Study Protocol P3-C1-002

10/05/2024

Version 3.1

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DOCUMENT HISTORY

VERSION	DATE	DESCRIPTION
V1.0	28/03/2024	**Submission to EMA**
V2.0	23/04/2024	**Second version following comments from EMA**
V3.0	08/05/2024	**Third version following comments from EMA**
V3.1	10/05/2024	**Public version uploaded in the HMA-EMA Catalogue**

Study Title	DARWIN EU® - Drug utilisation study on medicinal use of Pelargonii radix
Protocol version identifier	V3.1
Date of last version of protocol	10/05/2024
EU PAS register number	EUPAS1000000150
Active substance	Pelargonii radix (root of *Pelargonium sidoide*s DC / *Pelargonium reniforme* Curt.).
Medicinal product	N/A
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 of the drug of interest in terms of demographics and indication for prescribing/dispensing. Additionally, to determine dose/strength at the treatment initiation, duration of treatment episodes and number of prescriptions of the drug of interest per treatment episode. Results will be 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).
Country(ies) of study	Belgium and Germany
Author	Dina Vojinovic d.vojinovic@darwin-eu.org Nicolas Hunt n.hunt@darwin-eu.org

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

1. TITLE

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

2. RESPONSIBLE PARTIES – STUDY TEAM

The table below outlines the composition of the Study team, detailing the roles, names and organisations.

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 Erasmus MC Erasmus MC Erasmus MC Erasmus MC
Data Partner*	**Names**	**Organization**
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.

3. ABSTRACT (STAND ALONE SUMMARY OF THE STUDY PROTOCOL)

Title

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

Rationale and Background

Pelargonii radix is an herbal preparation that has received market authorisation in some European member states for 30 years. It is 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 of the drug of interest in terms of demographics and indication for prescribing/dispensing. Additionally, to determine dose/strength at the treatment initiation, duration of treatment episodes and number of prescriptions of the drug of interest per treatment episode. All results will be 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).

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/strength, 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).

Population

Patient-level utilisation of selected medicines of interest: Patient-level drug utilisation analyses will include all treatment initiations of pre-specified medicines of interest in the period between 1st of January 2014 and 31st of December 2023. Patients need to have at least 365 days of data visibility prior to the date of their first prescription/dispensing 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 will not hold for children <1 year of age.

Population-level utilisation of selected medicines of interest: Population-level drug utilisation analyses will include 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 will not hold for children <1 year of age.

Variables

Drug of interest

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 sample size has been calculated for this drug utilisation descriptive study, as our primary focus is to investigate 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 differ across databases and age groups. For children, the range varies from 100 (IQVIA LPD Belgium, IQVIA DA Germany) to 27,700 (IQVIA DA Germany). Among adolescents, the range spans from 100 (IQVIA LPD Belgium, IQVIA DA Germany) to 9,300 (IQVIA DA Germany), while in adults, it extends 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 will be conducted at index date. Index date will be the date at time of first prescription of each new treatment episode of the drug of interest for each person. The frequency of indication of drug use will be assessed by searching for predefined disease categories. Additionally, top 10 SNOMED codes reported in window around index date will be determined. Initial dose/strength will be estimated, and the minimum, quartiles and maximum values will be provided. Duration of treatment episodes will be calculated and summarized providing the minimum, quartiles, and maximum duration of treatment episodes. Number of prescriptions per treatment episode will be estimated and minimum, quartiles and maximum number of repeated prescriptions of the index drug will be reported. The statistical analyses will be conducted using the "*DrugUtilization*" R Package based on OMOP-CDM mapped data and will be 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, will be estimated in separate age categories (below 3; 3-5; 6-11; 12-17; 18-65, >65 years) (Objective 2). The statistical analyses will be performed based on OMOP-CDM mapped data using *"IncidencePrevalence"* R package.

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

4. AMENDMENTS AND UPDATES

NUMBER	DATE	SECTION OF STUDY PROTOCOL	AMENDMENT OR UPDATE	REASON

5. MILESTONES

Additional study specific deliverables (e.g. results of validation of new disease concepts, statistical analysis plan, etc.) might be requested but this will be on an individual basis.

STUDY SPECIFIC DELIVERABLE	TIMELINE
Draft Study Protocol	28th March 2024
Final Study Protocol	April 2024
Creation of Analytical code	April 2024
Registration in HMA-EMA Catalogue	May 2024
Execution of Analytical Code on the data	May 2024
Interim Study Report (if applicable)	Not applicable
Draft Study Report	May 2024
Final Study Report	June 2024

6. 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 not recommended for children under the age of 3 years old.[1] The EMA's Committee on Herbal Medicinal Products (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 utilization in various age groups, with a specific focus on the younger population of children under 12 years old.

7. RESEARCH QUESTION AND OBJECTIVES

Research question

What is 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/dispensing. Additionally, to determine dose/strength at the treatment initiation, duration of treatment episodes and number of prescriptions of the drug of interest per treatment episode. Results will be 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. Primary and secondary research questions and objective.

A. Primary research question and objective.

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/dispensing. Additionally, to determine dose/strength at the treatment initiation, duration of each treatment episode and number of prescriptions of the drug of interest per treatment episode. Results will be 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 will include all treatment initiations of Pelargonii radix in the period between 1st of January 2014 and 31st of December 2023. Patients need to

	have at least 365 days of data visibility prior to the date of their first prescription/dispensing 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 will 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 will 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 will start on the date of incident prescription/dispensation of Pelargonii radix (index date). **Objective 2:** Population-level drug utilisation: Follow-up with start 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. End of follow-up will be defined as the earliest of loss to follow-up, end of data availability, death, or end of study period (31st of December 2023), whichever comes first. Additionally, for objective 1, end of follow-up will be 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/strength of prescribed/dispensed selected pre-specified medication of interest expressed as the minimum, p25, median, p75 and maximum values stratified by age categories. Duration of treatment episodes of selected pre-specified medication of interest expressed as minimum, p25, median, p75 and maximum duration of treatment episodes stratified by age categories.

	Number of prescriptions of selected pre-specified 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 .

8. RESEARCH METHODS

8.1 Study type and Study Design

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

A cohort study will be conducted using routinely collected health data from 2 databases. The study will comprise two consecutive parts:

- A new drug user cohort study will be 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/dispensing and to determine dose/strength at the treatment initiation, 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 will be 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.

STUDY TYPE	STUDY DESIGN	STUDY CLASSIFICATION
Patient Level DUS	New drug/s user cohort	Off the shelf (C1)
Population Level DUS	Population Level Cohort	Off the shelf (C1)

8.2 Study Setting and Data Sources

This study will be 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/dispensed pre-specified 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 have data on selected pre-specified 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 the **Table 3.**

When it comes to assessing the reliability of data sources, the data partners are 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 utilize the Achilles tool, which systematically characterizes the data and presents it in a dashboard format that is inspected. The generated data characteristics such as age distribution, condition prevalence per year, data density, measurement value distribution can be compared against expectations for the data. Additionally, the data quality dashboard (DQD) provides more objective checks on plausibility consistently across the data sources. In terms of relevance, a more general-purpose diagnostic tools, CohortDiagnostics and DrugExposureDiagnostics, were developed. CohortDiagnostic package evaluates phenotype algorithms for OMOP CDM datasets, offering a standard set of analytics for understanding patient capture including data generation. It provides additional insights into cohort characteristics, record counts and index event misclassification. DrugExposureDiagnostic package assesses ingredient specific diagnostics for drug exposure records. Furthermore, timeliness is guarded by extracting the release dates for each dataset in the network and monitoring when data are out-of-date with the expected refresh cycle (typically quarterly or half-yearly). In addition, it is important to have clear understanding of the time period covered by each released database, as this can vary across different domains. To facilitate this, the CdmOnboarding (and Achilles) packages contain a 'data density' plot. This plot displays the number of records per OMOP domain on a monthly basis. This allows to get insights when data collection started, when new sources of data were added and when 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 active subjects	Data lock for the last update
Belgium	IQVIA LPD Belgium	Database covers primary care setting where selected pre-specified medication of interest may be prescribed/dispensed.	Primary care	EHR	0.4 million	23/01/2024
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	8.5 million	23/01/2024

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

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.

8.3 Study Period

The study period will be 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).

8.4 Follow-up

For patient-level drug utilisation of pre-selected medication of interest, study participants will be 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 comes first.

For population-level drug utilisation of pre-specified medication of interest, follow-up will start when study participants fulfil inclusion criteria (i.e. present in the database between 1st of January 2014 and 31st of December 2023 and with at least 1 year of data visibility (not for children < 1 year of age). End of follow-up will be defined as the earliest of loss to follow-up, end of data availability, death, or end of study period (31st December 2023), whatever comes first.

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

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

Incidence requires an appropriate denominator populations with individuals aged between below 3, 3-5, 6-11, 12-17, 18-65, >65 years and their contributed observation time to first be identified. Study participants in the denominator population will begin 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 will stop 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 enters study upon reaching a minimum age and leaves at the study end date. Person 2 enters study at study start date and exits upon reaching the maximum age. Person 3 has already sufficient prior history before the study start date but enters the study upon reaching a minimum age and leaves the study at the study end date. Person 4 enters the study upon reaching minimum age and leaves when exiting the database (the end of observation period). Person ID 5 enters the study only with sufficient prior history and exit at the study end date Lastly, person ID 6 has two observation periods in the database. The first period contributes time from study start until end of observation period, the second starts contributing time again once sufficient prior history is reached and exits at maximum age.

For additional information regarding the IncidencePrevalance package, please refer to the documentation available on CRAN - Package IncidencePrevalence (r-project.org).

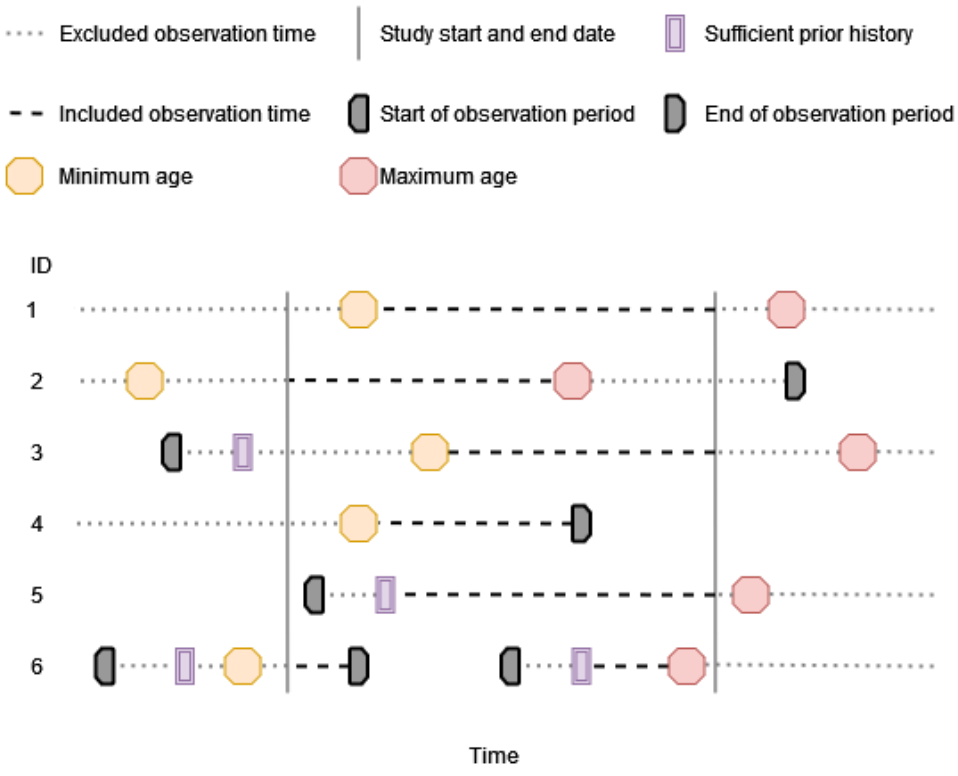

Figure 1: Included observation time for the denominator population

8.5 Study Population with inclusion and exclusion criteria

Patient-level utilisation of Pelargonii radix

All individuals who initiate treatment of selected 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 need to have at least 365 days of data visibility prior to the date of their first prescription/dispensing 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 will not hold for children <1 year of age.

Population-level utilisation of Pelargonii radix

The study cohort will include 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 will not hold for children <1 year of age.

Additional eligibility criteria will be applied for the calculation of incidence rates: The observation time of users of the selected pre-specified medication of interest is excluded during use and 30 days afterwards.

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] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, 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.

8.6 Variables

8.6.1. Exposure

For this study, exposure of interest is use (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] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable

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

8.6.2. Outcome

n/a

8.6.3. Other covariates, including confounders, effect modifiers and other variables

Covariates for patient-level drug utilisation study

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

Other covariates for patient-level drug utilisation study will include:

- A list of pre-specified conditions used to assess indication of use (the frequency of conditions of interest will be assessed at index date and as sensitivity analysis in 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 will be assessed at index date and as sensitivity analysis in window around index date (7 days before until 7 days after index date)).

The operational definition of the covariates is described in the **Table 7.**

7. Index date is the start of the (first) incident prescription of each new treatment episode during the study period. The preliminary of concepts for prespecified conditions of interest is described in **Appendix I.**

Covariates for population-level drug utilisation study

Covariate for stratification in population-level drug utilisation study will include 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

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

8.7 Study size

No sample size has been calculated for this drug utilisation descriptive study, as our primary focus is 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 differ across databases and age groups. For children, the range varies from 100 (IQVIA LPD Belgium, IQVIA DA Germany) to 27,700 (IQVIA DA Germany). Among adolescents, the range spans from 100 (IQVIA LPD Belgium, IQVIA DA Germany) to 9,300 (IQVIA DA Germany), while in adults, it extends from 100 (IQVIA LPD Belgium, IQVIA DA Germany) to 54,400 (IQVIA DA Germany) record counts.

8.8 Analysis

This section will describe 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.

The analysis will include calculation of population-based incidence rates, as described in section 8.8.5.

Table 8. Description of Study Types and Type of analysis.

STUDY TYPE	STUDY CLASSIFICATION	TYPE OF ANALYSIS
Patient Level DUS	Off-the-shelf (C1)	- Characterisation of patient-level features - Frequency and % of indication/s - Estimation of minimum, quartiles, and maximum values initially prescribed/dispensed dose - Duration of treatment episodes as minimum, quartiles and maximum number of treatment episodes - Number of prescriptions per treatment episode estimated as minimum, quartiles and maximum number of prescriptions.
Population Level DUS	Off-the-shelf (C1)	- Population-based incidence rates

8.8.1 Federated Network Analyses

Analyses will be conducted separately for each database. Before study initiation, test runs of the analytics are performed on a subset of the data sources or on a simulated set of patients and quality control checks are performed. Once all the tests are passed, the final package is released in the version-controlled Study Repository for execution against all the participating data sources.

The data partners locally execute the analytics against the OMOP-CDM in R Studio and review and approve the by default aggregated results before returning them to the Coordination Centre. Sometimes multiple

execution iterations are performed, and additional fine tuning of the code base is needed. A service desk will be available during the study execution for support.

The study results of all data sources are checked after which they are made available to the team in the Digital Research Environment (DRE) and the Study Dissemination Phase can start. All results are locked and timestamped for reproducibility and transparency.

8.8.2 Patient privacy protection

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

8.8.3 Statistical model specification and assumptions of the analytical approach considered

R-packages

We will use the R package "*DrugUtilization*" for patient-level drug utilisation analyses including patient-level characterisation and "IncidencePrevalence" for population-level estimation of drug utilisation.

Drug exposure calculations

Drug eras will be defined as follows: Exposure starts at date of the first prescription, e.g., the index date the person entered the cohort. For each prescription, the estimated duration of use is retrieved from the drug exposure table in the CDM, using the start and end date of the exposure. Subsequent prescriptions will be combined into continuous exposed episodes (drug eras) using the following specifications:

Two drug eras will be 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 will be 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 will be considered exposed by first prescription. No time will be added at the end of the combined drug era to account for the overlap.

Treatment initiation cohort

Individuals who initiate treatment will be 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 will be required prior

to a prescription. Individuals who initiate treatment are 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 does not fulfil the exposure washout criteria of 30 days of no use, the whole exposure will be eliminated.

8.8.4 Methods to derive parameters of interest

Age

Age at index date will be calculated using January 1st of the year of birth as proxy for the actual birthday. The following age categories will be considered: below 3; 3-5; 6-11; 12-17; 18-65, >65 years.

Indication

Indication will be determined based on recordings of pre-defined conditions (see 8.6.3 – other variables), 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 is recorded on index date or during the assessment window, but there is a record for any other condition, the person is considered having an "other" indication.

Characterisation of patient-level features

Large-scale patient-level characterisation will be conducted. Concepts in the "condition" domain will be assessed at index date and in the window around index date (7 days before until 7 days after index date). The top-10 conditions will be presented.

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

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 will be provided.

Indication

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

Initially prescribed or dispensed dose/strength

For each prescription at index date, the prescribed dose/strength will be 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 will be 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 will be conducted in. From this, the initial

dose/strength in the cohort will be characterised by the minimum dose/strength, p25, median, p75, and maximum dose/strength.

Treatment duration

Treatment duration will be calculated as the duration of each of treatment episode of the medication of interest during the study period. Treatment duration will be 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 will not be provided.

Count of repeated prescriptions

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

Population-level drug utilisation study

Incidence calculations

Annual incidence rates of the selected pre-specified medication of interest will be calculated as the number of treatment initiations after 30 days of no use per 100,000 person-years 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) will be excluded. Those study participants who enter the denominator population will then contribute time at risk up to their first prescription during the study period. If they do not have a drug exposure, they will contribute time at risk up as described above. Time-at-risk of subjects who die will be censored at the time of death. Similarly, time at risk of subjects who are lost to follow-up will be censored at the time of loss to follow-up [last contact]. Subjects with data until the end of the study period without experiencing exposure will be administratively censored at the end of the study period. Incidence rates will be 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 contribute time at risk up to the point at which they become incident users of selected pre-specified medication of interest. Patient ID 2 and 5 are not seen to use pre-specified medication of interest and so contribute time at risk but no incident outcomes. Meanwhile, patient ID 3 first contributes time at risk starting at the day when the washout period of a previous exposure, before study start, has ended, and ending when the next exposure of pre-specified medication of interest is starting. A second period of time at risk again starts after the washout period. For person ID 4, only the first and third exposures of pre-specified medication of interest count as incident use, while the second exposure starts within the washout period of the first exposure. The time between start of the first exposure until the washout period after the second exposure is not considered as time at risk.

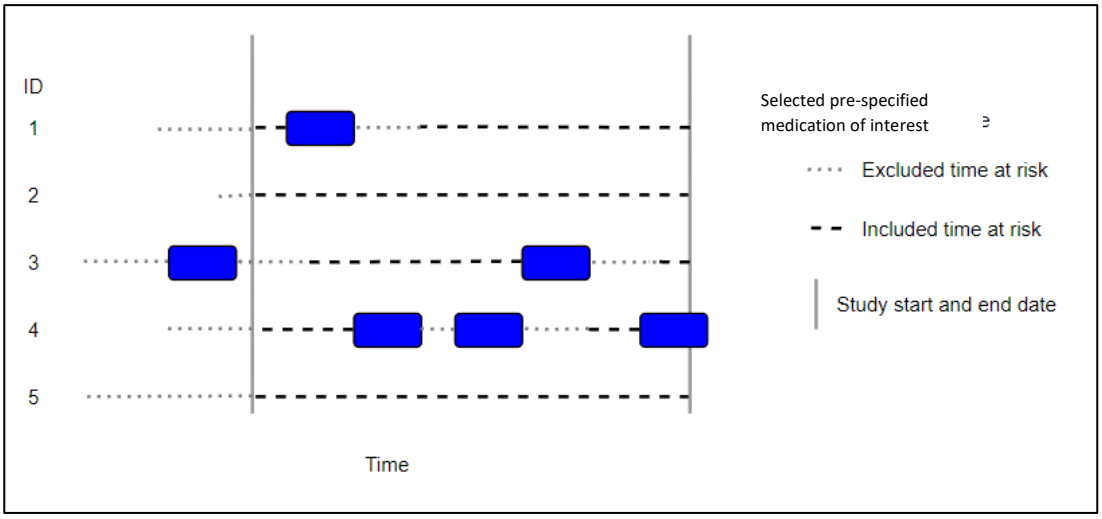

Figure 3: Incidence example

8.8.6 Methods to deal with missing data

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

8.8.7 Description of sensitivity analysis

Indication of use will be explored in a period of 7 days before and 7 after the index date.

8.8.8 Evidence synthesis

Results from analyses described in section 8.8 Data analysis will be presented separately for each database and no meta-analysis of results will be conducted.

9. DATA MANAGEMENT

9.1 Data management

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

The analytic code for this study will be written in R. Each data partner will execute the study code against their database containing patient-level data and will then return the results set which will only contain

aggregated data. The results from each of the contributing data sites will then be combined in tables and figures for the study report.

9.2 Data storage and protection

For this study, participants from various EU member states will process 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 have a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control are adhered to. In agreement with these regulations, rather than combining person level data and performing only a central analysis, local analyses will be run, which generate non-identifiable aggregate summary results.

The output files are stored in the DARWIN Digital Research Environment. These output files do not contain any data that allow identification of subjects included in the study. The DRE implements further security measures in order to ensure a high level of stored data protection to comply with the local implementation of the General Data Protection Regulation (GDPR) (EU) 679/20161 in the various member states.

10. 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 is expected that data partners will have run the OHDSI Data Quality Dashboard tool (https://github.com/OHDSI/DataQualityDashboard). This tool provides numerous checks relating to the conformance, completeness and plausibility of the mapped data. Conformance focuses on checks that describe the compliance of the representation of data against internal or external formatting, relational, or computational definitions, completeness in the sense of data quality is solely focused on quantifying missingness, or the absence of data, while plausibility seeks to determine the believability or truthfulness of data values. Each of these categories has one or more subcategories and are evaluated in two contexts: validation and verification. Validation relates to how well data align with external benchmarks with expectations derived from known true standards, while verification relates to how well data conform to local knowledge, metadata descriptions, and system assumptions.

Study specific quality control

When defining cohorts for drugs, a systematic search of possible codes for inclusion will be identified using CodelistGenerator R package (https://github.com/darwin-eu/CodelistGenerator). This software allows 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 will be run if needed to assess the use of different codes across the databases contributing to the study.

The study code will be based on two R packages namely the *DrugUtilization* package and the *IncidencePrevalence*. These packages will include numerous automated unit tests to ensure the validity of the codes, alongside software peer review and user testing. The R package will be made publicly available via GitHub.

11. LIMITATIONS OF THE RESEARCH METHODS

The study will be 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 recording of a prescription does not mean that the patient took the drug. Therefore, assumptions of actual use are 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 is not recorded as such in the databases. We assess indication via proxy based on a recording of pre-defined conditions recorded around the date of therapy initiation. Therefore, recording of potential indication might be incomplete.

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.

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

12. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

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

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

13. GOVERNANCE BOARD ASPECTS

Data sources included in this study do not require approval from their respective IRB board.

14. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

14.1 Study Report

A study report including an executive summary, and the specified tables and/or figures will be submitted to EMA by the DARWIN EU® CC upon completion of the study.

An interactive dashboard incorporating all the results (tables and figures) will be provided alongside the study report. The full set of underlying aggregated data used in the dashboard will also be made available if requested.

15. OTHER ASPECTS

n/a

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.

17. ANNEXES

17.1.1 **Appendix I**: List of preliminary concept definitions

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

Preliminary list of concepts for exposure

Drug	Concept id	Descendants	Excluded
Pelargonium sidoides root extract	42899638	Yes	41417046, 41422717, 41420548, 41416665, 41396625, 41393618, 41390652, 41396307, 41048266, 40931466, 41099645, 41068165, 40994010, 41235976, 42723167, 42724880, 40931467, 40850013, 42715990, 42724025, 40850012, 42715488, 41243974

Preliminary 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, 4110163, 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	

17.1.2 **Appendix II:** ENCePP checklist for study protocols

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

EU PAS Register® number: N/A
Study reference number (if applicable): N/A

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

Comments:

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

Comments:

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

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g., cohort, case-control, cross-sectional, other design)	☒	☐	☐	8.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8.2
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	8.8
3.4	Does the protocol specify measure(s) of association? (e.g., risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	8.2, 8.5
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	8.3
	4.2.2 Age and sex	☒	☐	☐	8.6
	4.2.3 Country of origin	☒	☐	☐	8.2
	4.2.4 Disease/indication	☒	☐	☐	8.6
	4.2.5 Duration of follow-up	☒	☐	☐	8.4
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g., event or inclusion/exclusion criteria)	☒	☐	☐	8.5

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorizing exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	8.6

Section 5: Exposure definition and measurement		Yes	No	N/A	Section Number
5.2	Does the protocol address the validity of the exposure measurement? (e.g., precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3	Is exposure categorized according to time windows?	☐	☐	☒	
5.4	Is intensity of exposure addressed? (e.g., dose, duration)	☒	☐	☐	
5.5	Is exposure categorized based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6	Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement		Yes	No	N/A	Section Number
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☐	☐	☒	8.6
6.2	Does the protocol describe how the outcomes are defined and measured?	☐	☐	☒	
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilization, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

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

Comments:

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

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g., pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	8.6
9.1.2 Outcomes? (e.g., clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☐	☐	☒	8.6
9.1.3 Covariates and other characteristics?	☒	☐	☐	8.6
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	8.6
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	8.6
9.2.3 Covariates and other characteristics? (e.g., age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	8.6
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	8.6
9.3.2 Outcomes? (e.g., International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	8.6
9.3.3 Covariates and other characteristics?	☒	☐	☐	8.6
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

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

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g., software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.2
11.2 Are methods of quality assurance described?	☒	☐	☐	10.0
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

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

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	13
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	9.2

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	4

Comments:

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

Comments:

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Date: 28th March 2024

Signature: