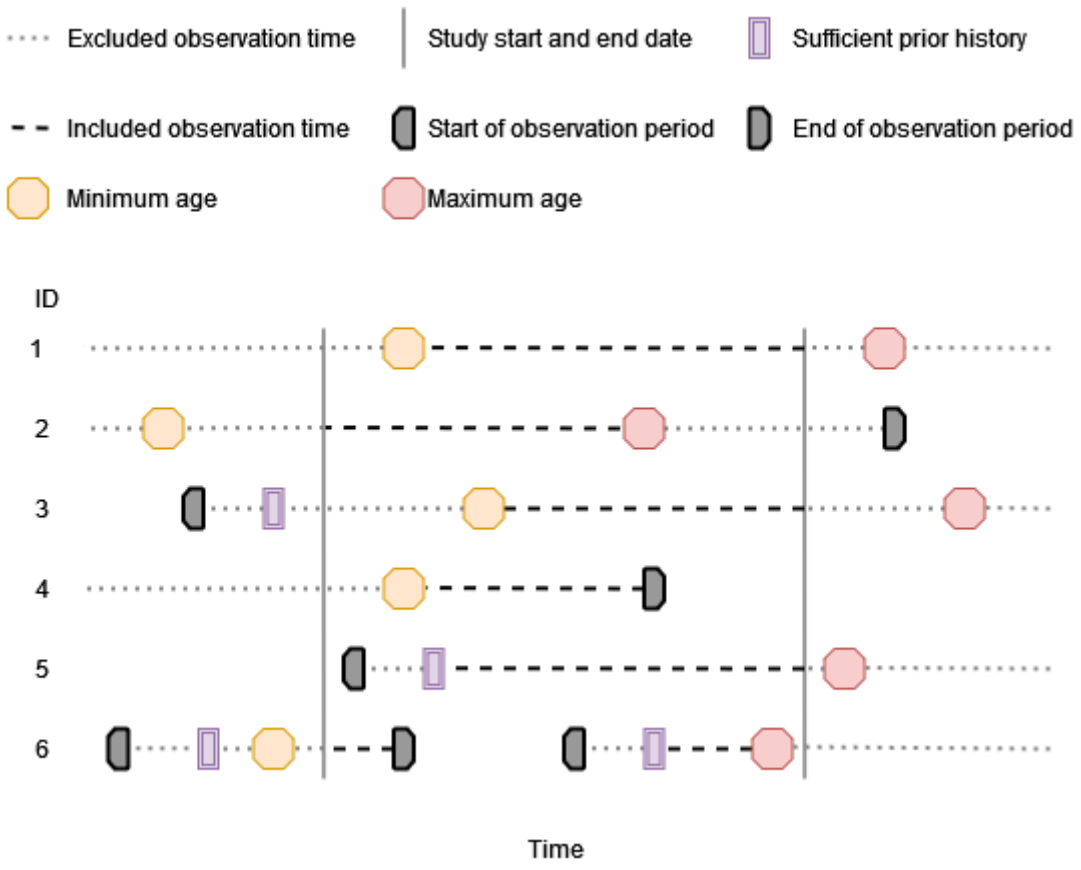


Figure 1. Included observation time for the denominator population.

9.5 Study population with eligibility criteria

Characterisation of the cohort of patients prescribed Pelargonii radix - Patient-level utilisation study

All individuals who initiated treatment with pre-specified medicine of interest in the period between 1st of January 2014 and 31st of December 2023 (or latest date available). Notably, all patients had at least 365 days of data visibility prior to the date of their first prescription and no use of the respective medication of interest in the previous 30 days. This requirement of at least 1 year of prior data history did not hold for children <1 year of age.

Incidence rates of prescribing of Pelargonii radix - Population-level utilisation study

The study cohort included all individuals registered in the database between 1st of January 2014 and 31st of December 2023, with at least 365 days 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 users of the selected pre-specified medication of interest was excluded during use and 30 days afterwards.

Operational definitions of inclusion criteria are described in **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/ 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)	After*	n/a	OP	n/a	n/a	All individuals within selected databases	n/a	n/a
Prior database history	Study participants will be required to have 365 days 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 will be required to have not used selected pre-specified medication of interest 30 days before a “new” prescription	After*	30 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 is required to be in the primary position (main reason for encounter)

*Order of application specifies whether the eligibility criterion is applied before or after selection of the study entry date. For instance, selecting 'after' means that the first possible study entry date is chosen, followed by the application of the inclusion and/or exclusion criteria.

9.6 Variables

9.6.1 Exposure

For this study, exposure of interest was prescribing (during study period) of selected pre-specified medication of interest including root of *Pelargonium sidoides* DC / *Pelargonium reniforme* Curt.

The list of medication of interest is described in **Appendix I**. Details of exposure are described in by means of **Table 6**.

Table 6. Operational definitions of exposure.

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/ validation	Source of algorithm
Pelargonii radix (root of Pelargonium sidoides DC / Pelargonium reniforme Curt.)	Preliminary code list provided in Appendix I	[-30, ID]	Calendar year	OP	RxNorm	n/a	All individuals present in the database during the study period	Previous use of selected pre-specified medication of interest	n/a	n/a

[1]OP = outpatient, ID = index date, n/a = not applicable

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

9.6.2 Outcome

No outcomes measured.

9.6.3 Other covariates, including confounders, effect modifiers and other variables

Covariates for the characterization of the cohort of patients with a prescription of Pelargonii radix - Patient-level drug utilisation study

Covariate for stratification in patient-level drug utilisation study included age categories: below 3; 3-5; 6-11; 12-17; 18-65, >65 years.

Other covariates for patient-level drug utilisation study included:

- A list of pre-specified conditions used to assess indication of use (the frequency of conditions of interest was assessed at index date and as sensitivity analysis in a window around index date (7 days before until 7 days after index date)):
  - Acute bronchitis
  - Acute rhinosinusitis
  - Common cold
  - Cough
  - Nasopharyngitis
  - Sinusitis
  - Tonsillitis
  - Upper respiratory infection

- Top 10 of most frequent comorbidities from large-scale characterisation (the frequency of comorbidities was assessed at index date and as sensitivity analysis in a window around index date (7 days before until 7 days after index date)).

- An overview of all Pelargonii radix products from large-scale characterisation (the frequency was assessed at index date).

The operational definition of the covariates is described in the **Table 7**. Index date was the start of the (first) incident prescription of each new treatment episode during the study period. The concept sets for prespecified conditions of interest are described in **Appendix I**.

Covariates for the analysis of incidence of use of Pelargonii radix - Population-level drug utilisation study

Covariate for stratification in population-level drug utilisation study included age categories: below 3; 3-5; 6-11; 12-17; 18-65, >65 years.

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/ validation	Source for algorithm
Indication of use	Check for conditions of interest related to use of Pelargonii radix	Counts	At index date and as sensitivity analysis in window around index date [-7, 7]	OP	SNOMED	n/a	Persons with new use during the study period	n/a	n/a
Comorbidity	Large-scale patient characterisation with regard to underlying comorbidity	Counts	At index date and as sensitivity analysis in window around index date [-7, 7]	OP	SNOMED	n/a	Persons with new use during the study period	n/a	n/a
Pelargonii radix products	Large-scale patient characterisation with regard to Pelargonii radix products	Counts	At index date	OP	RxNorm	n/a	Persons with new use during the study period	n/a	n/a

[1] IP = inpatient, OP = outpatient, n/a = not applicable
[2] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

9.7 Study size

No sample size was calculated for this drug utilisation descriptive study, as our primary focus was to examine medicinal use of Pelargonii radix, irrespective of the sample size. Based on a preliminary feasibility assessment, the expected number of record counts for the different products of the selected medication differed across databases and age groups. For children, the range varied from 100 (IQVIA LPD Belgium, IQVIA DA Germany) to 27,700 (IQVIA DA Germany). Among adolescents, the range spanned from 100 (IQVIA LPD Belgium, IQVIA DA Germany) to 9,300 (IQVIA DA Germany), while in adults, it extended from 100 (IQVIA LPD Belgium, IQVIA DA Germany) to 54,400 (IQVIA DA Germany) record counts.

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 on a simulated set of patients 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 against the OMOP-CDM 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 describes the details of the analysis approach and rationale for the choice of analysis, with reference to the D1.3.8.1 Draft Catalogue of Data Analysis which describes the type of analysis in function of the study type.

Description of Study types and types of analysis is shown in **Table 8**.

Table 8. Description of study types and types of analysis.

Study type	Study classification	Type of analysis
Patient Level DUS	Off-the-shelf	- Characterisation of patient-level features. - Frequency and % of indication/s. - Estimation of minimum, quartiles, and maximum values initially prescribed/dispensed dose. - Frequency of Pelargonii radix products with an overview of their strengths and formulation. - Duration of treatment episodes as minimum, quartiles and maximum number of treatment episodes. - Estimation of median and interquartile range of initial quantity of the product.

Study type	Study classification	Type of analysis
		- Number of prescriptions per treatment episode estimated as minimum, quartiles and maximum number of prescriptions.
Population Level DUS	Off-the-shelf)	- Population-based incidence rates

Note: Initial dose and duration of the treatment episode were excluded from the final analyses. This decision is detailed in section 9.9.8 Deviations from the protocol.

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 "*DrugUtilisation*" (https://darwin-eu-dev.github.io/DrugUtilisation/) and "*PatientProfiles*" (https://darwin-eu-dev.github.io/PatientProfiles/) for patient-level drug utilisation analyses including patient-level characterisation and "*IncidencePrevalence*" (https://darwin-eu.github.io/IncidencePrevalence/) for population-level estimation of drug utilisation.

Drug exposure calculations

Drug eras were defined as follows: Exposure started at date of the first prescription, e.g., the index date the person entered the cohort. 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 is ≤ 7 days. The time between the two joined eras was considered as exposed by the first era as shown in **Figure 2**, first row.

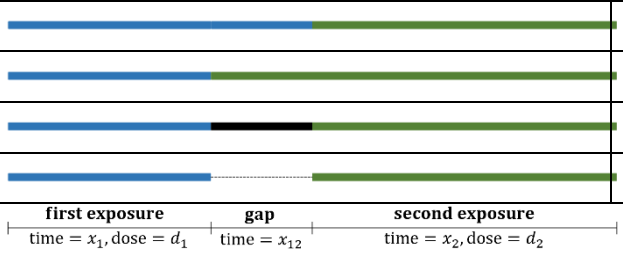
Gap era joint mode	Schematics	Dose in between	Cumulative dose	Cumulative time
"first"		d_1	$d_1 \cdot (x_1 + x_{12}) + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"second"		d_2	$d_1 \cdot x_1 + d_2 \cdot (x_2 + x_{12})$	$x_1 + x_{12} + x_2$
"zero"		0	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"join"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

Figure 2. Gap era joint mode.

If two prescriptions overlapped, the overlap time was considered exposed by first prescription. No time was added at the end of the combined drug era to account for the overlap.

New user cohort

Individuals who initiated treatment were selected based on their prescriptions of the respective drug of interest after the start of the study. For each patient, at least 365 days 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 30 days prior to the current prescription. If the start date of a prescription did not fulfil the exposure washout criteria of 30 days of no use, the whole exposure was eliminated.

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, to protect privacy. The following age categories were considered: below 3; 3-5; 6-11; 12-17; 18-65, >65 years.

Indication

Indication was determined based on recordings of pre-defined conditions (see 9.6.3 – other covariates), at the date of the first prescription of the respective drug (index date) [primary definition] or during assessment windows [sensitivity analyses - 7 days before until 7 days after 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 in the window around index date (7 days before until 7 days after index date). The top 10 conditions were presented.

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

Characterization of the cohort of patients with a prescription of Pelargonii radix - Patient-level drug utilisation study

New drug user patient-level characteristics on index date

For each concept extracted at index date, the number of persons (N, %) with a record within the pre-specified time windows were provided.

Indication

The number of persons (N, %) with a record of the respective indication were provided. If a person had a record of more than one specific indication, that person was included in both specific indication groups separately.

Initially prescribed or dispensed dose

For each prescription at index date, the prescribed dose was retrieved from the drug_exposure and drug_strength tables, where the amount quantity and units are available. The quality of recording of drug dose and drug strengths might be of varying quality for different (unmapped) databases. Therefore, data quality checks were conducted to evaluate the quality of the recording of units, dosage and strength (OMOP drug_exposure and drug_strength tables) for selected pre-specified medication of

interest in the databases this study was conducted in. From this, the initial dose in the cohort was characterised by the minimum dose/strength, p25, median, p75, and maximum dose/strength.

Product type

The frequency of all Pelargonii radix products recorded in the databases of interest at the index date was retrieved from the large-scale characterization analysis. Listed product names provided information on strength and formulation.

Treatment duration

Treatment duration was calculated as the duration of each of treatment episode of the medication of interest during the study period. Treatment duration was summarized providing the minimum, quartiles, maximum duration of treatment episodes. For databases, where duration cannot be calculated due to e.g., missing information on quantity or dosing, treatment duration was not provided. Note: Initial dose and duration of the treatment episode were excluded from the final analyses. This decision is detailed in section 9.9.8 Deviations from the protocol.

Initial quantity of the product

The initial quantity of product was retrieved from the column "quantity" of drug_exposure table. Quantity of the product varies with pharmaceutical form (bottles for oral solution and syrup and tablets for solid forms). It is called initial because it refers to the first prescription of each treatment episode The initial quantities were then summarized by calculating the median and interquartile range. For databases where the quantity data was missing, the initial quantity was not included in the summary.

Count of repeated prescriptions

Number of prescriptions per treatment episode was estimated and minimum, quartiles and maximum number of repeated prescriptions of the index drug were reported.

Analysis of incidence of use of Pelargonii radix - Population-level drug utilisation study

Incidence calculations

Annual incidence rates of the selected pre-specified medication of interest were calculated as the number of treatment initiations after 30 days of no use per 1,000 person-years (PY) of the population at risk of getting exposed during the period for each calendar year. Any study participants with use of the medication of interest prior to the date at which they would have otherwise satisfied the criteria to enter the denominator population (as described above) were excluded. Those study participants who enter the denominator population then contributed time at risk up to their first prescription during the study period. If they did not have a drug exposure, they contributed time at risk up as described above. Time-at-risk of subjects who die 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 start, had 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 counted 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.

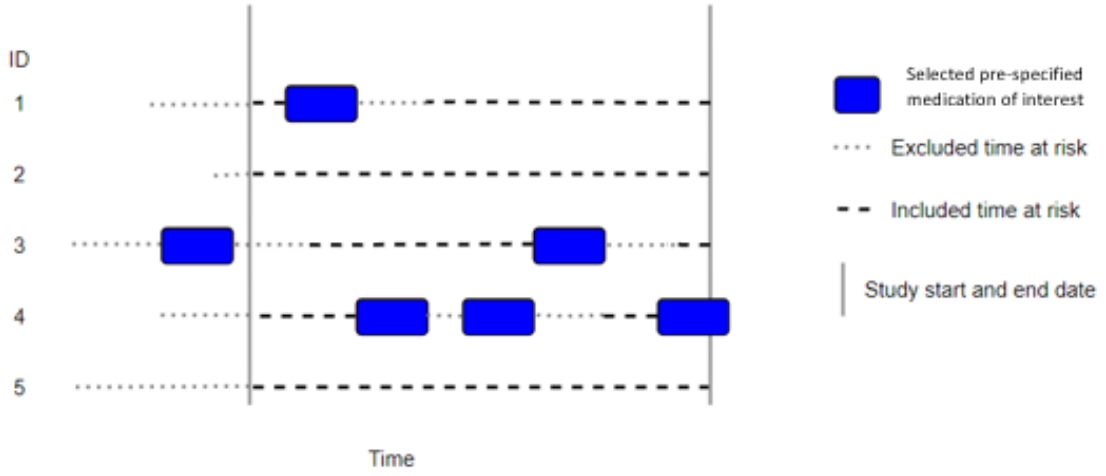


Figure 3. Incidence example.

9.9.5 Missing Values

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

9.9.6 Sensitivity Analysis

Indication of use and top 10 of most frequent comorbidities from large-scale characterisation were explored in a period of 7 days before and 7 after the index date.

9.9.7 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.

9.9.8 Deviations from the protocol

The initial daily dose and duration of treatment were originally intended to be presented. However, following OMOP CDM conventions, several assumptions and imputations were made regarding the calculation of dose and treatment duration for Pelargonii radix products, as such the data for these variables were not plausible. Therefore, duration of the treatment episode and dose at treatment initiation with Pelargonii radix products were excluded from the final analysis. To accurately reflect variables of interest for Pelargonii radix products, the report now presents the frequency of Pelargonii radix products and product names (including strength and formulation) recorded in the databases of interest, categorized by age groups, as well as the initial quantity of the product.

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/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 is collected in national/regional electronic health record databases. Due to the sensitive nature of this personal medical data, it is important to be fully aware of ethical and regulatory aspects and to strive to take all reasonable measures to ensure compliance with ethical and regulatory issues on privacy.

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

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/DataQuality.html). In particular, it was expected that data partners would have run the OHDSI Data Quality Dashboard tool (https://github.com/OHDSI/DataQualityDashboard). This tool provided numerous checks relating to the conformance, completeness and plausibility of the mapped data. Conformance focused on checks that described 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 aligned 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 defining cohorts for drugs, a systematic search of possible codes for inclusion was identified using "*CodelistGenerator*" R package (https://github.com/darwin-eu/CodelistGenerator). This software allowed the user to define a search strategy and using this will then query the vocabulary tables of the OMOP

common data model so as to find potentially relevant codes. In addition, "*DrugExposureDiagnostics"* was run to assess the use of different codes across the databases contributing to the study.

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

12. RESULTS

The full set of results from this study can be assessed through an interactive web-application ("shiny app") at https://data-dev.darwin-eu.org/P3C1002DrugUtilisationPelargonii/.

12.1 Patient-level drug utilisation

12.1.1 Participants

Table 9 provides the number of individuals who initiated treatment of the selected pre-specified medicines of interest and the number of treatment episodes by database.

Overall, in IQVIA DA Germany, initially, 131,723 individuals and 213,994 treatment episodes were identified based on exposure to Pelargonii radix products. After applying the inclusion criteria, which included, a 30-day washout period, restricting cohort start and end dates between 2014 and 2023 and ensuring one year of prior observation for all except for children under one year old and after applying the definition of a treatment episode and joining exposures separated by seven or fewer days, the final eligible cohort comprised 57,115 individuals and 84,698 treatment episodes of the selected medicines of interest.

In IQVIA LPD Belgium, initially, 13,968 individuals and 18,282 treatment episodes were identified based on exposure to Pelargonii radix products. After applying the inclusion criteria and the definition of a treatment episode, the final eligible cohort comprised 10,066 individuals and 13,020 treatment episodes of the selected medicines of interest.

IQVIA DA Germany made the most substantial contribution to the total number of individuals initiating treatment of pre-specified medicines of interest and the total number of treatment episodes in this study, reflecting the larger size of the database.

Table 9. Study attrition of individuals based on Pelargonii radix exposure and relevant inclusion criteria, per database

	IQVIA DA Germany		IQVIA LPD Belgium	
	Number of records*	Number of individuals**	Number of records*	Number of individuals**
Database population	-	43,058,712	-	1,119,527
Initial qualifying events (exposure to Pelargonii radix)	213,994	131,723	18,282	13,968
Join exposures separated by 7 or less days	211,712	131,723	18,226	13,968
Require prior use washout of 30 days	205,452	131,723	18,038	13,968
Restrict cohort_start_date on or after 2014-01-01	103,245	71,811	17,491	13,573

	IQVIA DA Germany		IQVIA LPD Belgium	
	Number of records*	Number of individuals**	Number of records*	Number of individuals**
Restrict cohort_end_date on or before 2023-12-31	103,245	71,811	17,491	13,573
1 year of prior observation or younger than 1 year old	84,698	57,115	13,020	10,066

LPD = Longitudinal Patient Database; DA = Disease Analyzer.
*Number of records = number of treatment episodes.
**Number of individuals = number of unique individuals.

12.1.2 Descriptive data

Table 1 in **Appendix II** provides a comprehensive overview of demographic characteristics of patients who were prescribed Pelargonii radix products at the time of first prescription for each new treatment episode across databases between 2014 and 2023.

Overall, in IQVIA DA Germany, the age of individuals ranged from 0 to 98 years, with female subjects comprising 53% of the population. In IQVIA LPD Belgium, the age range spanned from 0 to 103, with female subjects making up 58% of the population.

Table 10 provides a detailed overview of demographic characteristics of patients being prescribed selected products of interest at the time of first prescription for each new treatment episode, stratified by age group.

In IQVIA DA Germany, in absolute numbers, the lowest number of treatment episodes and individuals was recorded in the 0 to 2 years age group (4,978 records, 3,487 individuals). The number of treatment episodes and individuals increased in the subsequent age groups 3 to 5 and 6 to 11 years (8,283 records and 5,327 individuals; 11,147 records and 6,783 individuals, respectively) but decreased in the 12 to 17 years age group (5,626 records and 4,218 individuals). The highest number of treatment episodes and individuals was observed in the 18 to 65 years age group (45,317 records, 34,021 individuals). The median ages at index date were consistently aligned across all age group, reflecting expected age distributions. In terms of sex distribution, there was a balanced or slightly male-dominated younger age group and a higher proportion of females in the older age groups. The proportion of males in the 0 to 2 years age group was 54%, decreasing to 42% in the >65 years age group.

In IQVIA LPD Belgium, in absolute terms, the 0 to 2 years age group had the lowest number of treatment episodes and individuals, with 741 records and 638 individuals. The number of treatment episodes and individuals increased for the 3 to 5 and 6 to 11 years age groups (1,150 records and 914 individuals and 1,381 records and 1,091 individuals, respectively) but decreased in the 12 to 17 years age group (1,101 records and 894 individuals). The peak counts were in the 18 to 65 years age group, with 7,052 records and 5,646 individuals. The median ages at index date were consistent for each age group, reflecting expected age distributions. Regarding sex distribution, 0 to 2 years age group was male dominated, while the proportion of females was higher in all other age groups (3 to 5, 6 to 11, 12 to 17, 18 to 65 and >65 years age groups). Specifically, the proportion of males in the 0 to 2 age group was 54%, decreasing to 39% in the over 65 age group.

Table 10. Demographic characteristics of patients being prescribed Pelargonii radix products at the time of first prescription of each new treatment episode, stratified by age group, per database.

	IQVIA DA Germany						IQVIA LPD Belgium					
	0-2	3-5	6-11	12-17	18-65	>65	0-2	3-5	6-11	12-17	18-65	>65
Number of records*	4,978	8,283	11,147	5,626	45,317	9,347	741	1,150	1,381	1,101	7,052	1,595
Number of individuals**	3,487	5,327	6,783	4,218	34,021	6,993	638	914	1,091	894	5,646	1,336
Prior observation (days), Median (IQR)	525 (381 - 682)	1,162 (879 - 1,476)	2,118 (1,340 - 2,787)	2,771 (1,444 - 4,153)	2,056 (1,288 - 4,257)	3,491 (1,806 - 5,365)	420 (231 - 590)	933 (677 - 1,221)	1,342 (780 - 2,011)	1,398 (780 - 2,214)	1,284 (771 - 2,027)	1,442 (878 - 2,141)
Future observation (days), Median (IQR)***	1,240 (507 - 2,046)	1,275 (548 - 2,109)	1,271 (476 - 2,097)	1,205 (398 - 1,972)	1,358 (464 - 2,089)	1,345 (496 - 2,055)	838 (305-1,561)	899 (326 - 1,833)	936 (263 - 1,896)	974 (298 - 1,935)	1,310 (467 - 2,059)	1,360 (546 - 2,093)
Age at index (years), Median (IQR)	2 (1 - 2)	4 (3 - 5)	8 (7 - 10)	14 (13- 16)	44 (31 - 54)	74 (70-80)	1 (1 - 2)	4 (3 - 5)	8 (7 - 10)	15 (13 - 16)	43 (31-54)	73 (69 - 79)
Age range (years)	0 - 2	3 - 5	6 - 11	12 - 17	18 - 65	66 - 98	0 - 2	3 - 5	6 - 11	12 - 17	18 -65	66 - 103
Sex, n (%)												
• Female	2,279 (46)	4,042 (49)	5,555 (50)	2,813 (50)	25,118 (55)	5,383 (58)	344 (46)	609 (53)	737 (53)	594 (54)	4,314 (61)	966 (61)
• Male	2,699 (54)	4,241 (51)	5,590 (50)	2,811 (50)	20,162 (45)	3,954 (42)	397 (54)	541 (47)	644 (47)	507 (46)	2,738 (39)	629 (39)
• Missing	-	-	<5	<5	37 (0)	10 (0)	-	-				

LPD = Longitudinal Patient Database; DA = Disease Analyzer; IQR = interquartile range.

*Number of records refers to number of treatment episodes.

**Number of individuals = number of unique individuals per age group; some individuals meet criteria for multiple age groups within the dataset and may have participated with treatment episodes in more than one age group.

***Future observation refers to the available follow-up data after the index date. The end of follow-up is defined as the earliest of following events: loss to follow-up, end of data availability, death, or end of study period (31st December 2023), whichever came first.

12.1.3 Main results

12.1.3.1 Frequency of prespecified conditions by age group

Table 11 displays the frequency of the pre-specified conditions, used as proxy for indication, in individuals with a prescription of Pelargonii radix product in a window around the index date (7 days before until 7 after index date; index date is time of the first prescription for each new treatment episode), stratified by age group and database.

IQVIA DA Germany

In the 0 to 2 years age group, the most frequent pre-specified condition was upper respiratory infection, occurring in 31% of this very young population. Acute bronchitis was noted in 22% of treatment initiators, common cold in 9%, cough in 6%, while sinusitis and tonsillitis were observed in 2% and 3%, respectively.

For the 3 to 5 years age group, upper respiratory infection remained the most common condition, occurring in 34% of treatment initiators. Acute bronchitis was observed in 18%, and common cold in 8%. Cough was recorded in 8%, while sinusitis and tonsillitis were less frequent, at 3% and 5%, respectively.

In the 6 to 11 years age group, the pattern persisted with upper respiratory infection being the predominant condition at 36%. Acute bronchitis was noted in 14%, with common cold in 8%. Cough was present in 8%, and both sinusitis and tonsillitis were recorded in 3% and 6% of treatment initiators, respectively.

Among individuals aged 12 to 17 years, upper respiratory infection continued to be the most prevalent, affecting 35%. Common cold was reported in 7%, acute bronchitis and cough were observed in 9% and 5% respectively, while sinusitis and tonsillitis occurred in 5% and 6% respectively.

For the adult age groups, upper respiratory infection was observed in 41% of treatment initiators aged 18 to 65 years and in 24% of those over 65. Common cold was recorded in 5% of treatment initiators in the 18 to 65 years age group and 3% for those over 65. Acute bronchitis affected 12% treatment initiators aged 18 to 65 and 14% of those over 65 years. Cough was reported in 4% of treatment initiators aged 18 to 65 and 5% of those over 65 years, while sinusitis was observed in 7% and 4% of the respective age groups.

IQVIA LPD Belgium

In the 0 to 2 years age group, the most frequent condition was upper respiratory infection, reported in 63% of treatment initiators. The common cold was notably more prevalent in this group compared to other conditions, affecting 50%. Cough was observed in 13% and acute bronchitis in 6%. Sinusitis and tonsillitis were less common, at 5% and 1%, respectively.

For the 3 to 5 years age group, upper respiratory infection was the most frequent condition at 63%. Common cold was observed in 53%, cough was noted in 14%, while acute bronchitis was less common, affecting only 3%. Sinusitis and tonsillitis were recorded in 3% and 1%, respectively.

In the 6 to 11 years age group, upper respiratory infection continued to be the most frequent, affecting 56%. Common cold was reported in 44%, cough occurred in 10%, acute bronchitis in 3% while both sinusitis and tonsillitis were observed in 2% and 1%, respectively.

Among individuals aged 12 to 17 years, upper respiratory infection remained the most common, occurring in 45%. The common cold was reported in 36%, while acute bronchitis and cough were seen in 3% and 14%, respectively. Sinusitis and tonsillitis were recorded in 7% and 1% of treatment initiators.

For the adult age groups, upper respiratory infection was prevalent in 42% of treatment initiators aged 18 to 65 years and in 44% of those over 65 years. Common cold was reported in 30% of treatment initiators aged 18 to 65 and 31% for those over 65 years. Acute bronchitis occurred in 5% treatment initiators aged 18 to 65 and 7% of those over 65 years. Cough was present in 13% in treatment initiators aged 18 to 65 and 16% in those over 65 years, with sinusitis observed in 11% and 9% of the respective age groups.

Nasopharyngitis and acute rhinosinusitis were not detected in treatment initiators within the specified measurement window in both databases.

Table 11. Frequency of pre-specified comorbidities in individuals being prescribed Pelargonii radix products in a window around index date (7 days before until 7 days after index date), stratified by age group, per database.

	IQVIA_DA_Germany						IQVIA_LPD_Belgium					
	0 - 2	3 -5	6 - 11	12 -17	18 - 65	>65	0 - 2	3 -5	6 - 11	12 - 17	18 - 65	>65
Number records*	4,978	8,283	11,147	5,626	45,317	9,347	741	1,150	1,381	1,101	7,052	1,595
Number individuals**	3,487	5,327	6,783	4,218	34,021	6,993	638	914	1,091	894	5,646	1,336
Conditions												
• Acute bronchitis, n (%)	1,117 (22)	1,532 (18)	1,508 (14)	489 (9)	5,217 (12)	1,272 (14)	43 (6)	34 (3)	38 (3)	37 (3)	324 (5)	113 (7)
• Acute rhinosinusitis, n (%)	0	0	0	0	0	0	0	0	0	0	0	0
• Common cold, n (%)	466 (9)	688 (8)	858 (8)	371 (7)	2,417 (5)	292 (3)	373 (50)	604 (53)	612 (44)	391 (36)	2,134 (30)	495 (31)
• Cough, n (%)	305 (6)	688 (8)	903 (8)	259 (5)	1,923 (4)	506 (5)	94 (13)	157 (14)	143 (10)	149 (14)	892 (13)	254 (16)
• Nasopharyngitis, n (%)	0	0	0	0	0	0	0	0	0	0	0	0
• Sinusitis, n (%)	85 (2)	208 (3)	343 (3)	282 (5)	3,260 (7)	409 (4)	39 (5)	29 (3)	34 (2)	79 (7)	769 (11)	139 (9)
• Tonsillitis, n (%)	173 (3)	392 (5)	721 (6)	344 (6)	1,192 (3)	78 (1)	9 (1)	16 (1)	19 (1)	13 (1)	49 (1)	5 (0)
• Upper respiratory infection, n (%)	1,540 (31)	2,851 (34)	3,987 (36)	1,994 (35)	18,514 (41)	2,280 (24)	470 (63)	727 (63)	780 (56)	495 (45)	2,955 (42)	694 (44)

LPD = Longitudinal Patient Database; DA = Disease Analyzer; IQR = interquartile range.
*Number of records refer to number of treatment episodes.
**Number of individuals = number of unique individuals.

12.1.3.2 Frequency of top conditions by age group

Table 12 presents the frequency of top conditions in individuals being prescribed Pelargonii radix products. These conditions were disease codes rather than aggregated codes for a specific pre-specified condition of interest. The results are shown within a specified window around the index date (7 days before until 7 after index date (the time of first prescription of each new treatment episode)). The results are stratified by age groups and databases 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/P3C1002DrugUtilisationPelargonii/). Notably, respiratory tract infections emerged as the predominant conditions across different age groups and databases, consistent with the study's focus on specified pre-specified conditions.

IQVIA DA Germany

In the 0 to 2 years age group, the most frequent conditions were acute bronchitis (23%), acute respiratory infection (22%) and disorder of respiratory system (10%). Notably, additional conditions emerged within the top 10 included common cold (9%), otitis media (8%), viral disease (8%), cough (6%), bronchitis (6%) and fever (6%).

For the 3 to 5 years age group, acute bronchitis (19%) and acute respiratory infection (27%) were the most prevalent conditions. Other notable conditions included cough and common cold, each observed in 8% of cases, with viral diseases and bronchitis affecting 6% of individuals each.

In the 6 to 11 years age group, acute upper respiratory infection (28%) and acute bronchitis (14%) were the most commonly observed conditions. Cough and common cold each occurred in 8% of treatment initiators, while acute tonsillitis and viral diseases were less common, noted in 6% of treatment initiators.

Among individuals aged 12 to 17 years, acute upper respiratory infection (27%) continued to be the leading condition. Acute bronchitis was observed in 9%, with acute pharyngitis and common cold each appearing in 7% treatment initiators. Acute tonsillitis was noted in 6%, while bronchitis and cough were reported in about 5% of treatment initiators.

For adults aged 18 to 65, acute upper respiratory infection was the most frequent condition (34%). Acute bronchitis was observed in 12%, with various illnesses at 11%. Bronchitis and acute pharyngitis were noted in 8% and 7%, respectively. Other conditions such as common cold and viral diseases had frequencies of 5%.

In the over 65 years age group, acute upper respiratory infection was the most common condition (20%), followed by acute bronchitis (14%) and essential hypertension (9%). Bronchitis and cough were less frequent but still notable, observed in 8% and 6% treatment initiators, respectively.

IQVIA LPD Belgium

In the 0 to 2 years age group, the most frequent condition was common cold (50%), followed by acute upper respiratory infection (17%) and cough (13%). Other notable conditions included viral disease (11%), acute pharyngitis (7%), and acute suppurative otitis media (7%).

For the 3 to 5 years age group, common cold (53%) was the most frequent condition. Cough and acute upper respiratory infection were observed in 14% and 13% of treatment initiators, respectively. Viral diseases affected 11% of treatment initiators, while acute pharyngitis was noted in 8%. Conditions such as influenza (7%), disorder of the nasal cavity (5%), and acute suppurative otitis media (4%) were also notable but less frequent.

In the 6 to 11 years age group, common cold (44%) was the most frequent condition. Acute pharyngitis and acute upper respiratory infection were observed in 14% and 13% of treatment initiators, respectively. Viral diseases were noted in 12% of treatment initiators, while influenza and cough were each reported in 11% and 10% of treatment initiators, respectively. Conditions such as acute tracheitis, disorders of the nasal cavity, and allergic rhinitis were less common.

For individuals aged 12 to 17 years, common cold (36%) was also the most frequent condition. Acute pharyngitis and viral diseases were observed in 17% and 16% of cases, respectively. Influenza and cough were noted with frequencies of 16% and 14%, respectively. Acute upper respiratory infection was observed in 11% of treatment initiators, while other conditions such as acute sinusitis, allergic rhinitis, and acute bronchitis were less frequent (<6%).

In the 18 to 65 years age group, common cold remained the most frequent condition (30%). Viral diseases and influenza were observed in 16% of treatment initiators each, while acute pharyngitis was noted in 15% of treatment initiators. Acute upper respiratory infection and cough were each present in 13% of cases, with acute sinusitis observed in 10%. Other conditions such as essential hypertension and allergic rhinitis were less common.

In the over 65 years age group, common cold was again the most frequent condition (31%). Essential hypertension and cough were observed in 22% and 16% of treatment initiators, respectively. Acute upper respiratory infection and acute pharyngitis were each noted in 14% of cases, while other conditions such as viral diseases, influenza, and acute sinusitis were present but less frequent.

Table 12. Frequency of top comorbidities in individuals being prescribed Pelargonii radix products in a window around index date (7 days before until 7 days after index date), stratified by age group, per database.

IQVIA_DA_Germany

0 - 2 (N = 4,978)		3 -5 (N = 8,283)		6 - 11 (N = 11,147)		12 -17 (N = 5,626)		18 – 65 (N = 45,317)		>65 (N = 9,347)	
Comorbidities	n (%)	Comorbidities	n (%)	Comorbidities	n (%)	Comorbidities	n (%)	Comorbidities	n (%)	Comorbidities	n (%)
Acute bronchitis	1,122 (23%)	Acute upper respiratory infection	2,211 (27)	Acute upper respiratory infection	3,158 (28)	Acute upper respiratory infection	1,542 (27)	Acute upper respiratory infection	15,547 (34)	Acute upper respiratory infection	1,911 (20)
Acute upper respiratory infection	1,101 (22%)	Acute bronchitis	1,532 (19)	Acute bronchitis	1,515 (14)	Acute bronchitis	482 (9)	Acute bronchitis	5,239 (12)	Acute bronchitis	1,278 (14)
Disorder of respiratory system	518 (10%)	Cough	698 (8)	Cough	922 (8)	Acute pharyngitis	414 (7)	Illness	4,876 (11)	Essential hypertension	871 (9)
Common cold	467 (9%)	Common cold	692 (8)	Common cold	865 (8)	Common cold	375 (7)	Bronchitis	3,484 (8)	Bronchitis	756 (8)
Otitis media	397 (8%)	Viral disease	515 (6)	Acute tonsillitis	698 (6)	Acute tonsillitis	333 (6)	Acute pharyngitis	3,234 (7)	Cough	516 (6)
Viral disease	376 (8%)	Bronchitis	501 (6)	Viral disease	658 (6)	Bronchitis	276 (5)	Common cold	2,429 (5)	Acute pharyngitis	355 (4)
Cough	313 (6%)	Otitis media	430 (5)	Bronchitis	597 (5)	Cough	260 (5)	Viral disease	2,111 (5)	Viral disease	335 (4)
Bronchitis	308 (6%)	Disorder of respiratory system	423 (5)	Acute pharyngitis	460 (4)	Viral disease	239 (4)	Cough	1,968 (4)	Common cold	295 (3)
Disorder due to infection	299 (6%)	Disorder due to infection	398 (5)	Disorder due to infection	444 (4)	Illness	234 (4)	Disorder due to infection	1,474 (3)	Disorder due to infection	244 (3)
Fever	277 (6%)	Acute tonsillitis	372 (4)	Acute laryngitis	432 (4)	Acute laryngitis	166 (3)	Respiratory tract infection	1,276 (3)	Illness	233 (3)

IQVIA LPD Belgium

0 - 2 (n = 741)		3 -5 **(N = 1,150)**		6 - 11 **(N = 1,381)**		12 -17 **(N = 1,101)**		18 - 65 **(N = 7,052)**		>65 **(N = 1,595)**	
Comorbidities	n (%)	Comorbidities	n (%)	Comorbidities	n (%)	Comorbidities	n (%)	Comorbidities	n (%)	Comorbidities	n (%)
Common cold	373 (50)	Common cold	604 (53)	Common cold	612 (44)	Common cold	392 (36)	Common cold	2,140 (30)	Common cold	495 (31)
Acute upper respiratory infection	123 (17)	Cough	160 (14)	Acute pharyngitis	193 (14)	Acute pharyngitis	185 (17)	Viral disease	1,107 (16)	Essential hypertension	358 (22)
Cough	95 (13)	Acute upper respiratory infection	144 (13)	Acute upper respiratory infection	186 (13)	Viral disease	178 (16)	Influenza	1,097 (16)	Cough	258 (16)
Viral disease	81 (11)	Viral disease	126 (11)	Viral disease	169 (12)	Influenza	172 (16)	Acute pharyngitis	1,036 (15)	Acute upper respiratory infection	225 (14)
Acute pharyngitis	55 (7)	Acute pharyngitis	97 (8)	Influenza	149 (11)	Cough	149 (14)	Acute upper respiratory infection	929 (13)	Acute pharyngitis	224 (14)
Acute suppurative otitis media	53 (7)	Influenza	77 (7)	Cough	143 (10)	Acute upper respiratory infection	120 (11)	Cough	908 (13)	Viral disease	208 (13)
Acute bronchitis	43 (6)	Acute tracheitis	71 (6)	Acute tracheitis	79 (6)	Acute sinusitis	71 (6)	Acute sinusitis	703 (10)	Pure hypercholesterolemia	162 (10)
Acute tracheitis	39 (5)	Disorder of nasal cavity	61 (5)	Disorder of nasal cavity	42 (3)	Allergic rhinitis	49 (4)	Essential hypertension	405 (6)	Influenza	151 (9)
Acute sinusitis	37 (5)	Acute suppurative otitis media	41 (4)	Allergic rhinitis	40 (3)	Acute bronchitis	38 (3)	Acute bronchitis	336 (5)	Disorders of initiating and maintaining sleep	126 (8)
Disorder of nasal cavity	36 (5)	Acute bronchitis	36 (3)	Acute bronchitis	38 (3)	Acute tracheitis	32 (3)	Allergic rhinitis	250 (4)	Acute sinusitis	124 (8)

LPD = Longitudinal Patient Database; DA = Disease Analyzer;

12.1.3.3 Dose/strength, duration, quantity and number of prescriptions

The initial daily dose and duration of use were originally intended to be presented, but following OMOP CDM conventions, several assumptions and imputations were made regarding calculation of dose and treatment duration for Pelargonii radix products. As a result, the data for these variables were not plausible. Therefore, duration of the treatment episode and dose at treatment initiation with Pelargonii radix products were excluded from the final analyses. Instead, the frequency of use and the type of Pelargonii radix products used (formulation and strength) were presented, stratified by age groups, along with the initial quantity of product and number of exposures. This decision is detailed in section 9.9.8 Deviations from protocol.

Table 13 provides the frequency of different Pelargonii radix product types, including details on strength, and formulation, stratified by age group and database. Notably, the Pelargonii radix product types listed in **Table 13** may correspond to multiple Pelargonii radix products that share the same strength, volume and pharmaceutical formulation.

In IQVIA DA Germany, in the age group of 0 to 2 years, the most commonly used product is the 100 ML Pelargonium sidoides root extract 2.67 MG/ML oral solution, accounting for 86.7% of usage. Other oral solutions, available in volumes of 20 ML, 50 ML and 100 ML of 800 MG/ML, were used significantly less frequently. Similarly, in children aged 3 to 5 years, the 100 ML 2.67 MG/ML oral solution remained predominant choice, with 78.5% usage. Other oral solutions of 800 MG/ML in volumes of 20 ML, 50 ML and 100 ML were also used, though to a lesser extent. Among children aged 6 to 11 years, the 100 ML 2.67 MG/ML oral solution continued to be the most used product at 67.2%, followed by the 20 ML 800 MG/ML oral solution at 14.2%. There was a noticeable increase in the variety of products used, including the introduction of oral tablets. In the age group of 12 to 17 years, the 20 ML Pelargonium sidoides root extract 800 MG/ML oral solution became the most used product at 33%, with the 20 MG oral tablet also being significant at 20.0%. The usage of the 100 ML 2.67 MG/ML oral solution dropped to 17.1%. For adults aged 18 to 65 years, the 20 ML solution (800 MG/ML) was the leading product, with 41.2% usage. The 20 MG oral tablet followed with 27.6% and 50 ML 800 MG/ML oral solution followed with 15.9%. In the age group over 65 years, the 20 ML oral solution (800 MG/ML) was the most commonly used product at 33.5%. The 50 ML solution of the same strength and the 20 MG oral tablets were also frequently used at 21.8% and 20.2% respectively.

In IQVIA LPD Belgium, for children aged 0 to 2 years, the usage was exclusively the 100 ML Pelargonium sidoides root extract 2.67 MG/ML oral solution. In the age group of 3 to 5 years, the same product remained the sole product used, with 100% usage. Among children aged 6 to 11 years, the 100 ML Pelargonium sidoides root extract 2.67 MG/ML oral solution continued to be the predominant product, accounting for 89.1% of usage. The 20 MG oral tablet was also used by 10.6% of treatment initiators in this group. In the age group of 12 to 17 years, the 20 MG oral tablet became the most used product, with 76.2% usage. The 100 ML Pelargonium sidoides root extract 2.67 MG/ML oral solution usage dropped to 18.4%. For adults aged 18 to 65 years, the 20 MG oral tablet dominated usage at 90.8%. The 100 ML oral solution (2.67 MG/ML) was used by 4.5% of this group. In the age group over 65 years, the 20 MG oral tablet remained highly used, with 89.0% usage. The 100 ML oral solution (2.67 MG/ML) accounted for 6.0% of usage.

Table 14 provides the detailed information on initial quantity of product and number of prescriptions for Pelargonii radix per treatment episode, stratified by age groups and databases.

In IQVIA DA Germany, for age groups 0 to 2 years, 3 to 5 years and 6 to 11 years, median initial quantity was 1 bottle per prescription. For age groups 12 to 17 years, 18 to 65 years and >65 years, median initial

quantity was also 1 bottle per prescription. However, since oral tables were also used in these age group (**Table 13**), the interquartile range for initial quantity extends from 1 bottle to 15 oral tablets. In IQVIA LPD Belgium, data on the initial quantity for oral solutions was missing for ages below 6 years. For the age groups 6 to 11 years, 12 to 17 years, 18 to 65 years and above 65 years, median initial quantity was reported as 21 tablets per prescription.

In terms of number of prescriptions for Pelargonii radix per treatment episode, the median number of prescriptions across age groups in both databases was consistently 1. However, there were notable differences in the maximum number of prescriptions recorded.

In IQVIA DA Germany, for younger age groups, such as 0 to 2 years, 3 to 5 years, and 6 to 11 years, the maximum number of prescriptions ranged from 5 to 6. In contrast, in older age groups, particularly adults aged 18 to 65 and those over 65 years, the maximum number of prescriptions was higher. In IQVIA LPD Belgium, the maximum number of prescriptions per treatment episode was relatively low, ranging from 2 to 3 prescriptions across all age groups.

Table 13. Frequency of use, active ingredient name, strength information and formulation of Pelargonii radix products, stratified by age groups and databases.

IQVIA DA Germany	Product*	Frequency, n (%)
0 to 2		
	100 ML Pelargonium sidoides root extract 2.67 MG/ML Oral Solution	4,315 (86.7%)
	20 ML Pelargonium sidoides root extract 800 MG/ML Oral Solution Box of 1	436 (8.8%)
	100 ML Pelargonium sidoides root extract 800 MG/ML Oral Solution Box of 1**	118 (2.3%)
	50 ML Pelargonium sidoides root extract 800 MG/ML Oral Solution Box of 1	100 (2.0%)
3 to 5		
	100 ML Pelargonium sidoides root extract 2.67 MG/ML Oral Solution	6,502 (78.5%)
	20 ML Pelargonium sidoides root extract 800 MG/ML Oral Solution Box of 1	970 (11.7%)
	100 ML Pelargonium sidoides root extract 800 MG/ML Oral Solution Box of 1**	412 (4.9%)
	50 ML Pelargonium sidoides root extract 800 MG/ML Oral Solution Box of 1**	345 (4.1%)
	Pelargonium sidoides root extract 20 MG Oral Tablet Box of 60	<5
	Pelargonium sidoides root extract 20 MG Oral Tablet Box of 15	<5
	Pelargonium sidoides root extract 20 MG Oral Tablet Box of 30	<5
6 to 11		
	100 ML Pelargonium sidoides root extract 2.67 MG/ML Oral Solution	7,489 (67.2%)
	20 ML Pelargonium sidoides root extract 800 MG/ML Oral Solution Box of 1	1,582 (14.2%)
	100 ML Pelargonium sidoides root extract 800 MG/ML Oral Solution Box of 1	945 (8.5%)
	50 ML Pelargonium sidoides root extract 800 MG/ML Oral Solution Box of 1	935 (8.4%)
	Pelargonium sidoides root extract 20 MG Oral Tablet Box of 15	74 (0.7%)

IQVIA DA Germany	Product*	Frequency, n (%)
	Pelargonium sidoides root extract 20 MG Oral Tablet Box of 30	52 (0.5%)
	Pelargonium sidoides root extract 20 MG Oral Tablet Box of 60	9 (0.1%)
	50 ML Pelargonium sidoides root extract 824 MG/ML Oral Solution Box of 1	<5
	20 ML Pelargonium sidoides root extract 824 MG/ML Oral Solution Box of 1	<5
12 to 17		
	20 ML Pelargonium sidoides root extract 800 MG/ML Oral Solution Box of 1	1,856 (33%)
	Pelargonium sidoides root extract 20 MG Oral Tablet Box of 15	1,127 (20.0%)
	100 ML Pelargonium sidoides root extract 2.67 MG/ML Oral Solution	961 (17.1%)
	50 ML Pelargonium sidoides root extract 800 MG/ML Oral Solution Box of 1	721 (12.8%)
	100 ML Pelargonium sidoides root extract 800 MG/ML Oral Solution Box of 1	518 (9.2%)
	Pelargonium sidoides root extract 20 MG Oral Tablet Box of 30	373 (6.6%)
	Pelargonium sidoides root extract 20 MG Oral Tablet Box of 60	54 (1.0%)
	50 ML Pelargonium sidoides root extract 824 MG/ML Oral Solution Box of 1	<5
	20 ML Pelargonium sidoides root extract 824 MG/ML Oral Solution Box of 1	<5
	20 ML Pelargonium sidoides root extract 40 MG/ML Oral Solution Box of 1	<5
18 to 65		
	20 ML Pelargonium sidoides root extract 800 MG/ML Oral Solution Box of 1	18,658 (41.2%)
	Pelargonium sidoides root extract 20 MG Oral Tablet Box of 15	12,492 (27.6%)
	50 ML Pelargonium sidoides root extract 800 MG/ML Oral Solution Box of 1	7,188 (15.9%)
	Pelargonium sidoides root extract 20 MG Oral Tablet Box of 30	3,069 (6.8%)
	100 ML Pelargonium sidoides root extract 800 MG/ML Oral Solution Box of 1	2,939 (6.5%)

IQVIA DA Germany	Product*	Frequency, n (%)
	Pelargonium sidoides root extract 20 MG Oral Tablet Box of 60	711 (1.6%)
	100 ML Pelargonium sidoides root extract 2.67 MG/ML Oral Solution	78 (0.2%)
	20 ML Pelargonium sidoides root extract 824 MG/ML Oral Solution Box of 1	71 (0.2%)
	50 ML Pelargonium sidoides root extract 824 MG/ML Oral Solution Box of 1**	51 (0.1%)
	100 ML Pelargonium sidoides root extract 824 MG/ML Oral Solution Box of 1	<5
>65		
	20 ML Pelargonium sidoides root extract 800 MG/ML Oral Solution Box of 1	3,126 (33.5%)
	50 ML Pelargonium sidoides root extract 800 MG/ML Oral Solution Box of 1	2,039 (21.8%)
	Pelargonium sidoides root extract 20 MG Oral Tablet Box of 15	1,890 (20.2%)
	100 ML Pelargonium sidoides root extract 800 MG/ML Oral Solution Box of 1	1,309 (14.0%)
	Pelargonium sidoides root extract 20 MG Oral Tablet Box of 30	635 (6.8%)
	Pelargonium sidoides root extract 20 MG Oral Tablet Box of 60	298 (3.2%)
	100 ML Pelargonium sidoides root extract 2.67 MG/ML Oral Solution	15 (0.2%)
	20 ML Pelargonium sidoides root extract 824 MG/ML Oral Solution Box of 1**	15 (0.1%)
	50 ML Pelargonium sidoides root extract 824 MG/ML Oral Solution Box of 1**	15 (0.1%)
	100 ML Pelargonium sidoides root extract 824 MG/ML Oral Solution Box of 1	<5

IQVIA LPD Belgium	Product	Frequency
0 to 2		
	100 ML Pelargonium sidoides root extract 2.67 MG/ML Oral Solution	740 (99.9%)

IQVIA LPD Belgium	Product	Frequency
3 to 5		
	100 ML Pelargonium sidoides root extract 2.67 MG/ML Oral Solution	1,150 (100%)
6 to 11		
	100 ML Pelargonium sidoides root extract 2.67 MG/ML Oral Solution	1,231 (89.1%)
	Pelargonium sidoides root extract 20 MG Oral Tablet Box of 21	146 (10.6%)
	Pelargonium sidoides root extract 20 MG Oral Tablet Box of 42	6 (0.4%)
12 to 17		
	Pelargonium sidoides root extract 20 MG Oral Tablet Box of 21	839 (76.2%)
	100 ML Pelargonium sidoides root extract 2.67 MG/ML Oral Solution	203 (18.4%)
	Pelargonium sidoides root extract 20 MG Oral Tablet Box of 42	51 (4.6%)
	Pelargonium sidoides root extract 20 MG Oral Tablet Box of 63	6 (0.5%)
18 to 65		
	Pelargonium sidoides root extract 20 MG Oral Tablet Box of 21	6,402 (90.8%)
	100 ML Pelargonium sidoides root extract 2.67 MG/ML Oral Solution	317 (4.5%)
	Pelargonium sidoides root extract 20 MG Oral Tablet Box of 42	280 (4.0%)
	Pelargonium sidoides root extract 20 MG Oral Tablet Box of 63	42 (0.6%)
	Pelargonium sidoides root extract 20 MG Oral Tablet	19 (0.3%)
>65		
	Pelargonium sidoides root extract 20 MG Oral Tablet Box of 21	1,420 (89.0%)
	100 ML Pelargonium sidoides root extract 2.67 MG/ML Oral Solution	96 (6.0%)
	Pelargonium sidoides root extract 20 MG Oral Tablet Box of 42	60 (3.8%)

IQVIA LPD Belgium	Product	Frequency
	Pelargonium sidoides root extract 20 MG Oral Tablet Box of 63	16 (1%)
	Pelargonium sidoides root extract 20 MG Oral Tablet	<5

LPD = Longitudinal Patient Database; DA = Disease Analyzer;

*The Pelargonii radix product names listed in the "Product" column of Table 13 may represent multiple Pelargonii radix products that share the same strength, volume, and pharmaceutical formulation.

**Counts below 5 for Pelargonii radix products with the same strength, volume, and pharmaceutical formulation were replaced with a mean value of 3 to maintain data integrity and enable meaningful statistical reporting.

Table 14. Initial quantity of product and number of prescriptions of the drug of interest per treatment episode, stratified by age groups and databases.

	IQVIA_DA_Germany						IQVIA_LPD_Belgium					
	0 - 2	3-5	6-11	12-17	18 - 65	>65	0 - 2	3-5	6-11	12-17	18 - 65	>65
Number records*	4,978	8,283	11,147	5,626	45,317	9,347	741	1,15	1,381	1,101	7,052	1,595
Number individuals**	3,487	5,327	6,783	4,218	34,021	6,993	638	914	1,091	894	5,646	1,336
Initial quantity***, median [q25 – q75]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 15]	1 [1 - 15]	1 [1 - 15]	-	-	21 [21 – 21]	21 [21 – 21]	21 [21 – 21]	21 [21 – 21]
Number_exposures****, median [min; q25 - q75; max]	1 [1; 1 - 1; 6]	1 [1; 1 - 1; 5]	1 [1; 1 - 1; 6]	1 [1; 1 - 1; 3]	1 [1; 1 - 1; 9]	1 [1; 1 - 1; 16]	1 [1; 1 - 1; 3]	1 [1; 1 - 1; 2]	1 [1; 1 - 1; 2]	1 [1; 1 - 1; 2]	1 [1; 1 - 1; 2]	1 [1; 1 - 1; 3]

LPD = Longitudinal Patient Database; DA = Disease Analyzer; min = minimum; max = maximum; IQR = interquartile range;

*Number of records refer to number of treatment episodes.

**Number of individuals = number of unique individuals.

***Initial quantity refers to number of bottles (oral solution) or number of tablets. If the number above 5 is displayed that would indicate number of tablets.

****Number of prescriptions of selected pre-specified medication of interest per treatment episode;

12.2 Population-level drug utilisation

12.2.1 Participants

Table 15 shows the number of individuals in each age group included for the estimation of the incidence rates of prescriptions of Pelargonii radix products (population-level utilisation study of Pelargonii radix) per database for each calendar year during the study period. All results of the population-level utilisation of Pelargonii radix, 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/P3C1002DrugUtilisationPelargonii/.

Table 15. Number of individuals in each group of source population, per database.

	IQVIA DA Germany						IQVIA LPD Belgium					
Year	0-2	3-5	6-11	12-17	18-65	>65	0-2	3-5	6-11	12-17	18-65	>65
2014	143,706	189,398	374,888	394,362	4,701,175	1,928,929	6,713	4,887	6,739	6,973	116,497	51,280
2015	192,791	196,709	387,387	410,093	4,960,545	2,082,278	9,986	11,363	18,691	18,781	222,150	75,457
2016	226,998	201,942	394,144	418,191	5,158,930	2,211,829	12,905	14,364	24,695	24,522	251,298	81,382
2017	242,252	217,627	411,686	435,064	5,439,733	2,373,896	12,674	14,779	27,184	26,806	263,835	85,677
2018	247,555	230,502	421,724	444,782	5,592,207	2,467,018	12,070	14,187	27,345	27,909	267,745	88,613
2019	246,397	232,128	414,241	436,295	5,525,594	2,475,942	11,604	13,837	27,087	28,941	271,339	91,158
2020	234,520	229,764	402,259	423,964	5,444,295	2,505,092	10,017	12,993	26,171	30,058	274,354	93,377
2021	230,826	219,596	379,153	399,482	5,173,452	2,432,850	10,029	12,025	24,366	30,362	272,666	94,243
2022	217,084	199,673	341,688	344,937	4,456,326	2,183,648	9,220	10,389	21,362	26,372	257,530	93,348
2023	168,674	161,209	255,519	226,348	3,052,732	1,640,064	7,033	6,937	13,104	17,892	180,627	74,763

LPD = Longitudinal Patient Database; DA = Disease Analyzer;

12.2.2 Descriptive data and main results

Figure 4 and **Figure 5** show incidence rates of Pelargonii radix prescription, measured as the number of treatment initiations per 1,000 person-years (PY), broken down by age groups and databases across different calendar years.

In IQVIA DA Germany, a distinct trend emerged when comparing incidence rates across different age groups. Younger age groups (0 to 2 and 3 to 5 years of age) exhibited consistently higher incidence rates than older age groups (6 to 11, 12 to 17, 18 to 65, and over 65 years of age) (**Figure 4**). The highest incidence of Pelargonii radix use in IQVIA DA Germany was observed in the 3 to 5 age group (**Figure 5**). In 2014, the incidence rate in this age group was 7 initiated treatments/1,000 PY. This rate remained relatively stable over time until 2019, when it decreased slightly to 4 initiated treatments/1,000 PY in 2021, before coming back to initial 7/1,000 PY in 2023. For 0 to 2 years age group, incidence rate ranged from 6 initiated treatments/1,000 PY in 2014 to 3/1,000 PY in 2023, indicating a slight decline over time. The incidence rate for the 6 to 11 years age group remained steady at 4/1,000 PY, while the 12 to 17 age group maintained a stable rate at 2/1,000 PY. In adults (18 to 65 and over 65 years age groups), the incidence rate was also low and stable over time.

Similarly, in IQVIA LPD Belgium, higher incidence rates were also observed in younger age groups (0 to 2 and 3 to 5) compared to older age groups (6 to 11, 12 to 17, 18 to 65, and over 65 years of age) (**Figure 4**). The highest incidence of Pelargonii radix use was observed in the 3 to 5 age group (**Figure 5**). This group had the incidence rate of 27/1,000 PY in 2014, which decreased to 11/1,000 PY in 2020 but increased to 24/1,000 PY in 2022. The incidence rate in the 0 to 2 age group ranged from 16/1,000 PY in 2014, fluctuating over time with the lowest recorded at 9/1,000 PY in 2020 and the highest at 18/1,000 PY in 2021 and 2023. For the 6 to 11 age group, the incidence rate decreased from 18/1,000 PY in 2014 to 7/1,000 PY in 2021, followed by an increase to 19/1,000 PY in 2023. In the 12 to 17 age group, the incidence rate declined from 14/1,000 PY in 2014 to 3/1,000 PY in 2020, and then increased to 17/1,000 PY in 2023. In adults (18 to 65 and over 65 age groups), the incidence rate was low and stable over time.

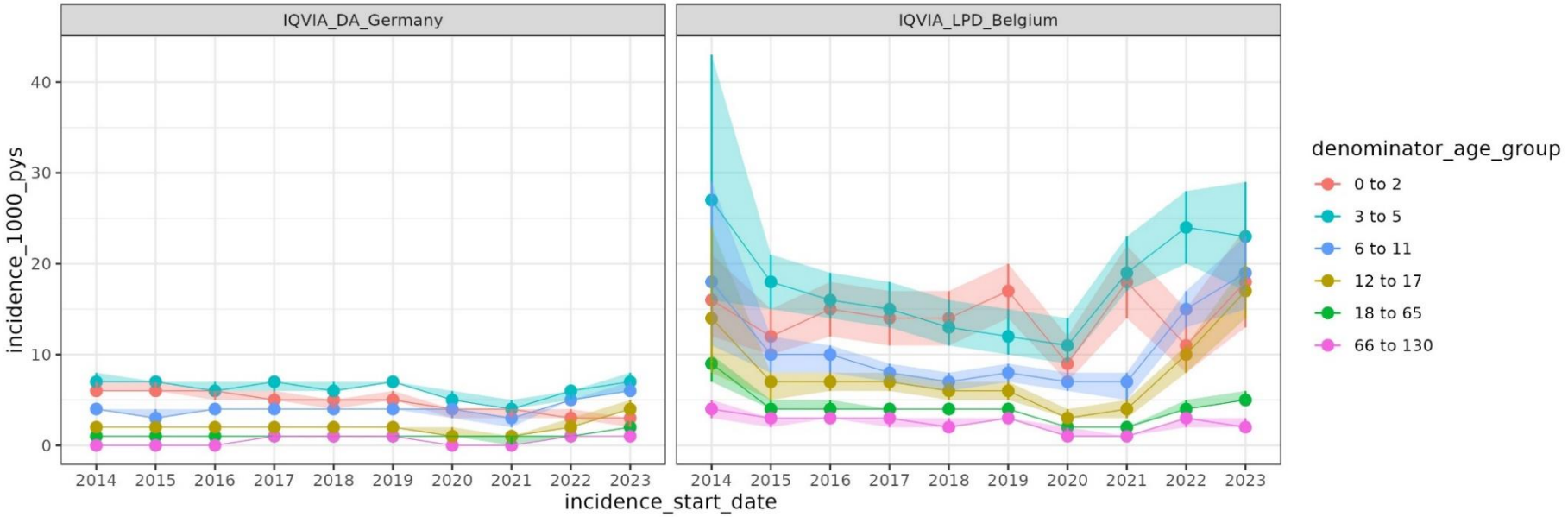


Figure 4. Incidence rate of use of Pelargonii radix products stratified by different age categories, per database.

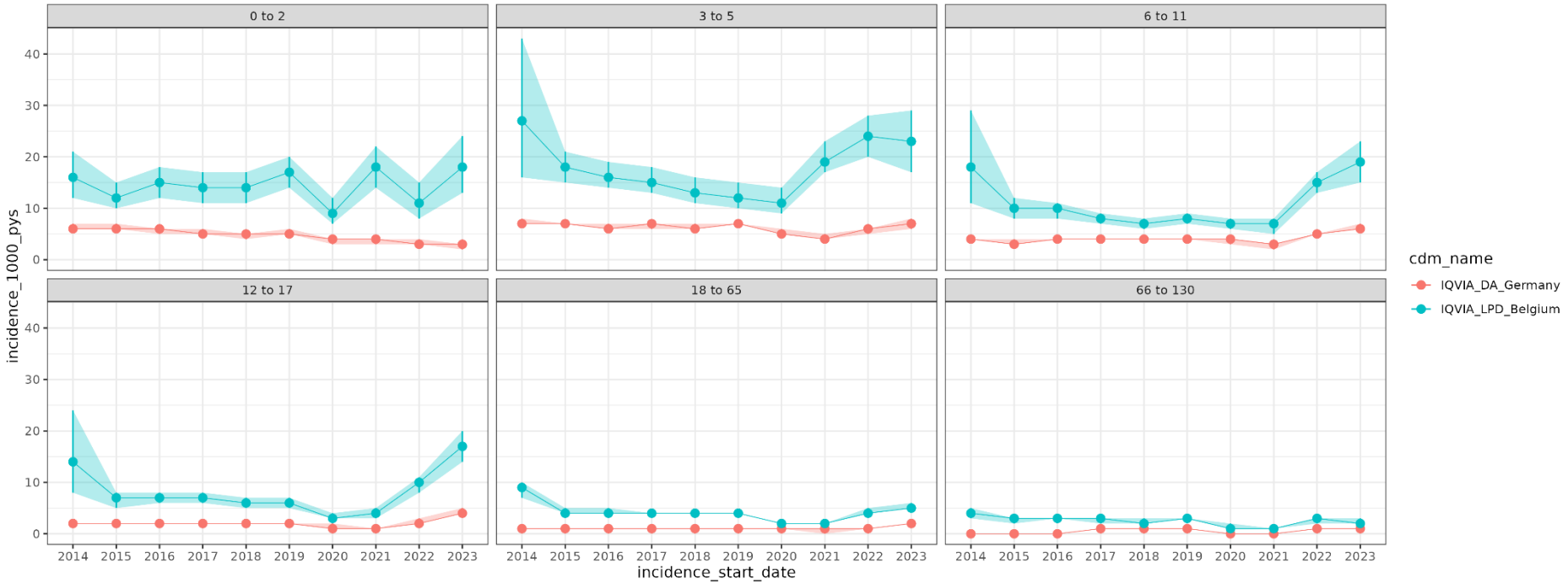


Figure 5. Incidence rate of Pelargonii radix use stratified by database, per age categories.

12.3 Other analysis

None.

13. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Adverse events/adverse reactions will not be collected or analysed as part of this evaluation, The nature of this non-interventional evaluation, through the use of secondary data, does not fulfil the criteria for reporting adverse events, according to module VI, VI,C,1,2,1,2 of the Good Pharmacovigilance Practices (https://www,ema,europa,eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vi-collection-management-submission-reports_en.pdf).

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

14. DISCUSSION

14.1 Key results

Characterisation of the cohort of patients with a prescription of Pelargonii radix - Patient-level drug utilisation

Overall population

In this study, the observed number of patients with new prescriptions of Pelargonii radix products was 57,115 individuals and 84,698 treatment episodes in IQVIA DA Germany and 10,066 individuals and 13,020 treatment episodes in IQVIA LPD Belgium, after applying inclusion criteria. In terms of sex distribution, IQVIA DA Germany showed a balanced or slightly male-dominated younger age group and a higher proportion of females in the older age groups. In IQVIA LPD Belgium, 0 to 2 years age group was male dominated, while the proportion of females was higher in all other age groups (3 to 5, 6 to 11, 12 to 17, 18 to 65 and >65 years age groups).

The frequency of pre-specified condition and top conditions associated with the initiation of Pelargonii radix treatment, as well as frequency and strength of Pelargonii radix products, quantity and number of prescriptions, showed distinct pattern in children and adults.

Children

In IQVIA DA Germany, children in all age groups who initiated treatment with Pelargonii radix products frequently presented with upper respiratory infections as the most common pre-specified condition. Acute bronchitis, common cold, and cough were also observed but varied in frequency, while sinusitis and tonsillitis were less common. The top conditions mirrored these findings, with acute upper respiratory infection and acute bronchitis being predominant. In IQVIA LPD Belgium, children aged 0 to 2 years showed a high prevalence of pre-specified conditions including upper respiratory infections and common cold, with a notable frequency of cough. However, the frequency of these conditions decreased in older child age groups. When analysing top conditions, the common cold was particularly prevalent in the 0 to 5 age group.

The product prescribed most often for children in IQVIA DA Germany was the 100 ML Pelargonium sidoides root extract 2.67 MG/ML oral solution. However, its usage declined with age. The most commonly prescribed products among children 12 to 17 years old were 20 ML 800 MG/ML oral solution and 20 MG oral tablets. Conversely, in IQVIA LPD Belgium, children were exclusively prescribed the 100 ML Pelargonium sidoides root extract 2.67 MG/ML oral solution up to age 11. In the 12-17 age group, the most frequently prescribed product was 20 MG oral tablet. In line with these findings, the median initial quantity of Pelargonii radix products in children in IQVIA DA Germany was generally one, while data for oral solutions in IQVIA LPD Belgium were not available. The median number of prescriptions for Pelargonii radix products per treatment episode in children was consistently one in both databases.

Adults

In IQVIA DA Germany, adult treatment initiators predominantly presented with upper respiratory infections as the most frequent pre-specified condition, with common cold, acute bronchitis, and cough being less prevalent and sinusitis slightly more common among younger adults. Upper respiratory infections were also the most common top condition. In IQVIA LPD Belgium, upper respiratory infections and the common cold were the most frequently observed pre-specified conditions, with upper respiratory infections again being the most common top prevalent condition.

Regarding Pelargonii radix use, the most common Pelargonii radix products prescribed in IQVIA DA Germany were the 20 ML (800 MG/ML) oral solution and 20 MG oral tablets for those aged 18-65 and over 65. In IQVIA LPD Belgium, adults were prescribed the 20 MG oral tablet most often, with minimal use of the 100 ML oral solution. The median initial quantity was one bottle of oral solution in IQVIA DA Germany and 21 tablets in IQVIA LPD Belgium. The median number of prescriptions per treatment episode for adults was consistently one across various age groups in both databases.

Incidence rates of prescriptions of Pelargonii radix - Population-level drug utilisation

The incidence of Pelargonii radix use across age groups and databases over time revealed distinct pattern. Notably, younger age groups, specifically those aged 0 to 2 and 3 to 5, consistently demonstrated higher incidence rates compared to older age groups (6 to 11, 12 to 17, adults aged 18 to 65 and over 65 years) in both IQVIA DA Germany and IQVIA LPD Belgium.

In IQVIA DA Germany, the highest incidence of Pelargonii radix use was observed in the 3 to 5 age group. In 2014, the incidence rate was estimated at 7 initiated treatments/1,000 PY in 2014 and remained relatively stable over time until 2019, when it decreased slightly to 4 initiated treatments/1,000 PY in 2021 before coming back to initial 7/1,000 PY by the end of the study period. The incidence in 0 to 2, 6 to 11 and 12 to 17 age groups remained stable over time.

In IQVIA LPD Belgium, the highest incidence of Pelargonii radix use was also observed in the 3 to 5 age group. The incidence rate was estimated at 27 initiated treatments/1,000 PY in 2014 and showed a decline to 11/1,000 PY in 2020, followed by subsequent increase to 24/1,000 PY in 2022. The 0 to 2 age group experienced fluctuating incidence rates, while the 6 to 11 and 12 to 17 age groups showed both declines at the start of study period and increases in incidence rates over the last few years of study period.

In adults aged 18 to 65 and those over 65, incidence rates remained low and stable over time in both databases.

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

Drug prescriptions: A prescription record did not mean that the patient took the drug. Therefore, assumption of actual use was made.

Characterisation/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 by analysing pre-defined conditions recorded around the date of therapy initiation. As a result, the estimation of potential indications may be incomplete, given that the actual indications were not directly recorded in the data.

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

Mapping: While OMOP provides mappings to established vocabularies like SNOMED CT and RxNorm. Inaccuracies or gaps in these mappings can occur, impacting the accuracy and completeness of data analysis.

The mapping of Pelargonii radix products was performed with a high level of granularity, preserving essential details for each product, such as the active ingredient, strength, volume, and pharmaceutical formulation. However, source brand names were mapped with lower granularity and as such they are not represented in the standardised drug name.

Other limitations: Over the counter use of Pelargonium products was not captured.

Study-specific limitations

The assumptions and imputations required for analysing the dose and treatment duration for Pelargonii radix products using the OMOP CDM framework are necessary for handling missing data and standardising heterogeneous data sources. However, these did not plausibly reflect the real-world use of Pelargonii radix products.

14.3 Interpretation

Evidence from observational studies examining the usage of Pelargonii radix products or profiling the individuals who use them in real-world settings in both adults and paediatric patients is lacking. To our knowledge, there are no observational studies examining the utilisation of Pelargonii radix products or characterisation of the patients who use them in real-world settings. In our study, we specifically examine prescribing pattern of Pelargonii radix products across various age groups, investigating both patient-level characterisation and population-level utilisation.

In the large-scale characterisation of the ten most common conditions within the 7 days before and after the index date, we found that most of the conditions were related to acute upper respiratory tract infections including acute bronchitis and to a lesser extent, common cold in both databases. This is in line with what is expected for the indication of Pelargonii radix use, given that these were also chosen as the prespecified conditions. Pelargonium has been on the market for more than 30 years and is herbal medicinal product for the symptomatic treatment of common cold and acute bronchitis.[1, 10] Furthermore, systematic literature reviews on Pelagonii radix containing products indicate its usage is primarily for managing acute bronchitis and common colds.[2, 3, 12] Young paediatric patients (0-5 years) in particular had higher frequencies of acute respiratory infections including acute bronchitis around the index date.[2, 3, 12]

In the large-scale characterisation of the ten most common conditions for prescribing Pelargonii radix products, other non-respiratory infections identified in paediatric patients were viral disease and otitis media. Studies have been undertaken investigating Pelargonii radix products antibacterial properties, however, its antibacterial activity is significantly inferior to conventional antibiotics [10]. This indicates that despite this, patients may be prescribed Pelargonii radix products for mild symptomatic bacterial and viral (including acute respiratory) infections. Patients in the >65-year age group were also frequently diagnosed with essential hypertension in both data sources, while sleep disorders and pure hypercholesterolaemia were identified for Belgium only. These findings are likely related to the high incidence of these conditions for older adult age groups more generally as frequent comorbidities in this age group and are presumably not indications for Pelargonii radix prescription.

In terms of population-level drug utilisation to describe incidence rates of Pelargonii radix prescribing, we found distinct trend when comparing incidence rates across different groups in IQVIA DA Germany and IQVIA LPD Belgium. In general, paediatric patients and more specifically those in the 0-2 and 3-5-years age groups, exhibited higher incidence of prescription than the older paediatric and adult patients in both databases. Declining usage among adults/adolescents could be attributed to fewer upper respiratory tract infections or lack of health insurance coverage for such products in individuals above 12 years of age in Germany. In addition, this trend may reflect a higher rate of prescription for use for children and potentially more frequent over-the-counter use by adults, possibly due to health insurance coverage for such products in children (at least in Germany), parents preferring to consult a doctor for their children's prescriptions for safety reasons, or needing a sick note attest from a doctor so they can stay home with their sick child. There is RCT evidence supporting the use of products containing Pelargonii radix in young children[7-9]. However, despite our findings of use in young paediatric patients, is important to note that in some EU countries Pelargonii radix products are not recommended for children under the age of 3 years old[1]. However, the lower age limit was set but is not mandatory, meaning some products may still be suitable for children younger than 3 years. Interestingly, individuals aged 0-2 and 3-5-years age initiating treatment with Pelargonii radix, had most frequently a record of an acute respiratory infection or common cold. This indicates that the greater use in these age groups is more likely prescribed for the indication of Pelargonii radix products. There was a notable decrease in use of Pelargonii radix products in the period between 2019 and 2020/2021 across all age groups but particularly in paediatric patients 0-2 years of age in the Belgian data source. The decline in incidence rate between 2019 to 2020/2021 might be due to SARs-CoV-2 pandemic in the same period, which is known to have reduced health care interactions, especially for non-severe indications such as those that Pelargonii radix products might be used for. However, changes in incidence rates in IQVIA DA Germany around 2020 were not pronounced.

Finally, Pelargonii radix products were presented using standardized OMOP terminologies, including standard names and concepts, as part of a structured data processing approach. However, a discrepancy may arise when comparing these standardized names to how the products are represented in the market, where brand names are more commonly recognized by healthcare professionals and consumers. For instance, Umckaloabo, a well-known over the counter remedy for respiratory infections in Germany, is widely used. In standardized terminologies (e.g., RxNorm) for Pelargonii radix, products like Umckaloabo are categorized by their active ingredient rather than their brand name. This can lead to classifications that may not fully reflect how these products are marketed. It is important to acknowledge that in the real-world market, brand-specific products like Umckaloabo dominate the use of Pelargonii radix in Germany. In IQVIA DA Germany, various Umckaloabo products available on the German market are represented by standard concepts based on their active ingredient, strength and volume such as 20 ML, 50 ML and 100 ML Pelargonium sidoides root extract 800 MG/ML oral solution, 100 ML Pelargonium sidoides root extract 2.67 MG/ML oral solution and Pelargonium sidoides root extract 20 MG oral tablet.

14.4 Generalisability

While our study comprised data from 2 EU countries and covers a primary care and outpatient specialist settings, findings from this study are not to be generalised to other countries or databases but only reflect the situation in the specific region and setting covered by the respective database.

14.5 Other information

None.

15. CONCLUSION

This study examined the use of Pelargonii radix products across different age groups in a real-world setting, focusing on both patient-level characterisation and population-level utilisation. At patient-level, patients initiating treatment with Pelargonii radix products are frequently diagnosed with conditions related to acute respiratory infections including bronchitis and common in both children and adults across both databases. Product usage varied by age group and region, with distinct patterns emerging in the types and strengths of products prescribed. At population-level, the incidence of Pelargonii radix prescribing across age groups and over time revealed distinct pattern. The incidence rates of Pelargonii radix products prescribing were consistently higher in younger age groups and remained low and stable in older adults across both databases. Specifically, the observed incidence rates appeared higher in younger children, particularly those aged 3 to 5 and 0 to 2 years compared to older children and adults.

16. REFERENCES

1. EMA, *European Union herbal monograph on Pelargonium sidoides DC and/or Pelargonium reniforme Curt., radix*. 2015.
2. Wopker, P.M., et al., *Complementary and alternative medicine in the treatment of acute bronchitis in children: A systematic review.* Complementary therapies in medicine, 2020. **49**.
3. Kardos, P., et al., *Effects of Pelargonium sidoides extract EPs 7630 on acute cough and quality of life – a meta-analysis of randomized, placebo-controlled trials.* Multidisciplinary Respiratory Medicine, 2022. **17**.
4. Matthys, H. and P. Funk, *EPs 7630 improves acute bronchitic symptoms and shortens time to remission. Results of a randomised, double-blind, placebo-controlled, multicentre trial.* Planta medica, 2008. **74**(6): p. 686-692.
5. Matthys, H., et al., *Efficacy and safety of an extract of Pelargonium sidoides (EPs 7630) in adults with acute bronchitis. A randomised, double-blind, placebo-controlled trial.* Phytomedicine : international journal of phytotherapy and phytopharmacology, 2003. **10 Suppl 4**(SUPPL. 4): p. 7-17.
6. Chuchalin, A.G., B. Berman, and W. Lehmacher, *Treatment of acute bronchitis in adults with a pelargonium sidoides preparation (EPs 7630): a randomized, double-blind, placebo-controlled trial.* Explore (New York, N.Y.), 2005. **1**(6): p. 437-445.
7. Kamin, W., et al., *Efficacy and tolerability of EPs 7630 in children and adolescents with acute bronchitis - a randomized, double-blind, placebo-controlled multicenter trial with a herbal drug preparation from Pelargonium sidoides roots.* International Journal of Clinical Pharmacology and Therapeutics, 2010. **48**(3): p. 184-191.
8. Kamin, W., et al., *Efficacy and tolerability of EPs 7630 in patients (aged 6–18 years old) with acute bronchitis.* Acta Pædiatrica, 2010. **99**(4): p. 537-543.
9. Kamin, W., et al., *Treatment of acute bronchitis with EPs 7630: Randomized, controlled trial in children and adolescents.* Pediatrics International, 2012. **54**(2): p. 219-226.
10. EMA, *Assessment report on Pelargonium sidoides DC; Pelargonium reniforme Curt., radix*. 2023.
11. Rathmann W, B.B., Carius HJ, Kruppert S, Kostev K, *Basic characteristics and representativeness of the German Disease Analyzer database.* International Journal of Clinical Pharmacology and Therapeutics, 2018. **56**(10): p. 459-466.
12. Hoang, M.P., et al., *Herbal Medicines for Rhinosinusitis: A Systematic Review and Network Meta-analysis.* Current Allergy and Asthma Reports, 2023. **23**(2): p. 93-109.

17. ANNEXES

17.1 Appendix I. List of concept sets

Final list of concepts for exposure is provided below. The list was reviewed once protocol approved and prior to parametrization of the study code.

List of concepts for exposure

Drug	Concept id	Descendants	Excluded
Pelargonium sidoides root extract	42899638	Yes	36277198, 41144081, 41111339, 588921, 586556, 36789578, 36789577, 36270288, 36272355, 42715488, 41243974, 42724025, 40850012, 40850013, 42715990, 42724880, 40931467, 41235976, 42723167, 40994010, 41068165, 41099645, 40931466, 41048266, 41396307, 41390652, 41393618, 41396625, 36280221, 36280091, 36280118, 36779763, 42683758, 42658459, 36779760, 36779761, 36779762, 36779764, 41416665, 41420548, 41422717, 41417046

List of concepts for indication

Concept name	Concept ID	Descendants	Excluded
Acute bronchitis	260139	Yes	
Acute rhinosinusitis	4329087	n/a	
Common cold	260427	n/a	
Cough	254761	Yes	4109381, 4128692, 4144508, 4195384, 4199298, 4263877, 4270340, 35626061, 4125451, 44789249, 4266667
Nasopharyngitis	4197268	Yes	439851, 24978, 441321
Sinusitis	4283893	Yes	
Tonsillitis	4234533	Yes	
Upper respiratory infection	4181583	Yes	

17.2 Appendix II. Supplementary Tables

Table 1. Demographic characteristics of patients being prescribed Pelargonii radix products at the time of first prescription of each new treatment episode, per database.

	IQVIA_DA_Germany	IQVIA_LPD_Belgium
Number records*	84,698	13,020
Number individuals	57,115	10,066
Prior observation, Median (IQR)**	2,073 (1,055 - 3,731)	1,176 (711 - 1,912)
Future observation, Median (IQR)**	1,325 (476 - 2,077)	1,185 (407 - 1,998)
Age at index (years), Median IQR	32 (10 - 54)	34 (11 - 54)
Age range (years)	0 - 98	0 - 103
Sex		
• Female, n (%)	45,190 (53)	7,564 (58)
• Male, n (%)	39,457 (47)	5,456 (42)
• Missing, n (%)	51 (0)	-

LPD = Longitudinal Patient Database; DA = Disease Analyzer; IQR = interquartile range.

*Number of records refer to number of treatment episodes.

**Prior observation refers to the available number of days of data before the index date, while future observation refers to the amount of available follow-up data after the index date.