Study Protocol

P4-C1-018

DARWIN EU® – Drug Utilisation Study of terbinafine-containing products

22/10/2025

Version 2.0

Authors: Ellen Gerritsen, Dina Vojinovic

Public

CONTENTS

Study title	DARWIN EU® – Drug Utilisation Study of terbinafine-containing products
Protocol version	V2.0
Date	22/10/2025
EUPAS number	EUPAS1000000790
Active substance	• Terbinafine for topical use, WHO ATC code D01AE15 • Terbinafine for systemic use, WHO ATC code D01BA02
Medicinal product	A complete list of included terbinafine-containing products is provided in ANNEX III.
Research question and objectives	Research question: What are the patterns of use of terbinafine-containing products in Europe, 2015–2024? Study objectives: 1. To calculate the monthly and annual incidence of terbinafine use, overall and stratified by age and sex. 2. To characterise patients at the time of terbinafine treatment initiation in terms of i) demographics, ii) indication for use, iii) comorbidities, iv) other antifungal and antibiotic treatments (6, 3, and 1 month prior to treatment initiation and 6 months following initiation for antifungal treatment), and v) disease code for resistance (6 months before and 6 months after treatment initiation). 3. To report the number of treatment initiations, dose (initial, cumulative), and duration of terbinafine use, overall and stratified by type of dermatophytosis. 4. To explore the treatment pattern following new terbinafine treatment initiation, overall and stratified by type of dermatophytosis, including transitions between topical to systemic and combination therapies.
Countries of study	Croatia, Denmark, Finland, Germany, Spain, United Kingdom
Authors	Ellen Gerritsen, e.gerritsen@darwin-eu.org Dina Vojinovic, d.vojinovic@darwin-eu.org

LIST OF ABBREVIATIONS

Acronyms/term	Description
ATC	Anatomical Therapeutic Chemical
CC	Coordinating centre
CDM	Common Data Model
CPRD GOLD	Clinical Practice Research Datalink GOLD
DA	Disease Analyzer
DARWIN EU®	Data Analysis and Real-World Interrogation Network
DK-DHR	Danish Data Health Registries
DOI	Declaration of Interests
DQD	Data Quality Dashboard
DRE	Digital Research Environment
EHR	Electronic Health Records
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EUPAS	EU Post-Authorisation Studies Register
FinOMOP-THL	Finnish Care Register for Health Care
GDPR	General Data Protection Regulation
GP	General Practitioner
ICD	International Classification of Diseases
IP	Inpatient
IRB	Institutional Review Board
NAJS	Croatian National Public Health Information System
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
OP	Outpatient
RxNorm	Medical prescription normalized
SIDIAP	The Information System for Research in Primary Care
SNOMED	Systematized Nomenclature of Medicine
WHO	World Health Organisation

1. TITLE

DARWIN EU® - Drug Utilisation Study of terbinafine-containing products

2. DESCRIPTION OF THE STUDY TEAM

Study team role	Names	Organisation
Principal Investigators	Ellen Gerritsen Dina Vojinovic	IQVIA
Data Scientists	Akram Mendez Gargi Jadhav	IQVIA
Study Manager	Natasha Yefimenko	Erasmus MC
Data Partner*	**Names**	**Organisation**
NAJS	Ivan Pristaš Marko Čavlina Antea Jezidžić Jakov Vuković Anamaria Jurčević Karlo Pintarić	Croatian Institute for Public Health
DK-DHR	Elvira Bräuner Susanne Bruun	Danish Medicines Agency
FinOMOP-THL	Toni Lehtonen Tiina Wahlfors Gustav Klingstedt	Finnish Care Register for Health Care
IQVIA DA Germany	Isabella Kaczmarczyk James Brash	IQVIA
SIDIAP	Anna Palomar Cros Agustina Giuliodori Picco Laura Granés González (Invitado) Irene López Sánchez	Institute for Primary Health Care Research Jordi Gol i Gurina
CPRD GOLD	Antonella Delmestri Marta Pineda Moncusí	University of Oxford

*Data partners do not have an investigator role. Data partners execute code at their data source, review and approve their results.

3. ABSTRACT

Title

DARWIN EU® – Drug Utilisation Study of terbinafine-containing products

Rationale and background

Terbinafine is an antifungal agent indicated for the treatment of superficial mycoses, with widespread use across Europe in both oral and topical formulations. Monitoring its utilisation is essential to informing regulatory decision-making, particularly in relation to emerging safety concerns, such as antifungal resistance. This study aims to characterise the incidence and patterns of terbinafine use, describe the clinical profiles of treated patients, and examine treatment pathways.

Research question and objectives

Research question

What are the patterns of use of terbinafine-containing products in Europe, 2015–2024?

Objectives

The specific objectives of this study are:

1. To calculate the monthly and annual incidence of terbinafine use, overall and stratified by age and sex.
2. To characterise patients at the time of terbinafine treatment initiation in terms of i) demographics, ii) indication for use, iii) comorbidities, iv) other antifungal and antibiotic treatments (6, 3, and 1 month prior to treatment initiation and 6 months following initiation for antifungal treatment), and v) disease code for resistance (6 months before and 6 months after treatment initiation).
3. To report the number of treatment initiations, dose (initial, cumulative), and duration of terbinafine use, overall and stratified by type of dermatophytosis.
4. To explore the treatment pattern following new terbinafine treatment initiation, overall and by type of dermatophytosis, including transitions between topical to systemic and combination therapies.

Methods

Study design

This retrospective cohort study aims to estimate population-level drug utilisation of terbinafine-containing products (*objective 1*), characterise individuals being treated with terbinafine *(objective 2),* evaluate treatment utilisation at the patient-level by assessing dose and treatment duration *(objective 3)*, and describe patient-level treatment patterns *(objective 4).*

Population

Population-level cohort (objective 1): The study population will include all individuals present in the data source during the study period between 1 January 2015 and 31 December 2024 (or latest date available), and with at least 1 year of data visibility prior to the index date. Children <1 year of age will be excluded.

New terbinafine user cohort (objectives 2, 3, and 4): All individuals with a first recorded prescription of a terbinafine-containing product during the study period, defined as 1 January 2015 to 31 December 2024 (or latest date available). Eligible individuals must have at least 1 year of data visibility prior to the date of treatment initiation and no recorded use of terbinafine in the 180 days preceding treatment initiation. The cohort will focus on terbinafine initiators, specifically the initial treatment episode. To ensure sufficient

follow-up, only individuals who initiate terbinafine treatment at least 1 year prior the end of data availability in each data source will be included. Children <1 year of age will be excluded.

For *objective 3,* an additional cohort will include all new terbinafine treatment episodes meeting the washout criteria. Individuals may contribute multiple treatment episodes, provided each is preceded by 180 days washout period.

Variables

Exposure: Terbinafine for topical use (WHO ATC code D01AE15) and terbinafine for systemic use (WHO ATC code D01BA02)

Condition of interest:

1. Dermatophytosis (Tinea infections) including:
    a. Tinea corporis (Ringworm of the body)
    b. Tinea cruris (Jock itch)
    c. Tinea pedis (Athlete's foot)
    d. Tinea manuum (Hand ringworm)
    e. Tinea capitis (Scalp ringworm)
    f. Tinea barbae (Beard ringworm)
    g. Tinea unguium (Onychomycosis (nail))
2. Other fungal infections including:
    a. Cutaneous candidiasis
    b. Sporotrichosis
    c. Pityriasis versicolor

Data source

1. Croatia: Croatian National Public Health Information System (NAJS)
2. Denmark: Danish Data Health Registries (DK-DHR)
3. Finland: Finnish Care Register for Health Care (FinOMOP-THL)
4. Germany: IQVIA Disease Analyzer Germany (IQVIA DA Germany)
5. Spain: The Information System for Research on Primary Care (SIDIAP)
6. United Kingdom: Clinical Practice Research Datalink GOLD (CPRD GOLD)

Study size

No sample size has been calculated, as this is a drug utilisation study which will not test a specific hypothesis. Based on a preliminary feasibility assessment, the expected number of person counts for terbinafine-containing products in the data sources included in this study ranges from 208,400 (IQVIA DA Germany) to 1,185,000 (DK-DHR).

Statistical analysis

Population-level utilisation of terbinafine-containing products (objective 1): Monthly and annual incidence rates of terbinafine use will be estimated and expressed as the number of terbinafine treatment initiations per 1,000 person-years among individuals fulfilling the inclusion and exclusion criteria. Incidence rates will be calculated overall and stratified by age group (≤18 years, 19–65 years, ≥66 years) and sex. Estimates will

be given together with 95% Poisson confidence intervals. The statistical analyses will be performed based on OMOP CDM mapped data using the *IncidencePrevalence* R package.

Patient-level characterisation and utilisation (objectives 2, 3, and 4): Patient demographics (age, sex) will be assessed at the date of the first recorded terbinafine prescription during the study period (index date). The indication for terbinafine use will be inferred based on diagnosis codes recorded within predefined time windows relative to treatment initiation: i) from 180 days before to 7 days after, ii) from 90 days before to 7 days after, iii) from 30 days before to 7 days after. Comorbidities will be evaluated at the index date and within one year prior to the terbinafine initiation. Pre-specified antifungal and antibiotic treatments will be evaluated 6, 3, and 1 month prior to treatment initiation. Post-initiation antifungal treatments will be evaluated up to 6 months following initiation, while post-initiation antibiotic treatments will not be considered. The proportion of patients with a disease code for resistance will be evaluated 6 months before and 6 months after the index date. Initial and cumulative dose, as well as treatment duration, will be estimated, and the minimum, p25, median, p75, and maximum will be provided. These analyses will be conducted using *CohortCharacteristics* and *DrugUtilisation* R packages based on OMOP CDM mapped data. *DrugUtilisation* R packages based on OMOP CDM mapped data.

The treatment pattern following the first recorded terbinafine prescription during the study period will be presented by Sunburst and Sankey diagrams, which will provide information on sequences of terbinafine-containing products and other antifungal products over time. These analyses will be stratified by type of dermatophytosis. The statistical analysis will be performed based on OMOP CDM mapped data using the *TreatmentPatterns* R package.

Patient-level utilisation (objective 3) for multiple treatment episodes: Number of treatment initiations will be reported. Initial and cumulative dose, as well as treatment duration, will be estimated, and the minimum, p25, median, p75, and maximum will be provided. These analyses will be conducted using the *DrugUtilisation* R package based on OMOP CDM mapped data.

A minimum cell counts of 5 will be used when reporting results, with any smaller count reported as “<5”.

4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

Study milestones and deliverables	Planned dates*
Final Study Protocol	October 2025
Creation of Analytical code	September/October 2025
Execution of Analytical Code on the data	November 2025
Draft Study Report	28 November 2025
Final Study Report	December 2025/January 2026

*Planned dates are dependent on obtaining approvals from the internal review boards of the data sources.

6. RATIONALE AND BACKGROUND

Terbinafine is a widely used antifungal drug indicated for the treatment of superficial mycoses, including tinea pedis (athlete's foot), tinea corporis (ringworm), and onychomycosis (fungal nail infections). It works by inhibiting the enzyme squalene epoxidase, which is essential for the synthesis of ergosterol, a critical component of fungal cell membranes. This leads to disruption of membrane integrity, leading to fungal cell death. Terbinafine is available in both oral and topical formulations and is widely prescribed in clinical practice across Europe.[1, 2]

Understanding the real-world utilisation of terbinafine is essential for monitoring prescribing practices, identifying clinical characteristics, and evaluating potential safety concerns. Real-world data can provide valuable insights into treatment patterns, including transitions between topical and systemic therapies, and help identify populations at risk of resistance or treatment failure.[3] These insights will support regulatory activities, including the periodic assessment of benefits and risks, and contribute to a broader understanding of antifungal use in Europe as well as resistance.

This study aims to describe the incidence and patterns of terbinafine use, characterise the clinical profiles of patients receiving the medication, and explore treatment pathways.

7. RESEARCH QUESTION AND OBJECTIVES

Research question

What are the patterns of use of terbinafine-containing products in Europe, 2015–2024?

Objectives

The specific objectives of this study are:

1. To calculate the monthly and annual incidence of terbinafine use, overall and stratified by age and sex.
2. To characterise patients at the time of terbinafine treatment initiation in terms of i) demographics, ii) indication for use, iii) comorbidities, iv) antifungal and antibiotic treatments (6, 3, and 1 month prior to treatment initiation and 6 months following initiation for antifungal treatment), and v) disease code for resistance (6 months before and 6 months after treatment initiation).
3. To report the number of treatment initiations, dose (initial, cumulative), and duration of terbinafine use, overall and stratified by type of dermatophytosis.

4. To explore the treatment pattern following each terbinafine treatment initiation, overall and by type of dermatophytosis, including transitions between topical to systemic and combination therapies.

8. RESEARCH METHODS

8.1. Study design

A retrospective cohort study will be conducted using routinely collected health data from 6 data sources from 6 countries across Europe and in 5 EU member states. The study will include:

- A population-level drug utilisation study conducted to address *objective 1,* estimating the incidence of terbinafine-containing product use in the study population (**Figure 1a**).
- A patient-level characterisation and drug utilisation study conducted to address *objectives 2, 3, and 4,* characterising individuals initiating terbinafine treatment, evaluating treatment utilisation, including dose and duration, and treatment patterns (**Figure 1b**).
- A patient-level drug utilisation study conducted to address *objective 3,* evaluating treatment utilisation of all new terbinafine treatment initiations, including dose and duration (**Figure 1c**).

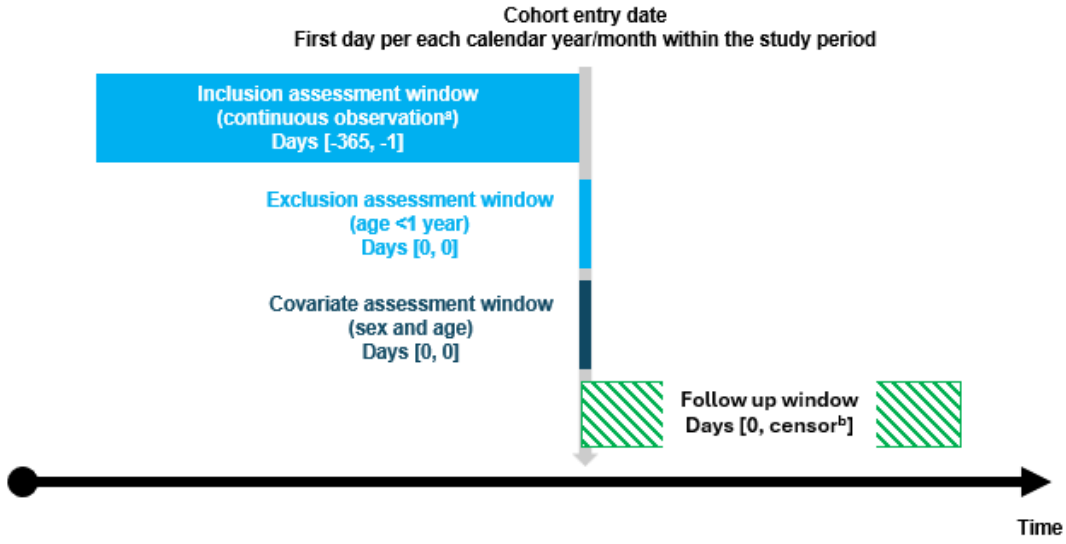


Figure 1a. Graphical depiction of the study design for *objective 1*.

a. Applies to individuals older than one year.
b. Death, loss to follow-up, end of data source availability, end of each calendar year/month (i.e., 31 December), or end of the study period (31/12/2024).

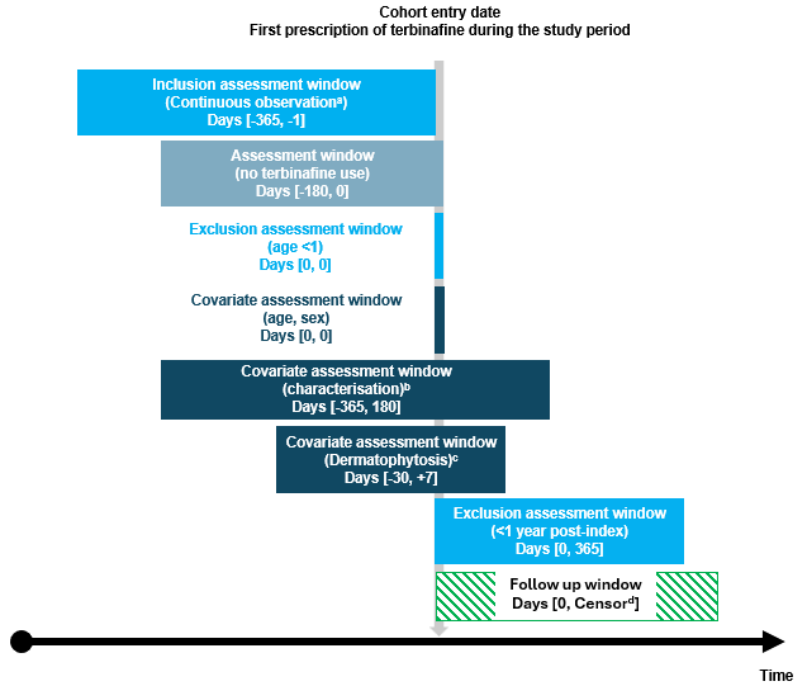


Figure 1b. Graphical depiction of the study design for *objectives 2, 3,* and *4*.

a. Applies to individuals older than one year.
b. Indication of use, comorbidities, fungal and antibiotic treatment prior to and following treatment initiation and resistance to terbinafine (all defined in **section 8.6.3**).
c. Applies to *objectives 2* and *4* and stratification by type of dermatophytosis.
d. Death, loss to follow-up, end of data source availability, or end of the study period (31/12/2024).

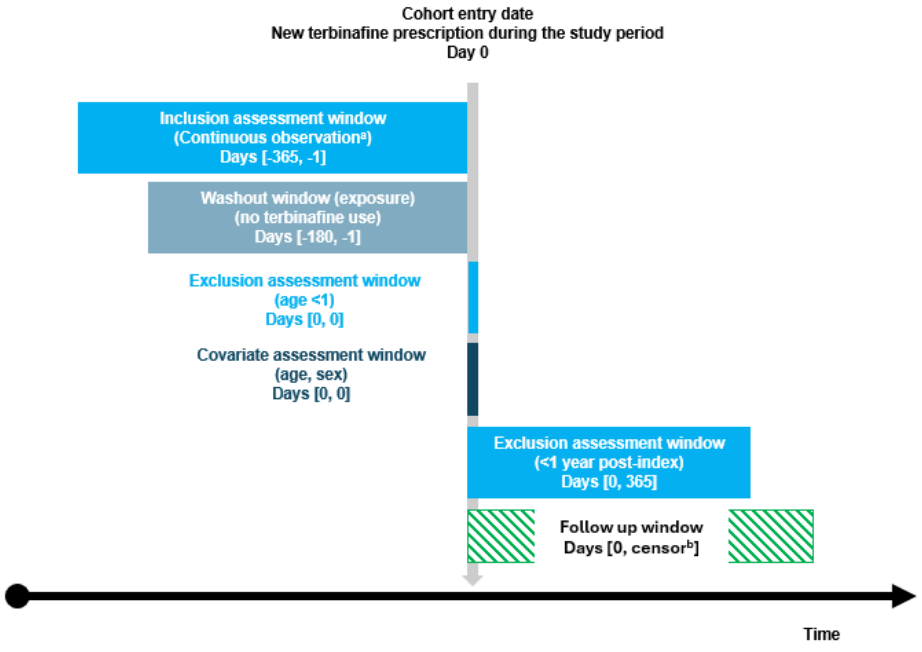


Figure 1c. Graphical depiction of the study design for *objective 3*.

Individuals may contribute multiple terbinafine treatment episodes during the study period. Each episode is defined by a new prescription following a ≥180-day washout period without terbinafine use. The timeline and assessment windows apply to each qualifying episode, anchored to its respective index date.

a. Applies to individuals older than one year.
b. Death, loss to follow-up, end of data source availability, or end of the study period (31/12/2024).

8.2. Study setting and data sources

This study will be conducted using routinely collected data from 3 registries and 3 primary care data sources in the DARWIN EU® network of data partners from 6 European countries in 5 EU member states. All data were a priori mapped to the OMOP CDM.

Data sources

1. Croatia: Croatian National Public Health Information System (NAJS)
2. Denmark: Danish Data Health Registries (DK-DHR)
3. Finland: Finnish Care Register for Health Care (FinOMOP-THL)
4. Germany: IQVIA Disease Analyzer Germany (IQVIA DA Germany)
5. Spain: The Information System for Research on Primary Care (SIDIAP)
6. United Kingdom: Clinical Practice Research Datalink GOLD (CPRD GOLD)

Data Selection

These data sources fulfil the criteria required in terms of data quality, completeness, timeliness, and representativeness for drug utilisation study while covering different regions of Europe.

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 utilised the *Achilles* tool,[4] which systematically characterises the data and generates data characteristics such as age distribution, condition prevalence per year, and data density. Data density includes information on 1) monthly record counts by data domain (which offers insights into data collection patterns and the start date of each data source), and 2) measurement value distribution (i.e., min, max, quartiles for numeric values per measurement concept and per unit and counts for discrete measurement-value pairs). The latter can be compared against expectations for the data based on predefined standards, historical trends, or known epidemiological patterns to identify potential anomalies or inconsistencies. Additionally, the data quality dashboard (DQD) provides more objective checks on plausibility of data completeness, consistency, and conformity across the data sources.

In terms of relevance, the selection of data sources was based on the availability of data on the selected terbinafine-containing products and dermatophytosis to perform the described analyses. In addition, the data sources were chosen considering their ability to support timely IRB approvals, thus ensuring alignment with the timeline established by stakeholders for the conduct of this study.

The DARWIN EU® portal, as well as information from the onboarding documents, were used to assess whether data sources have information on terbinafine-containing products and dermatophytosis. Data within the DARWIN EU® portal is maintained up to date 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 covered by each released data source, as this can vary across different domains. To facilitate this, the *CDMOnboarding* (and *Achilles*) packages [4] contain a 'data density' plot. This plot displays the number of records per OMOP domain monthly. This allows getting insights into when data collection started, when new sources of data were added, and until when data was included. In addition, at the time of inviting data partners, they were informed about study objectives and asked whether they could participate in the study.

More general-purpose diagnostic tools, *CohortDiagnostics* [5] and *DrugExposureDiagnostics* [6], have been developed. The *CohortDiagnostics* package provides additional insights into cohort characteristics, record counts, and index event misclassification. The *DrugExposureDiagnostics* package evaluates ingredient-specific attributes and patterns in drug exposure records. Upon finalisation of the study protocol and

creation of the disease and drug cohorts of interest by DARWIN EU® Coordination Centre, these packages will be executed in each data sources by each data partners.

Data source justification and key characteristics

Multiple data sources will be included in this study, as they represent registry-based and outpatient general practitioner care databases that provide relevant information on terbinafine exposure and dermatophytosis diagnoses in the general population. Based on preliminary feasibility assessments, the expected number of individuals with terbinafine use ranges from approximately 208,400 (IQVIA DA Germany) to 1,185,000 (DK-DHR), while the number of individuals with dermatophytosis diagnoses ranges from 280,200 (FinOMOP-THL) to over 1,000,000 (IQVIA DA Germany). Data availability and follow-up are sufficient to support the study objectives, with data collection start years ranging from 1987 (CPRD GOLD) to 2014 (NAJS), and the most recent data being between June 2023 (SIDIAP) and February 2025 (NAJS). Median follow-up durations vary across sources, ranging from 116 days (IQVIA DA Germany) to 7,920 days (DK-DHR), ensuring adequate longitudinal coverage. While most data sources align with the planned study period (1 January 2015 to 31 December 2024), the actual study period will extend until the last available observation period month in each source, specifically October 2024 for FinOMOP-THL, November 2024 for DK-DHR, and June 2023 for SIDIAP. NAJS will be included from January 2017 onwards due to data reliability constraints. Institutional Review Board (IRB) approvals are either covered under existing umbrella protocols or expected to be obtained within 1 to 3 months (FinOMOP-THL, SIDIAP), supporting timely execution of the study within the established timelines.

Information on the data sources planned for use in this study is provided in **Table 1** and **ANNEX I. Description of data sources**

Table 1. Data source justification and key characteristics.

Country	Data source acronym	Type of data	Terbinafine users (n)[a]	Dermatophytosis diagnosis (n)[b]	Data collection start year	Source release date	Last observation period month	Follow-up duration (days), median (IQR)[c]	IRB approval
Croatia	NAJS	Registry	224,400	456,200	2014 (from 2017 reliable IDs)	08/02/2025	01/2025	3,640 (3,110-3,740)	Umbrella protocol
Denmark	DK-DHR	Registry	1,185,000	324,000	1995	18/01/2025	11/2024	7,920 (2,610-10,900)	Umbrella protocol
Finland	FinOMOP-THL	Registry	472,800	280,200	2011	01/10/2024	10/2024	5,020 (4,030-5,020)	1-3 months
Germany	IQVIA DA Germany	Outpatient General Practitioner and Specialist Care	208,400	1,024,600	1989	31/12/2024	12/2024	116 (0-1,610)	Not needed
Spain	SIDIAP	Outpatient General Practitioner Care	269,800	629,200	2006	30/06/2023	06/2023	5,670 (2,220-6,390)	1-3 months
UK	CPRD GOLD	Outpatient General Practitioner Care	724,400	736,400	1987	01/01/2025	12/2024	2,150 (727-4,930)	Umbrella protocol

NAJS = Croatian National Public Health Information System; DK-DHR = Danish Data Health Registries; FinOMOP-THL = Finnish Care Register for Health Care; IQVIA DA Germany = IQVIA Disease Analyzer Germany; SIDIAP = The Information System for Research on Primary Care; CPRD GOLD = Clinical Practice Research Datalink GOLD; GP = general practitioner.
[a] = person counts at drug era (as generated from drug era, this also includes the descendant PC of terbinafine at the clinical drug level (drug exposure table)).
[b] = descendant person counts for dermatophytosis.
[c] = median follow-up of the first observation period.

8.3. Study period

The study period is from 1 January 2015 to 31 December 2024, or the most recent data available for each contributing data source.

It should be noted for several data sources that the availability of the accurate data deviates from the start or end date of the study period. Detailed information about the study period per data partner can be found in **Section 8.2**.

8.4. Follow-up

For calculation of incidence rates of terbinafine-containing product use *(objective 1),* follow-up will start on the respective date of the latest of the following: i) study start date 1 January 2015 or ii) date at which individuals have 1 year of prior history. End of follow-up will be defined as the earliest of i) loss to follow-up, ii) death or iii) end of observation period (the latest available data), whichever occurs first.

For patient-level characterisation of terbinafine-containing product users *(objective 2),* estimation of drug utilisation *(objective 3),* and the description of treatment patterns *(objective 4)*, follow-up will start on the date of a first recorded terbinafine-containing product prescription between 1 January 2015 and 31 December 2024 (or latest date available). Eligible individuals must have at least 1 year of data visibility prior to the index date and no use of terbinafine products in the 180 days preceding treatment initiation. To ensure sufficient follow-up, only individuals who initiated terbinafine treatment at least one year before the end of data availability in each data source will be included. Children under 1 year of age will be excluded. End of follow-up will be defined as the earliest of i) loss to follow-up, ii) death, or iii) end of observation period (the latest available data), whichever occurs first.

Additionally, for estimation of drug utilisation for multiple treatment episodes *(objective 3)*, follow-up will start on the date of a new recorded terbinafine-containing product prescription between 1 January 2015 and 31 December 2024 (or latest date available) and will correspond to each new treatment episode. Eligible individuals must have at least 1 year of data visibility prior to the index date and meet the criteria washout period of 180 days. To ensure sufficient follow-up, only individuals who initiated terbinafine treatment at least one year before the end of data availability in each data source will be included. Children under 1 year of age will be excluded. End of follow-up will be defined as the earliest of i) loss to follow-up, ii) death, or iii) end of observation period (the latest available data), whichever occurs first.

Estimating incidence requires an appropriate denominator population and contributed observation time to first be identified. Study participants in the denominator population will begin contributing person time at risk as described above in the current section.

An example of entry and exit into the denominator population is shown in **Figure 2**. In this example, person ID 1 already has sufficient prior history before the study start date and the observation period ends after the study end date, so this person will contribute time during the complete study period. Person IDs 2 and 4 enter the study only when they have sufficient prior history. Person ID 3 leaves when exiting the data source (the end of the observation period). Lastly, person ID 5 has two observation periods in the data source. 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 study end date.

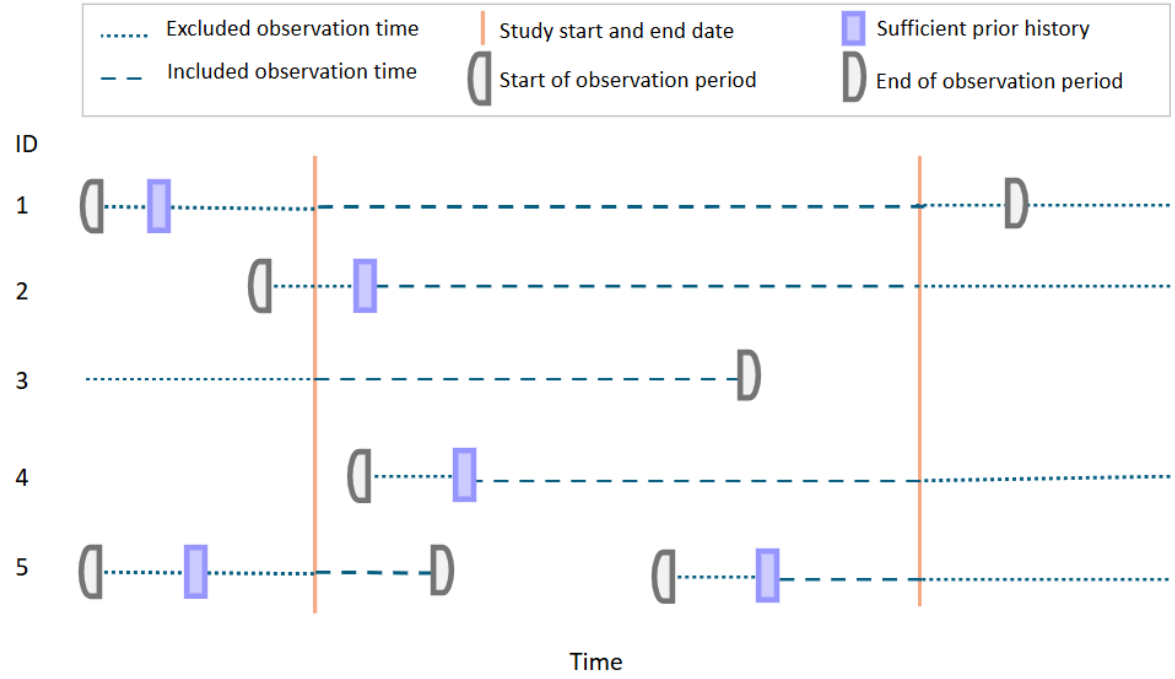


Figure 2. Included observation time for the denominator population.

8.5. Study population with inclusion and exclusion criteria

For calculation of incidence rates of terbinafine-containing product use, the study population will include the general population *(objective 1)*.

Inclusion criteria:

- All individuals present in the data source between 1 January 2015 and 31 December 2024 (or latest available date).
- At least 1 year of data visibility prior to the index date.

Exclusion criteria:

- Children aged <1 year at any time during the study period.

For characterisation of terbinafine treatment initiators *(objective 2),* estimation of treatment utilisation *(objective 3),* and description of treatment patterns *(objective 4)*, the study population will include individuals with a first recorded prescription of a terbinafine-containing product prescription during the study period.

Inclusion criteria:

- First record of a terbinafine-containing product between 1 January 2015 and 31 December 2024 (or latest available date).
- At least 1 year of data visibility prior to the index date.
- No use of terbinafine products in previous 180 days.

Exclusion criteria:

- Children aged <1 year at the index date.
- Individuals initiating terbinafine treatment <1 year before the end of data availability in the respective data source (to ensure sufficient follow-up).

Additionally, for estimation of treatment utilisation *(objective 3),* multiple treatment episodes will be considered.

Inclusion criteria:

- New record of a terbinafine-containing product between 1 January 2015 and 31 December 2024 (or latest available date).
- At least 1 year of data visibility prior to the index date.
- No use of terbinafine products 180 days before each treatment episode.

Exclusion criteria:

- Children aged <1 year at the index date.
- Individuals initiating terbinafine treatment <1 year before the end of data availability in the respective data source (to ensure sufficient follow-up).

8.6. Variables

8.6.1. Exposure

The primary exposure is defined as a prescription or dispensing record of the drug terbinafine, representing the new recorded prescription in the study period with no prior terbinafine use in the 180 days prior to the index date. For o*bjectives 2*, *3,* and *4*, only the first terbinafine initiation per individual during the study period will be considered as the index treatment. For *objective 3,* all new treatment episodes during the study period will be included.

To define treatment episodes, sequential prescriptions will be grouped into drug eras, allowing a maximum gap of 30 days between the end of one prescription and the start of the next.

The preliminary concept sets used for the identification of exposures are described in **ANNEX III**. These codes will be refined during the study execution following the DARWIN EU® phenotyping standard processes, which involves the review of code lists, and the review of phenotypes after their execution in the participating data sources.

8.6.2. Outcome

The outcomes are as follows:

- Incidence rate of terbinafine use *(objective 1)*
- Characterisation of terbinafine initiators *(objective 2)*
- Initial and cumulative dose, and duration of first terbinafine treatment initiation *(objective 3)*
- Number of treatment initiations, initial and cumulative dose, and duration of all terbinafine treatment initiations *(objective 3)*
- Treatment patterns following first terbinafine treatment initiation during the study period *(objective 4)*

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

The covariates for calculation of incidence rates of terbinafine-containing product use *(objective 1)* are as follows:

- Calendar year
- Calendar month
- Age groups (overall, ≤18 years, 18–65 years, ≥66 years)
- Sex (overall, males, females)

The variables for characterisation of terbinafine users *(objective 2)* are as follows:

- Indication of use: Pre-specified conditions will be used as a proxies to assess the indication for terbinafine use, including both authorised and non-authorised indications. Primary assessment window will be 30 days prior to the index date to 7 days after [-30, +7]. Additional sensitivity windows will be 90 days prior to the index date to 7 days after [-90, +7] and 180 days prior to the index date to 7 days after [-180, +7].
    - Dermatophytosis (Tinea infections) including:
        - Tinea corporis (Ringworm of the body)
        - Tinea cruris (Jock itch)
        - Tinea pedis (Athlete's foot)
        - Tinea manuum (Hand ringworm)
        - Tinea capitis (Scalp ringworm)
        - Tinea barbae (Beard ringworm)
        - Tinea unguium (Onychomycosis (nail))
    - Other fungal infections including:
        - Cutaneous candidiasis
        - Sporotrichosis
        - Pityriasis versicolor
    - Other
    - Missing
- Comorbidities: The top 10 most frequent diagnostic codes (comorbidities) will be identified through large-scale characterisation. These will be assessed at the index date [0, 0] and 1 year prior to the index date [-365, 0].
- Antifungal and antibiotic treatment: Exposure to antifungal and antibiotic medications will be evaluated 6, 3, and 1 month prior to treatment initiation and for antifungal treatments, up to 6 months post-initiation.
    - Antifungals for topical use (WHO ATC D01A)
    - Antifungals for systemic use (WHO ATC D01B)
    - Antibiotics for topical use (WHO ATC D06A)
    - Antibacterials for systemic use (WHO ATC J01)

- Resistance: Diagnostic codes indicating resistance will be assessed 6 months before and 6 months after treatment initiation.

The variables for stratification by type of dermatophytosis in drug utilisation *(objective 3)*:

- Superficial Tinea infections (tinea pedis, tinea manuum, tinea corporis)
- Hair Follicle-involving Tinea infections (tinea capitis, tinea barbae)
- Onychomycosis

The variables for treatment patterns following first terbinafine treatment initiations during the study period (*objective 4*) are as follows:

- Treatment:
    - Antifungal drugs, other
        - Ciclopirox (cutaneous)
        - Methylrosaniline (cutaneous)
        - Terbinafine (cutaneous)
        - Terbinafine (systemic)
    - Antimycotic antibiotics
        - Griseofulvin (systemic)
    - Corticosteroids, combination preparations cutaneous
        - Miconazole/hydrocortisone (cutaneous)
    - Combination preparations
        - Benzoic acid/salicylic acid (cutaneous)
    - Imidazoles, cutaneous
        - Clotrimazole (cutaneous)
        - Ketoconazole (cutaneous)
        - Miconazole (cutaneous)
        - Sulconazole (cutaneous)
    - Triazoles
        - Fluconazole (systemic)
        - Itraconazole (systemic)

Types of dermatophytosis, for stratification by indication:

- Superficial Tinea infections (tinea pedis, tinea manuum, tinea corporis)
- Hair follicle-involving Tinea infections (tinea capitis, tinea barbae)
- Onychomycosis

The preliminary concept sets used for the identification of covariates are described in **ANNEX III**. These codes will be refined during the study execution following the DARWIN EU® phenotyping standard processes, which involves the review of code lists, and the review of phenotypes after their execution in the participating data sources.

8.7. Study size

No sample size has been calculated, as this is a drug utilisation study with a descriptive design and no formal hypothesis testing. The study will rely on existing routinely collected data to estimate incidence rates of terbinafine-containing product use and to describe treatment patterns. Thus, the sample size is driven by the availability of data for eligible individuals within the included data sources.

8.8. Analysis

8.8.1. Federated network analyses

All analyses will be conducted separately for each data source, and will be carried out in a federated manner, allowing analyses to be run locally without sharing patient-level data.

Before sharing the study package, test runs of the analytics will be performed on a subset of the data sources and quality control checks will be performed. After all the tests are passed (see section **ANNEX II**), the final package will be released in a version-controlled study repository for execution against all the participating data sources.

The data partners will locally execute the analytics against the OMOP CDM in R Studio and review and approve the default aggregated results. They will then be made available to the Principal Investigators and study team in secure online repository (Data Transfer Zone). The study results of all data sources are checked, after which they are made available to the team, and the Study Dissemination Phase can start. All results are locked and timestamped for reproducibility and transparency.

8.8.2. Patient privacy protection

All analyses will be conducted separately for each data source, and will be carried out in a federated manner, allowing analyses to be run locally without sharing patient-level data. Cell counts <5 will be suppressed when reporting results to comply with the data source's privacy protection regulations.

8.8.3. Statistical model specification and assumptions of the analytical approach considered

R-packages

The incidence of terbinafine-containing product use *(objective 1)* will be estimated based on OMOP CDM mapped data using the *IncidencePrevalence* R package, developed by DARWIN EU® (https://darwin-eu.github.io/IncidencePrevalence/). Patient-level characterisation of terbinafine initiators and treatment utilisation *(objectives 2* and *3)* will be assessed using *CohortCharacteristics* and *DrugUtilisation* R packages (https://github.com/darwin-eu/DrugUtilisation), while patient-level characterisation of treatment patterns *(objective 4)* will be described using *TreatmentPatterns* (https://github.com/darwin-eu-dev/TreatmentPatterns).

Incidence rate estimation of terbinafine use *(objective 1)*

Monthly and annual incidence rates of terbinafine use will be calculated as the number of treatment initiations after 180 days of no use of terbinafine-containing product per 1,000 person-years, among individuals fulfilling the inclusion and exclusion criteria. Individuals who enter the denominator population contribute time at risk from cohort entry until the earliest of the following: initiation of terbinafine treatment during the study period, death, loss to follow-up (defined as the date of last contact), or end of the study period. Participants who do not initiate terbinafine treatment during the study period are administratively censored at the end of follow-up.

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 contribute 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 start 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 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 was not considered as time at risk.

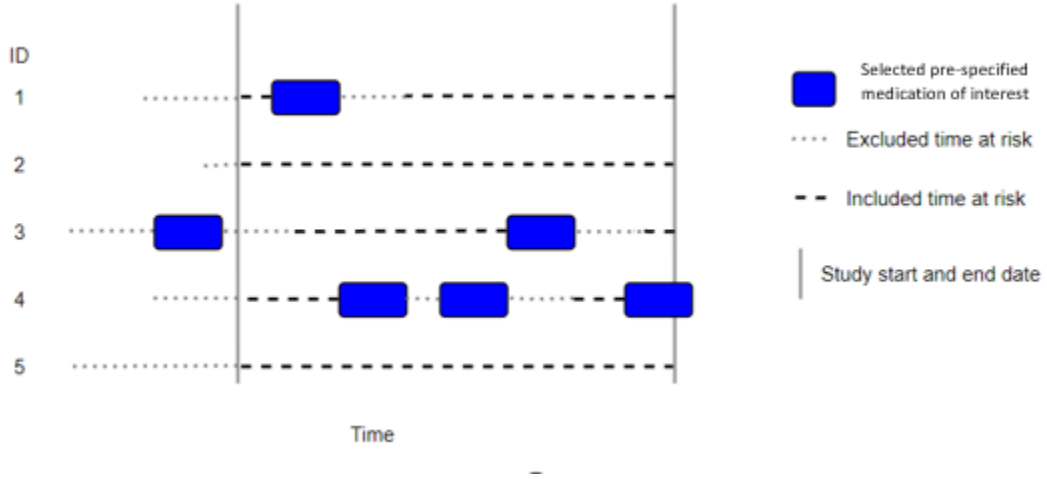


Figure 3. Incidence example.

Drug exposure calculations

Drug eras will be defined as follows: exposure starts at the date of a new prescription of terbinafine containing product during the study period after a washout of 180 days. 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 ≤30 days. The time between the two joined eras will be considered as exposed by the first era as shown in **Figure 4**, first row.

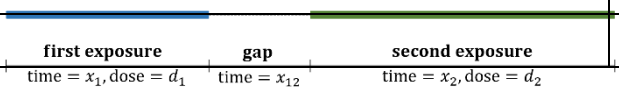
Gap era joint mode	Schematics	Dose in between	Cumulative dose	Cumulative time
"first"		d_1	$d_1 \cdot (x_1 + x_{12}) + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"second"		d_2	$d_1 \cdot x_1 + d_2 \cdot (x_2 + x_{12})$	$x_1 + x_{12} + x_2$
"zero"		0	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"join"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

Figure 4. Gap era joint mode.

If two exposures overlap, the overlap time will be considered exposed to the first exposure (**Figure 5**). No time will be added at the end of the combined drug era to account for the overlap. If two exposures start at the same date, the overlapping period will be considered exposed to both.

Overlap mode	Schematics	Dose overlap
"first"		d_1
"second"		d_2
"both"		$d_1 + d_2$
"maximum"		$\max(d_1, d_2)$

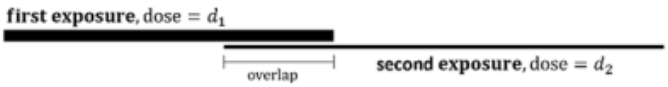


Figure 5. Gap era overlap mode.

New terbinafine user cohort *(objectives 2, 3, 4)*

Initial terbinafine users will be selected based on the first recorded prescription of a terbinafine-containing products during the study period. Eligible individuals must have at least 1 year of data visibility prior to the date of treatment initiation and no recorded use of terbinafine in the 180 days preceding treatment initiation. Repeated treatment episodes will be excluded. To ensure sufficient follow-up, only individuals who initiate terbinafine treatment at least 1 year prior the end of data availability in each data source will be included. Children <1 year of age will be excluded. The new terbinafine user cohort study will be used to characterise patient-level drug utilisation in terms of indication, comorbidities, antifungal and antibiotic treatment, resistance, evaluate treatment by assessing dose and duration of terbinafine use, and describe treatment patterns.

New terbinafine treatment episode cohort *(objective 3)*

New users will be selected based on their new terbinafine-containing product prescription during the study period after a washout of 180 days. The cohort will include all new terbinafine treatment episodes meeting the washout criteria. For each patient, at least one year of data visibility was required prior to becoming eligible for study inclusion. The new terbinafine treatment episode cohort study will be used to characterise patient-level drug utilisation in terms of dose and duration.

Treatment duration *(objective 3)*

Treatment duration will be calculated separately for first treatment episode and for multiple treatment episodes of the medication of interest during the study period (provided the episode meets the washout criteria). Treatment duration will be summarised providing the minimum, quartiles, and 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.

Treatment patterns (*objective 4*)

The number and percentage of patients receiving each of the pre-specified treatment options, as well as treatment combinations, will be described in the study population of new terbinafine users (*objective 4*). Additionally, Sunburst plots and Sankey diagrams will be used to visualise treatment patterns and sequences over time per data source. Sankey diagrams will be censored at end of follow-up as described in **Section 8.4**.

To construct treatment pathways, various parameters can be defined in the *TreatmentPatterns* package (**Figure 6**).

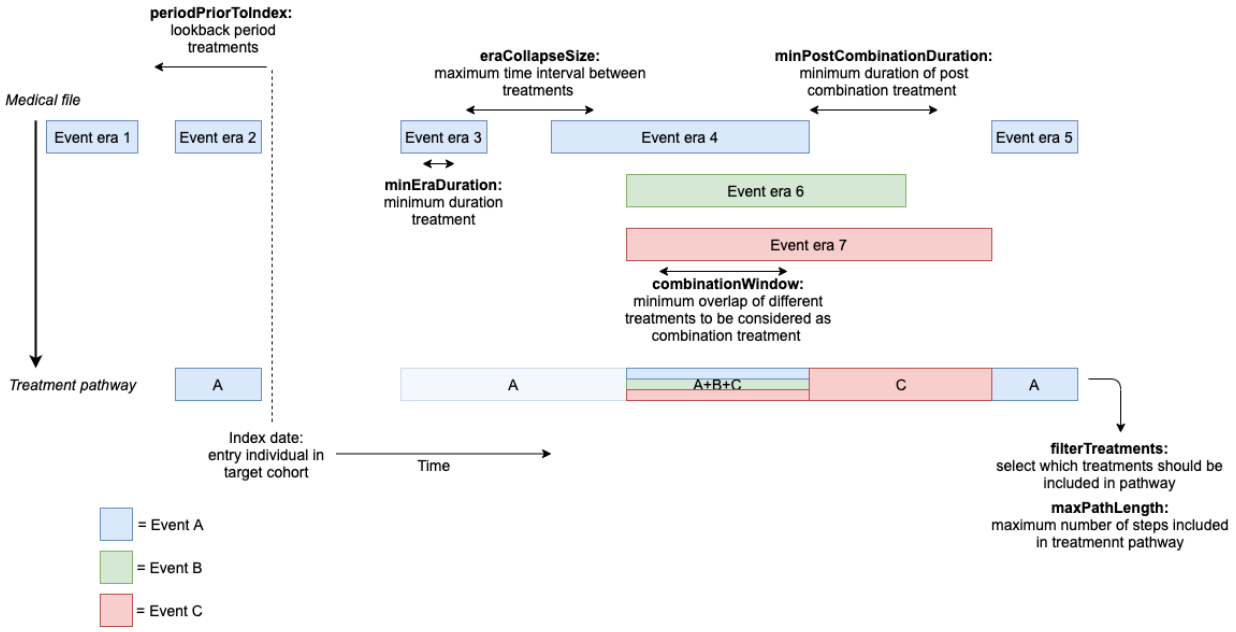


Figure 6. Parameters in *TreatmentPatterns* package.

The preliminary parameters outlined in this study are described in **Table 2**.

Table 2. List of pathway settings with description and expected input.

Individual pathway settings		
periodPriorToIndex	The period (number of days) prior to the index date of the target cohort from which treatments should be included	0
minEraDuration	Minimum time an event era should last to be included in the analysis	0
eraCollapseSize	Maximum gap within two eras of the same event cohort which would still allow the eras to be collapsed into one era	30 days
combinationWindow	Time that two event eras need to overlap to be considered a combination treatment	7 days
minPostCombinationDuration	Minimum time that an event era before or after a generated combination treatment should last to be included in the pathway as a separate treatment	7 days
filterTreatments	Select which treatments should be included in pathway: first time occurrences of treatments ('First'), remove sequential repeated treatments ('Changes'), all treatments ('All')	Changes
maxPathLength	Maximum number of treatments included in pathway	5
Aggregate pathway settings		
minCellCount	Minimum number of persons with a specific treatment pathway for the pathway to be included in analysis	5
minCellMethod	Select to completely remove / sequentially adjust (by removing last step as often as necessary) treatment pathways below minCellCount	Adjust
groupCombinations	Select to group all non-fixed combinations in one category 'other' in the sunburst plot	TRUE
addNoPaths	Select to include untreated persons without treatment pathway in the sunburst plot	TRUE

Method to deal with missing data

We assume that the absence of a prescription record in the data source means that the person does not receive the respective treatment. Similarly, for assessment of comorbidities, we assume that the absence of a recorded diagnostic code for a given condition means that that condition is not present or not recorded in the context of routine clinical care.

8.8.4. Output

Output will include the following:

A PDF report including an executive summary, and the following tables and figures.

- Table 1. Attrition table.
- Table 2. Number of study participants and total number of terbinafine treatment episodes in each source population during the study period *(objective 1).*
- Table 3. Baseline characteristics of terbinafine- users at the time of therapy initiation, including pre-specified indications *(objective 2).*

- Table 4. Frequency of comorbidities in terbinafine-containing product users at the time of therapy initiation (*objective 2*).
- Table 5. Frequency of antifungal and antibiotic prescription records in terbinafine-containing product users (*objective 2*).
- Table 6. Frequency of antifungal resistance codes in terbinafine-containing product users (objective 2).
- Table 7. Descriptive measures of initial and cumulative dose and treatment duration in terbinafine initiators, overall *(objective 3).*
- Table 8. Descriptive measures of initial and cumulative dose and treatment duration in terbinafine initiators, stratified by type of dermatophytosis (*objective 3*).
- Table 9. Descriptive measures of number of treatment initiations, initial and cumulative dose, and treatment duration considering multiple treatment episodes, overall (*objective 3*).
- Table 10. Descriptive measures of number of treatment initiations, initial and cumulative dose, and treatment duration considering multiple treatment episodes, stratified by type of dermatophytosis (*objective 3*).
- Figure 1. Incidence rates of terbinafine-containing product use over calendar time (per year) overall (*objective 1*).
- Figure 2. Incidence rates of terbinafine-containing product use over calendar time (per month) overall (*objective 1)*.
- Figure 3. Sunburst plot depicting treatment patterns after terbinafine initiation *(objective 4).*
- Figure 4. Sankey plot depicting treatment sequence after terbinafine initiation *(objective 4).*

Sunburst and Sankey plots will be generated for each participating data source, for overall analysis and stratified by type of dermatophytosis.

An interactive dashboard will be generated by incorporating all the results (tables and figures) included in the PDF report mentioned above.

8.9. Evidence synthesis

Results from the analyses described in **Section 8.8.** will be presented separately for each data source. No meta-analysis of results will be conducted.

9. STRENGTHS AND LIMITATIONS

Strengths

This study will leverage a large, diverse set of real-world data sources across multiple European countries, including registry-based and outpatient general practitioner care databases. The inclusion of six data sources, spanning Croatia, Denmark, Finland, Germany, Spain, and the United Kingdom, will ensure broad geographic coverage. The longitudinal nature of data sources will support the assessment of treatment patterns over time. Additionally, the use of the OMOP CDM will facilitate standardised data structuring, variable harmonisation, consistent cohort definitions, and analysis across data sources.

Limitations

This study will be informed by routinely collected health care data, which introduces several important considerations that may influence the interpretation of the findings.

The study will include data from six European countries. As such, the results reflect only the populations captured within these data sources and may not be generalisable to other countries or healthcare systems.

Electronic health records are primarily designed for clinical purposes rather than research, and as such, may contain incomplete, inconsistent, or variably recorded information. Therefore, the documentation of comorbidities, necessary for patient-level characterisation, may vary across data sources. The actual clinical indication for prescribing terbinafine is not directly recorded in the databases. Instead, proxy measures, based on diagnosis codes around the time of treatment initiation, are used. Consequently, the estimation of potential indications may be incomplete or imprecise as this might not be recorded in all patients.

Some data sources may face challenges in reliably determining treatment duration due to documentation gaps. End-of-treatment dates are not consistently available, and when direct observation is not possible, imputation methods using fixed duration assumptions (aligned with OMOP CDM conventions) are applied during the ETL process. While this promotes consistency across sources, it may not fully capture true treatment variability and should be interpreted with caution.

Additionally, a recorded prescription does not guarantee that the medication was dispensed or consumed, therefore assumptions of actual use have been made.

Terbinafine might be available over-the-counter (OTC). Since the study relies on healthcare databases, only individuals who seek medical care and receive a recorded prescription of terbinafine will be included. This potentially excludes individuals with mild or self-managed dermatophytosis who opt for OTC treatments. As OTC medication use is not captured in the data sources used for this study, the overall incidence of terbinafine use, particularly topical formulations, is likely to be underestimated.

10. REFERENCES

1. Pappas, P.G., *Terbinafine.* Essentials of Clinical Mycology, 2011.
2. Barac, A., et al., *Dermatophytes: Update on Clinical Epidemiology and Treatment.* Mycopathologia, 2024. **189**(6): p. 101.
3. Dolton, M.J., et al., *Terbinafine in combination with other antifungal agents for treatment of resistant or refractory mycoses: investigating optimal dosing regimens using a physiologically based pharmacokinetic model.* Antimicrob Agents Chemother, 2014. **58**(1): p. 48-54.
4. DeFalco, F., et al., *Achilles: Achilles Data Source Characterization. R package version 1.7.2.* 2023.
5. Gilbert, J., et al., *CohortDiagnostics: Diagnostics for OHDSI Cohorts. R package version 3.3.0, https://github.com/OHDSI/CohortDiagnostics, https://ohdsi.github.io/CohortDiagnostics.* 2024.
6. Inberg, G., E. Burn, and T. Burkard, *DrugExposureDiagnostics: Diagnostics for OMOP Common Data Model Drug Records. R package version 1.0.9, https://github.com/darwin-eu/DrugExposureDiagnostics, https://darwin-eu.github.io/DrugExposureDiagnostics/.* 2024.
7. Rathmann, W., et al., *Basic characteristics and representativeness of the German Disease Analyzer database* Int J Clin Pharmacol Ther, 2018. **56**(10): p. 459-466.
8. Tanislav, C., et al., *No increased incidence of venous thrombosis or pulmonary embolism after SARS-CoV-2 vaccination in Germany.* Public Health, 2022. **207**: p. 14-18.
9. Ly, N.F., et al., *Impact of European Union Label Changes for Fluoroquinolone-Containing Medicinal Products for Systemic and Inhalation Use: Post-Referral Prescribing Trends.* Drug Saf, 2023. **46**(4): p. 405-416.
10. Herrett, E., et al., *Data Resource Profile: Clinical Practice Research Datalink (CPRD).* Int J Epidemiol, 2015. **44**(3): p. 827-36.
11. Carey, I.M., et al., *Prevalence of co-morbidity and history of recent infection in patients with neuromuscular disease: A cross-sectional analysis of United Kingdom primary care data.* PLoS One, 2023. **18**(3): p. e0282513.
12. Wigglesworth, S., et al., *The incidence and prevalence of epilepsy in the United Kingdom 2013-2018: A retrospective cohort study of UK primary care data.* Seizure, 2023. **105**: p. 37-42.
13. Fahmi, A., et al., *Combinations of medicines in patients with polypharmacy aged 65-100 in primary care: Large variability in risks of adverse drug related and emergency hospital admissions.* PLoS One, 2023. **18**(2): p. e0281466.

11. ANNEXES

ANNEX I. Description of data sources

Croatian National Public Health Information System (NAJS), Croatia

The National Public Health Information System (Nacionalni javnozdravstveni informacijski sustav - NAJS) is an organised system of information services by the Croatian Institute of Public Health. This database was established in 1998, with nationwide coverage, representing approximately 5.4 million inhabitants. Settings covered include public primary, secondary/outpatient, and inpatient care. Data is retrieved primarily from EHR and holds information on demographics, inpatient and outpatient visits, conditions and procedures, drugs (outpatient and inpatient prescriptions), measurements, and inpatient and outpatient dates of death. NAJS provides linkage between medical and public health data collected and stored in health registries and other health data collections, including cancer registry, mortality, work injuries, occupational diseases, communicable and non-communicable diseases, health events, disabilities, psychosis and suicide, diabetes, drug abuse, and others. The CDM population comprises all publicly insured persons residing in Croatia starting in 2015. NAJS will provide data from 2017 onwards only, as prior data might include information on duplicated patients.

Danish Data Health Registries (DK-DHR), Denmark

Denmark Danish health data is collected, stored, and managed in national health registers at the Danish Health Data Authority and covers the entire population which makes it possible to study the development of diseases and their treatment over time. There are no gaps in terms of gender, age, and geography in Danish health data due to mandatory reporting on all patients from birth to death, in all hospitals and medical clinics. Personal identification numbers enable linking of data across registers, so it captures data on all Danes throughout their lives, regardless of whether they have moved around the country. The high quality of Danish health data is attributed to standardisation, digitisation, and comprehensive documentation, which together enhance accuracy, consistency, and reliability, minimising potential for interpretation errors. The Danish Health Data Authority is responsible for the national health registers and for maintaining and developing standards and classifications in the Danish healthcare system. Legislation ensures balance between personal data protection and use. The current data release includes data on the entire Danish population of 5.9 million persons from 1995. It includes data from the following registries: The central Person Registry, The National Patient Registry, The Register of Pharmaceutical Sales, The National Cancer Register, The Cause of Death registry, the Laboratory Database (including coronavirus disease 2019 test results), and the Vaccination Registry (including COVID-19 vaccinations).

Finnish Care Register for Health Care (FinOMOP-THL), Finland

This database covers both public and private, primary, and specialised inpatient and outpatient health care encounters in Finland starting from 2011. The entire public sector and private inpatient encounters have been included since 2011, while private outpatient encounters, including occupational care, are included since 2020. The main content of the THL CDM is The Finnish Care Register for Health Care, which is a continuation of the former Hospital Discharge Register, which originally gathered data on patients discharged from hospitals. The Care Register has comprehensive data on the use of services and service users from Finnish public inpatient and outpatient primary and specialised care nationwide. Since 1998, the register has covered both public outpatient and inpatient specialised care and private inpatient care (TerveysHilmo). From 2011 the register has covered public primary care (AvoHilmo). From 2020 the register has covered private outpatient care and occupational care. In addition, the CDM also contains the vaccination data from the Finnish National Vaccination Register, the vaccination data from the Finnish National Vaccination Register, and COVID-19 test results from the Finnish National Infectious Diseases Register, which is maintained by THL. The CDM includes all the above-mentioned data sources and is limited to observation periods commencing after 1/1/2011. The National Population is used to form the base population. This ensures up-to-date location (municipality of residence) of patients and complete

death occurrences (although not the cause of death). Using the complete population as a basis for the person table also facilitates calculations on a population level, e.g., incidence rates. The current CDM population comprises all persons having been alive and residing in Finland since the beginning of 2011.

IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany

IQVIA Disease Analyzer (DA) Germany is a database of de-identified electronic medical records from specialised and general primary practices (GP) in Germany since 1992.[7] This dataset encompasses approximately 3% of all outpatient practices within Germany, ensuring a substantial representation of the national healthcare landscape. The sampling methods used for practice selection, taking into account physician's demographics, specialty focus, community size category and federal state location, were instrumental in constructing a database that accurately mirrors the diverse spectrum of healthcare providers in the country. Consequently, data within IQVIA DA Germany database has been demonstrated to be representative of general and specialised practices throughout Germany.

The database contains demographics records, basic medical data, disease diagnoses according to the International Classification of Diseases, 10th revision (ICD-10), and prescription records. While the database partly records information on deaths and procedures, it currently does not support linkage with external data sources and therefore, information on mortality is incomplete. Routine updates are conducted at regular intervals. Data quality is assessed based on several criteria, including completeness of information and correctness (e.g. linkage between diagnosis and prescriptions).

No registration or approval is required for drug utilisation studies. As previously demonstrated, IQVIA DA Germany is suitable for pharmacoepidemiologic and pharmacoeconomic studies.[8, 9]

The Information System for Research on Primary Care (SIDIAP), Spain

The Information System for Research in Primary Care (SIDIAP) is a clinical database of anonymized patient records in Catalonia, Spain. The Spanish public healthcare system covers more than 98% of the population, and more than two thirds of the Catalan population see their GP at least once a year. The computerisation of the primary care patient records of the Catalan Health Institute (CHI) was complete in 2005. SIDIAP was designed to provide a valid and reliable database of information from clinical records of patients registered in primary care centres for use in biomedical research. SIDIAP contains data of anonymized patients' healthcare records for nearly six million people (approximately 80% of the Catalan population) registered in 287 primary care practices throughout Catalonia since 2005. It includes data collected by health professionals during routine visits in primary care, including anthropometric measurements, clinical diagnoses (International Classification of Diseases 10th revision ICD-10), laboratory tests, prescribed and dispensed drugs, hospital referrals, demographic, and lifestyle information. It was previously shown that SIDIAP population is highly representative of the entire Catalan region in terms of geographic, age, and sex distributions. The high quality of these data has been previously documented, and SIDIAP has been successfully applied to epidemiological studies of key exposures and outcomes. Quality checks to identify duplicate patient IDs are performed centrally at each SIDIAP database update. Checks for logical values and data harmonisation are performed. For biochemistry data, consistency for measurements taken in different laboratories is assessed, and unit conversion is undertaken when needed.

Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom

The Clinical Practice Research Datalink (CPRD) GOLD is a database of anonymised electronic health records (EHR) from General Practitioner (GP) clinics in the UK that use the Vision® software system for their management.[10] The source population encompasses 98% of the UK, registered with GPs responsible for non-emergency care and referrals. Participating GPs provide CPRD EHR for all registered patients who did not specifically request to opt out of data sharing. Covering 4.6% of the current UK population, GOLD includes 4.9% of contributing GP practices, providing comprehensive information within its defined source population. GOLD contains data from all four UK constituent countries, and the current regional

distribution of its GP practices is 5.7% in England, 55.6% in Scotland, 28.4% in Wales, and 10.2% in Northern Ireland (May 2022).

GOLD data include patient's demographic, biological measurements, clinical symptoms and diagnoses, referrals to specialist/hospital and their outcome, laboratory tests/results, and prescribed medications. GPs receive information about patient contacts with secondary care, but this information must be manually entered into the patient record and therefore, may be incomplete. GOLD has been assessed and found broadly representative of the UK general population in terms of age, gender, and ethnicity.[10] GOLD has been widely used internationally for observational research to produce nearly 3,000 peer-reviewed publications, making GOLD the most influential UK clinical database so far.[11-13]

In terms of quality checks, the integrity, structure, and format of the data is reviewed. Collection-level validation ensures integrity by checking that data received from practices contain only expected data files and ensures that all data elements are of the correct type, length, and format. Duplicate records are identified and removed. Transformation-level validation checks for referential integrity between records ensure that there are no orphan records included in the database (for example, that all event records link to a patient), while research-quality-level validation covers the actual content of the data. CPRD provides a patient-level data quality metric in the form of a binary 'acceptability' flag. This is based on recording and internal consistency of key variables including date of birth, practice registration date and transfer out date.

ANNEX II. Additional information

DATA MANAGEMENT

Data management

All data sources have previously mapped their data to the OMOP common data model. This enables the use of standardised analytics and using DARWIN EU® tools across the network since the structure of the data and the terminology system is harmonised. The OMOP CDM was 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 and will use standardised analytics wherever possible. Each data partner will execute the study code against their data source containing patient-level data and then return the results (csv files) which will only contain aggregated data. The results from each of the contributing data sites will then be combined in tables and figures for the study report.

Data storage and protection

For this study, participants from various EU member states will process personal data from individuals which is collected in national/regional electronic health record data sources. 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 data sources 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 EU® Remote Research Environment (RRE). These output files do not contain any data that allow identification of subjects included in the study. The RRE implements further security measures 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.

QUALITY CONTROL

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

Study specific quality control

When defining cohorts for indications, 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, the *CohortDiagnostics* R package (https://github.com/OHDSI/CohortDiagnostics) will be run if needed to assess the use of different codes across the data sources contributing to the study and identify any codes potentially omitted in error.

The study code will be based on R packages to (1) estimate Incidence, (2) characterise participants and drug utilisation, and 3) describe Treatment Patterns using the OMOP common data model. 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.

PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

A PDF 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 PDF report. The full set of underlying aggregated data used in the dashboard will also be made available if requested.

ANNEX III: List of stand-alone documents

Table S1. Preliminary list of medicines definitions that will be used for *TreatmentPatterns*.

Substance Name	Concept name	Class	ATC code	Concept ID	Include descendants
Terbinafine, topical	Terbinafine topical	Other antifungals for topical use	D01AE15	21601954	Yes
Terbinafine, systemic	Terbinafine, systemic	Antifungals for systemic use	D01BA02	21601967	Yes
Ciclopirox, topical	Ciclopirox	Other antifungals for topical use	D01AE14	21601953	Yes
Methylrosaniline, topical	Methylrosaniline	Other antifungals for topical use	D01AE02	21601941	Yes
Griseofulvin, oral	Griseofulvin	Antifungals for systemic use	D01BA01	21601966	Yes
Miconazole/hydrocortisone, topical	Miconazole/hydrocortisone	Imidazole and triazole derivatives	D01AC20	21601936	Yes
Benzoic acid/salicylic acid, topical	Benzoic acid/salicylic acid	Imidazole and triazole derivatives	D01AE20	21601959	Yes
Clotrimazole, topical	Clotrimazole	Imidazole and triazole derivatives	D01AC01	21601920	Yes
Ketoconazole, topical	Ketoconazole	Imidazole and triazole derivatives	D01AC08	21601927	Yes
Miconazole, topical	Miconazole	Imidazole and triazole derivatives	D01AC02	21601921	Yes
Sulconazole, topical	Sulconazole	Imidazole and triazole derivatives	D01AC09	21601928	Yes
Fluconazole, systemic	Fluconazole	Imidazole and triazole derivatives	J02AC01	21603080	Yes
Itraconazole, systemic	Itraconazole	Imidazole and triazole derivatives	J02AC02	21603081	Yes

Table S2. Preliminary list of conditions definitions.

Phenotype	Concept name	Concept id (including descendants)	Exclude concept id	Vocabulary
Dermatophytosis	Tinea corporis	4224968	-	SNOMED
Dermatophytosis	Tinea cruris	4160328	-	SNOMED
Dermatophytosis	Tinea pedis	133141	-	SNOMED
Dermatophytosis	Tinea manus	80946	-	SNOMED
Dermatophytosis	Onychomycose	4215978	-	SNOMED
Dermatophytosis	Tinea capitis	4182398	-	SNOMED
Dermatophytosis	Tinea barbae	4163426	-	SNOMED
Other fungal infections	Cutaneous candidiasis	4104522	-	SNOMED
Other fungal infections	Sporotrichosis	434859	-	SNOMED
Other fungal infections	Pityriasis versicolor	134870	-	SNOMED

Table S3. Preliminary list of resistance codes.

Phenotype	Concept name	Concept id	Include descendants
Drug resistance	Drug resistance	4150981	Yes

ANNEX IV: ENCePP checklist for study protocols

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

Study title: DARWIN EU® - Drug Utilisation Study of terbinafine-containing products

EU PAS Register® number: EUPAS1000000790
Study reference number (if applicable): P4-C1-018

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]	☒	☐	☐	
	1.1.2 End of data collection[2]	☒	☐	☐	
	1.1.3 Progress report(s)	☐	☐	☒	5
	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)	☒	☐	☐	
	2.1.2 The objective(s) of the study?	☒	☐	☐	7
	2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	
	2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
	2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	

Comments:

[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 categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	8.6.1
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3	Is exposure categorised according to time windows?	☐	☐	☒	
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	8.8.3
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6	Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

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

Comments:

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

Comments:

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

Comments:

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	8.2, 8.6

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	8.2, 8.6
	9.1.3 Covariates and other characteristics?	☒	☐	☐	8.2, 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)	☒	☐	☐	8.2, 8.6
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	8.2, 8.6
	9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	8.2, 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)	☒	☐	☐	8.2, 8.6
	9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	8.2, 8.6
	9.3.3 Covariates and other characteristics?	☒	☐	☐	8.2, 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?	☐	☐	☒	

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)	☒	☐	☐	11

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.2 Are methods of quality assurance described?	☒	☐	☐	11
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?	☒	☐	☐	9
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).	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	8.2, 8.7

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?	☒	☐	☐	8.2
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	8.2
13.3 Have data protection requirements been described?	☒	☐	☐	11

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)?	☒	☐	☐	11

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	11

Comments:

ANNEX V: Glossary

Additional definitions are available in the EMA Glossary of terms https://www.ema.europa.eu/en/about-us/glossaries.

Aggregated Data

Data collected and combined from multiple sources to generate summary information, typically anonymised.

Benefit-Risk Assessment

Evaluation of the positive therapeutic effects of a medicine compared to its risks (e.g., side effects).

Common Data Model (CDM)

A standardized data structure that enables data from multiple sources to be harmonized, making analysis consistent and reproducible. DARWIN EU® utilises the OMOP CDM maintained by the OHDSI community.

Complex Studies (C3)

Studies requiring the development or customisation of specific study designs, protocols, and Statistical Analysis Plans (SAPs), with extensive collection or extraction of data. Examples include etiological studies measuring the strength and determinants of an association between an exposure and the occurrence of a health outcome in a defined population considering sources of bias, potential confounding factors, and effect modifiers.

Coordination Centre (CC)

The central hub responsible for managing and overseeing the activities within DARWIN EU®. It is based at Erasmus University Medical Centre in Rotterdam, the Netherlands.

Data Access

The process of obtaining permission to use specific datasets for regulatory or scientific studies.

Data Quality Framework

A set of standards and procedures to ensure accuracy, completeness, timeliness, and consistency of data used in DARWIN EU®.

Data Source

A database or repository of structured health-related data, such as electronic health records (EHRs), insurance claims, or registries.

DARWIN EU®

The European Medicines Agency's (EMA) federated network of real-world data sources designed to generate evidence to support regulatory decision-making.

EMA (European Medicines Agency)

The regulatory body responsible for the evaluation and supervision of medicinal products in the EU, overseeing DARWIN EU®.

Evidence Generation

The process of analysing real-world data to produce scientific information that can inform healthcare or regulatory decisions.

Federated Network

A data infrastructure where data remain at their original location but can be analysed in a harmonised way across multiple partners using a common model and tools.

GDPR (General Data Protection Regulation)

The EU regulation governing the protection of personal data and privacy, crucial to how DARWIN EU® handles health data.

Health Technology Assessment (HTA)

A systematic evaluation of properties and impacts of health technology, often using DARWIN EU® data to support assessments.

Metadata

Descriptive information about a data source (e.g., its content, quality, and structure), essential for identifying relevant databases in DARWIN EU® studies.

Off-the-Shelf Studies (OTS)

Studies for which a standard protocol per study/analysis type and standardised analytics may be developed and applied or adapted, typically relating to a descriptive research question. This includes studies on disease epidemiology, for example, the estimation of the prevalence or incidence of health outcomes in defined time periods and population groups, or drug utilisation studies at the population or patient level.

OHDSI (Observational Health Data Sciences and Informatics)

An open-science collaborative community that develops tools and standards (including the OMOP CDM) to enable large-scale analytics of observational health data. OHDSI provides the technical and scientific foundation for DARWIN EU®'s analytical ecosystem.

Patient-Level Data

Data related to individuals, de-identified, used for longitudinal or detailed analyses.

OMOP (Observational Medical Outcomes Partnership)

A common data model (CDM) that standardises the structure and content of observational healthcare data, enabling systematic analysis across disparate datasets. DARWIN EU® uses the OMOP CDM to ensure interoperability and consistency in real-world evidence generation.

Real-World Data (RWD)

Data relating to individual health status or healthcare delivery that is collected from routine clinical practice rather than from randomised controlled trials.

Real-World Evidence (RWE)

Clinical evidence derived from the analysis of RWD, used to inform decisions by regulators, payers, or clinicians.

Regulatory Decision-Making

The process by which authorities like EMA assess data to authorise, monitor, or modify the use of medicines in the EU.

Routine Repeated Studies (RR)

Studies that are either Off-the-Shelf or Complex studies repeated on a regular basis, following the same protocol and study code, but with updated data and/or different data partners.

Study Protocol

A detailed plan describing how a specific real-world study will be conducted, including objectives, design, data sources, and analyses.

Very Complex Studies (C4)

Studies which cannot rely only on electronic health care databases, or which would require complex methodological work, for example, due to the occurrence of events that cannot be defined by existing diagnosis codes, including events that do not yet have a diagnosis code, where it may be necessary to combine a diagnosis code with other data such as results of laboratory investigations. These studies might require the collection of data prospectively, or the inclusion of new (not previously onboarded) data sources.

Name of the main author of the protocol: Dina Vojinovic

Date: 22/10/2025

Signature: